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CONTENTS

Blood loss and transfusion rate in patients undergoing two-stage exchange in infected total knee arthroplasty

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Two-stage exchange in infected total knee arthroplasty is a reliable technique, but it has a high rate of blood loss. The study aims to compare the pre-operative and post-operative haemoglobin levels, the rate of transfusion, and the blood loss in two-stage exchange. From July 2018 to July 2019, eighteen patients underwent two-stage exchange of their infected total knee arthroplasty. Local and systemic tranexamic acid was administered in both surgical stages. Calculated blood loss was 2246 mL (range 1528 – 2850) in the first stage and 2388 mL (1873 – 2829) during reimplantation, respectively. The corresponding transfusion rate was 55 % and 67%, respectively. With the numbers available, these differences were not significant. In conclusion, this study shows that the blood loss and transfusion rate are similar during the two stages of exchange knee arthroplasty for infection.

Periprosthetic joint infection (PJI) is one of the most important complications following total knee arthroplasty (TKA) and has an incidence rate of 1-2% (1, 2). The preferred surgical treatment for PJI is two-stage exchange, consisting of removal of the components and insertion of an antibiotic spacer (static or articulated) in first stage and reimplantation of revision TKA in the second stage, assisted by targeted antibiotic therapy (3, 4).

Although this procedure is most effective for eliminating infection, it typically results in an increased risk for blood loss and the need for blood transfusion at one or both surgeries in the two-stage procedure. Furthermore, blood management programs in these patients seems to be crucial to minimize allogenic transfusion (5). The use of tranexamic acid (TXA) represents nowadays a standard of care to reduce bleeding and the need of allogenic transfusion after total joint replacement without increasing the risk of thromboembolic events (6-9). However, there is only minimal literature on the effect and complication rates of TXA in septic revisions (10). This study aimed to compare the blood loss and transfusion rates during two-stage exchange in patients who received local and systemic TXA administration.

MATERIALS AND METHODS

This prospective study evaluated all consecutive patients who underwent two-stage exchange for PJI of the knee from July 2018 to July 2019. The inclusion criteria were age >18 years and the need for resection arthroplasty with a spacer, either static or articulating, for chronic infection. Patients were excluded from the study if they had less than 35 days between the resection and reimplantation stages, had a revision arthroplasty for non-infected TKA, or their clinical and laboratory data were unavailable for either stage. Preoperative hemoglobin

Key words: total knee arthroplasty, prosthetic joint infection, blood loss, transfusion, two-stage

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(Hgb) level of <8 g/dL was also considered an exclusion criterion.

The two-stage exchange procedure was performed by the same orthopedic surgeon and consisted of infected implant removal and spacer placement, followed by an antibiotic treatment course lasting for 10 and 12 weeks prior to prosthetic implant replacement. The hospital blood management protocol consisting of local and systemic perioperative administration of tranexamic acid (TXA) was applied for either surgical procedure.

One gram of TXA was diluted in 50 mL of 0.9% sodium chloride for intravenous administration before the incision; the second dose was administered after lowering the tourniquet. Local TXA was prepared using 3 g of TXA (500 mg/5 ml) dissolved in 50 ml of 0.9% sodium chloride solution (total of 80 ml of TXA solution) and applied to the wound for 5 minutes by the surgical team following component placement and was removed by suction. A suction drain was used in all the cases and was removed one day after the operation.

Patient demographic data (age and sex), body mass index, body surface area, Charlson comorbidity index, and operation time (minutes) were collected. Hgb levels and hematocrit (Hct) values were obtained preoperatively and daily thereafter until postoperative day (POD) 3. A standardized postoperative transfusion protocol was used. Patients were transfused when the Hgb level was <7 g/dL in all cases and in cases of anemia that was believed to be symptomatic (e.g., chest pain, arrhythmia, shortness of breath, and syncope) by either the surgeon, anesthesiologist, or physician. Total blood loss was calculated using a previously validated formula recommended by the Orthopaedic Surgery Transfusion Hemoglobin European Overview study group (11, 12).

Statistical analysis

Continuous variables were expressed as median (interquartile range). Qualitative variables were presented as a number and percentage. The Mann–Whitney U test was used for continuous variables. Fisher's exact test was used for categorical variables. $P<0.05$ was considered significant. SPSS software program (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses.

Table I: *Patient demographics.*

Male	*4 (22%)*
Age (years)	70 [61-74]
BMI (Kg/m^2)	31,1 [27,1-40,4]
Body Surface Area (m^2)	1.9 [1.7 – 1.9]
Charlson Comorbidity Index	2,8 [0-5]

Table II: *Comparison between 1° and 2° stage during two-stage exchange.*

	1° Stage	***2° Stage***	***P value***
Operative time (minutes)	180 [153.7 – 211.2]	210 [155 – 246.2]	0.54*
Pre-operative Hemoglobin (g/dl)	13.3 [10.4 – 14.3]	13 [11.8 – 14.1]	0.43*
Pre-operative Hematocrit (%)	39.8 [33.3 – 43.7]	41.1 [37 – 42.2]	0.19*
Transfusion Required n patient (%)	10 (55%)	12 (67%)	0.36**
Units transfused	1 [0 -2]	1 [0 -2]	0.41*
Calculated Blood Loss (mL)	2246 [1528 – 2850]	2388 [1873 – 2829]	0.314*

RESULTS

Eighteen patients (median age 70 (61–74) years, males 22%) with chronic periprosthetic knee infection were considered for the study. Demographic and clinical characteristics of the included cases are outlined in Table I. All patients underwent a two-stage exchange with the implantation of a static and an articulating spacer in 4 and 14 patients, respectively. The median duration of time between revision and reimplantation arthroplasty procedures was 10 (8–12) weeks.

First stage

The median preoperative Hgb level was 13.3 (10.4–4.3) mg/dL, and the median preoperative Hct value was 39.8% (33.3%–43.7%). The lowest Hgb level and Hct value were 8.3 (7.2–10) g/dL and 25.70% (23.2%–30.7%) on POD 2, respectively. Transfusions were performed in 55% of the patients. The median operation time was 180 (153.7–211.2) minutes, and the median calculated blood loss was 2246 (1528–2850) mL.

Second stage

The median preoperative Hgb level was 13 (11.8–14.1) mg/dL, and the median preoperative Hct value was 41.1 (37–42.2). The lowest Hgb level and Hct value were 8.2 (7.4–10.3) g/dL and 25.70% (22%–31.8%) on POD 3, respectively. Transfusions were performed in 67% of the patients. The median operation time was 210 (155–246.2) minutes, and the median calculated blood loss was 2388 (1873–2829) ml.

Table II shows the summary statistics for operative time, preoperative Hgb level (g/dL), preoperative Hct value, transfusion required, the number of allogenic blood units transfused, and the calculated blood loss between the two stages. No statistical differences were observed in all the variables analyzed.

DISCUSSION

Two-stage exchange is the preferred treatment strategy for infected TKA (3-5, 13-19). Patients undergoing two-stage exchange are at an increased risk of blood loss and require blood transfusions (5). In our study, the total blood loss during the stage 2 was greater than in stage 1 (2388 mL *vs* 2246 mL), but this difference was not statistically significant.

In previous literature, increased blood loss in stage 2 reimplantation procedures could be attributed to a longer operative time, greater surgical aggression in the preparation of joint surfaces and intramedullary canals of the femur and tibia, and the preoperative Hgb level and Hct value, which can increase the amount of total blood loss (20). In our series, no differences in terms of preoperative Hgb level and Hct value were observed; hence, the increase in operative time during the second stage could be considered the only factor responsible for this result. In addition, our results are lower than those reported in a series evaluating the blood loss in aseptic and septic revision (21).

There was no difference in terms of transfusion rate; it could be attributed to no difference in the blood loss and no homogeneity of the population. The results in terms of transfusion rate, either the during the first and second stages, are inferior than those presented in a previous study (5). Pagnano et al. reported a transfusion rate of 80% and 82% in the first and second stages, respectively.

In the present study, we reported a transfusion rate of 55% in the first stage and 67% in the second stage with the same unit transfused. One possible reason for these results is the application of a strict blood management protocol that included the use of systemic and local TXA in the perioperative period. The use of TXA conferred a significantly decreased risk for transfusion requirement after stage 2 procedure and decreased risk that approached significance in stage 1 (20).

Our results are in line with those reported in the literature (21). Reichel et al. have suggested that the use of TXA reduces blood loss in revision TKA without increasing the risk of thromboembolic events. The present study has some limitations. First, small number of patients were enrolled in the study. Second, the lack of stratification based on patient's comorbidity could influence the blood loss and the secondary transfusion rate. Furthermore, this prospective study has some points of strength.

First, this is a single-center study in which all the patients were treated by the same surgeon. Second, we adopted a strict blood management protocol for all the patients included in the study.

In conclusion, the current study shows that the amount of blood loss is similar in the first and second surgical stage. The use of blood management protocol including the use of TXA helped us to reduce the transfusion rate.

REFERENCES

1. Kurtz SM, Ong KL, Lau E, et al. Prosthetic joint infection risk after TKA in the Medicare population. Clin Orthop Relat Res. 2010; 468:52-56.
2. Efremov K, Benedetti, Valentini M, et al. Periprosthetic hip and knee infections: comparison of etiology, perioperative management and costs. Eur Rev Med Pharmacol Sci. 2019; 23(2 Suppl):217-23.
3. Spivey JC, Guild GN, Scuderi GR. Use of articulating spacer technique in revision total knee arthroplasty complicated by sepsis: a systematic meta-analysis. Orthopedics. 2017; 40:212-20.
4. Ascione T, Pagliano P, Balato G et al. Oral therapy, microbiological findings, and comorbidity influence the outcome of prosthetic joint infections undergoing 2-stage exchange. J Arthroplasty. 2017; 32:2239-43.
5. Pagnano M, Cushner FD, Hansen A, Scuderi GR, Scott WN. Blood management in two-stage revision knee arthroplasty for deep prosthetic infection. Clin Orthop Relat Res. 1999; 367:238-42.
6. Lee SY, Chong S, Balasubramanian D, Na YG, Kim TK. What is the Ideal Route of Administration of Tranexamic Acid in TKA? A Randomized Controlled Trial. Clin Orthop Relat Res. 2017; 475:1987-96.
7. Yue C, Pei F, Yang P, Xie J, Kang P. Effect of Topical Tranexamic Acid in Reducing Bleeding and Transfusions in TKA. Orthopedics. 2015; 38:315-24.
8. Xie J, Hu Q, Huang Q, Ma J, Lei Y, Pei F. Comparison of intravenous versus topical tranexamic acid in primary total hip and knee arthroplasty: An updated meta-analysis. Thromb Res. 2017; 153:28-36.
9. White CC, Eichinger JK, Friedman RJ. Minimizing Blood Loss and Transfusions in Total Knee Arthroplasty. J Knee Surg. 2018; 31:594-9.
10. Waddell BS, Zahoor T, Meyer M, Ochsner L, Chimento G. Topical Tranexamic Acid Use in Knee Periprosthetic Joint Infection Is Safe and Effective. J Knee Surg. 2016; 29:423-9.
11. Rosencher N, Kerkkamp HE, Macheras G, et al; OSTHEO Investigation. Orthopedic Surgery Transfusion Hemoglobin European Overview (OSTHEO) study: blood management in elective knee and hip arthroplasty in Europe. Transfusion. 2003; 43:459-69.
12. Gao FQ, Li ZJ, Zhang K, Sun W, Zhang H. Four Methods for Calculating Blood-loss after Total Knee Arthroplasty. Chin Med J (Engl). 2015; 128:2856-60.
13. Ascione T, Balato G, Mariconda M, Rotondo R, Baldini A, Pagliano P. Continuous Antibiotic Therapy Can Reduce Recurrence of Prosthetic Joint Infection in Patients Undergoing 2-Stage Exchange. J Arthroplasty. 2019; 34:704-9.
14. Balato G, Roscetto E, Vollaro A, et al. Bacterial biofilm formation is variably inhibited by different formulations of antibiotic-loaded bone cement in vitro. Knee Surg Sports Traumatol Arthrosc. 2019; 27:1943-52.
15. Balato G, Franceschini V, Ascione T, et al. High performance of α-defensin lateral flow assay (Synovasure) in the diagnosis of chronic knee prosthetic infections. Knee Surg Sports Traumatol Arthrosc. 2018; 26:1717-22.
16. Ascione T, Pagliano P, Mariconda M, et al. Factors related to outcome of early and delayed prosthetic joint infections. J Infect. 2015; 70:30-6.
17. Balato G, Ascione T, Mariconda M et al. Release of gentamicin from cement spacers in two-stage procedures for hip and knee prosthetic infection: an in vivo pharmacokinetic study with clinical follow-up. J Biol Regul Homeost Agents. 2015; 29:63-72
18. De Luna V, Mancini F, De Maio F, Bernardi G, Ippolito E, Caterini R. Intraoperative Disinfection by Pulse Irrigation with Povidone-Iodine Solution in Spine Surgery. Adv Orthop. 2017; 1-8.
19. Ippolito E, Farsetti P, Valentini MB, Potenza V. Two-stage surgical treatment of complex femoral deformities with severe coxa vara in polyostotic fibrous dysplasia. J Bone Joint Surg Am. 2015; 97:119-25.
20. Goel R, Buckley P, Sterbis E, Parvizi J. Patients with infected total hip arthroplasty undergoing 2-stage

exchange arthroplasty experience massive blood loss. J Arthroplasty. 2018; 33:3547-3550.

21. Reichel F, Peter C, Ewerbeck V, Egermann M. Reducing Blood Loss in Revision Total Hip and Knee Arthroplasty: Tranexamic Acid Is Effective in Aseptic Revisions and in Second Stage Reimplantations for Periprosthetic Infection. Biomed Res Int. 2018; 15:3891870.

The role of six biomarkers in diagnosis of hemophilic arthropathy: review of the literature

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The aim of our narrative review of the literature is to identify the role of six important biomarkers: synovial fluid thrombomodulin, fibroblast-like synoviocytes, synovial tissue growth factor , vascular endothelial growth factor in synovium and peripheral blood, urinary C-terminal telopeptide of type II collagen, and synovial fluid tumor necrosis factor alpha. These urinary, serum and synovial biomarkers illustrated should be evaluated in patients with hemophilic arthropathy for early diagnosis of hemophilic arthropathy, because they have important implications in the development of arthrofibrosis, altered inflammatory response and bleeding. Moreover, better knowledge of their biological activity is important to identify possible new biological treatment options.

Hemophilia is an inherited recessive, sex-linked bleeding disorder. Lack of clotting factors VIII and IX causes hemophilia A and B, respectively (1). Arthropathy is the most common clinical manifestation in patients with hemophilia and the knee is the most frequently affected joint. Repeated bleedings may lead to chronic synovitis, resulting in chronic, painful arthropathy and disability. This disease evolves through three stages: the early stage is characterized by recurrent hemarthroses, the second by a chronic synovitis and the end-stage by a degenerative arthritis with various deformities, including axial deviation, stiffness and chronic pain (2).

Biomarkers could be useful in the future to control the impact of hemarthrosis and evaluate its treatment: in fact, in patients with hemophilic arthropathy, biomarkers could detect a greater degradation of cartilage and bone and altered inflammatory activity (3). Therefore, biomarkers could be used in the future to identify patients with progressive joint disease. The aim of our review is to identify the role of six important biomarkers that could be helpful for:

- Differentiation Arthrofibrosis/Osteoarthritis
- To explain the altered inflammatory process in hemophilic patients
- To explain the increased predisposition to bleeding
- Targeted treatment of hemophilic arthropathy

MATERIAL AND METHODS

Our study group searched the PubMed database and Web of Science using the terms "biomarker" "hemophilic arthropathy" "hemarthrosis" in the "all terms" field and this produced 127 results. The abstracts were then reviewed to determine suitability for inclusion in the review. The research question and inclusion/exclusion criteria were determined *a*

Key words: hemophilia, hemophilic arthropathy, biomarkers, hemarthrosis, synovitis

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priori and included English language studies of all levels of evidence on humans. We excluded studies not reporting data concerning hemophilic disease, article prior to the year 2000 and instructional course lectures. We included in the study only studies reporting data of easily to find biomarkers (serum, urine and synovial fluid). The implications that the determination of biomarkers has in the pathogenesis and evolution of hemophilic arthropathy has measured with *in vivo* and *in vitro* tests. Finally, a total of 9 articles met the inclusion criteria. The main conclusions drawn from the papers were then compared to produce the findings of this review. Unfortunately, a meta-analysis was not feasible because there were no intra-study comparison data as the studies showed variability in test measures.

RESULTS

We identified six biomarkers: synovial fluid thrombomodulin, fibroblast-like synoviocytes, connective tissue growth factor, vascular endothelial

Table I. *Biological activity and potential role of each biomarker in clinical practice.*

BIOMARKERS	BIOLOGICAL ACTIVITY	CLINICAL IMPLICATIONS
Thrombomodulin (TM)	Natural anticoagulant, an essential cofactor for activation of protein C by thrombin. Patients with Hemophilic arthropathy (HA) had significantly higher synovial fluid TM levels	The combined effect of low TF expression into joints associated with an inflammatory synovial fluid containing high-TFPI and TM levels may explain why hemophilic joints are more likely to develop haemorrhages.
Fibroblast-like synoviocytes (FLS)	Key mediators of inflammation and joint destruction through aggressive invasion of the extracellular matrix and production of cartilage-degrading proteases and inflammatory cytokines. Pro-apoptotic Fas receptor is highly expressed on HA-FLS and that its stimulation by agonistic anti-Fas IgM mAb is effective in inducing HA-FLS apoptosis	Anti-Fas mAb could exert its potent in vitro pro-apoptotic effects also in the presence of the strong proliferative stimuli of TNF-α and bFGF, suggesting that it might also be effective in the treatment of severe HA synovitis in vivo.
Connective tissue growth factor (CTGF)	CTGF has been documented as a secreted protein that is required for the development of fibrotic tissues in a variety of organs	CTGF expression is elevated in hemophilia patients with arthrofibrosis and absent in patients with osteoarthritis, examinating human synovial tissues
Vascular endothelial growth factor (VEGF)	The principal signaling molecule in angiogenesis, with of de novo blood vessel formation, including endothelialization of the synovium.	De novo blood vessel formation could play a major role in the pathogenesis of hemophilic joint disease (HJD), so there is a a potential to develop surrogate biologic markers to identify the onset and progression of hemophilic synovitis.
Urinary C-terminal telopeptide of type II collagen (u-CTXII)	Product of degradation of type II collagen, the major component of the articular cartilage matrix	To allow to quantify the extent of this catabolic process. This biomarker may be related to hemarthrosis; in fact it was possible to observe a statistically significant increase of the biomarker value, five days after the acute event
Synovial fluid tumor necrosis factor alpha (TNF-α)	to trigger the cascade that leads to destruction of cartilage and joint tissues (in particular through type I receptors) and angiogenesis (type II receptors). In hemophilic patient it is possible to observe, a higher basal level of TNF-α at the level of synovial fluid, and an increased iron intracellular concentration in TNF-mediated synovial macrophages	An inactivation of iRhom2 / ADAM17 / TNF- α complex leads to the reduction of cartilage and joint tissue destruction, neoangiogenesis and, above all, a reduction of osteopenia through reduction of mediated TNF osteoclastogenesis, of synovial hypertrophy and reduction of the expression of calprotectin

growth factor in synovium and peripheral blood, urinary C-terminal telopeptide of type II collagen, and synovial fluid tumor necrosis factor alpha. Biomarkers are specifically evaluated, and their biological activity is explained. In Table I we summarize their biological activity and the role they could have in clinical practice.

Synovial fluid thrombomodulin ™

Thrombomodulin (TM) is a natural anticoagulant, an essential cofactor for activation of protein C by thrombin. TM is expressed on endothelial cells, mesothelial surfaces, megakaryocytes, in smooth muscle cell lines and on human mononuclear cells. Moreover, a recent study on synovial lining cells, in culture, demonstrated that synovial cells were able to express TM (4). It has also been reported that a concerted action of neutrophils on cytokine-activated endothelial cells, resulted in TM release from endothelial cells into the culture supernatant (5). In patients with rheumatoid polyarthritis and osteoarthritis, it has been previously shown that synovial liquid contains high levels of TM (6). Therefore, Dargaud et al. (7) presented the potential effect of synovium-derived TM on the pathophysiology of hemarthroses.

The concentration of TM and tissue factor pathway inhibitor (TFPI) was measured in knee synovial fluid of patients with hemophilia and controls. They used these concentrations of TM and TFPI in a thrombin generation (TG) model to analyse their, in vitro, effects on coagulation in plasma of six male controls and six severe hemophiliacs. The expression of TM in synovial tissue was also studied in controls and hemophiliacs. Patients with Hemophilic arthropathy (HA) had significantly higher synovial fluid TFPI and TM levels, with a mean of 47 ± 27 ng/mL ($P = 0.033$) and 56 ± 25 ng/ mL ($P = 0.031$), respectively, compared to the control group which presented lower levels of synovial fluid TFPI (26 ± 9 ng/mL) and TM concentrations (39 ± 21 ng/mL). TG capacity was significantly reduced in the presence of TM 56 ng/ mL ($P = 0.02$), concentration observed in the synovial fluid of patients with HA.

The concomitant addition of TM 56 ng/mL and TFPI 47 ng/mL induced a highly significant inhibition of TG in the same samples ($P = 0.008$). No significant inhibition of TG capacity was observed in the presence of control synovial concentration of TM ($P > 0.05$). For these reasons, Dargaud et al. showed that synovial fluid of patients with severe HA contained significantly higher levels of TM compared to controls, suggesting that the increase of TM into the synovial fluid may locally induce a significant inhibition of TG in hemophilic joints. The combined effect of low TF expression into joints associated with an inflammatory synovial fluid containing high-TFPI and TM levels may explain why hemophilic joints are more likely to develop haemorrhages.

Fibroblast-like synoviocytes (FLS)

Although the pathogenesis of HA is still unknown, recent studies indicate that HA not only has similarities with degenerative joint modifications such as osteoarthritis, but also develops an inflammatory process and excessive growth of actively proliferating synovial tissue similar to rheumatoid arthritis (RA) (8). Increasing evidence indicates that fibroblast-like synoviocytes (FLS) take centre stage in synovitis. FLS are key mediators of inflammation and joint destruction through aggressive invasion of the extracellular matrix and production of cartilage-degrading proteases and inflammatory cytokines (9).

Previous studies demonstrated that RA-FLS were sensitive to pro-apoptotic signals, and treatment with agonistic anti-Fas mAb was effective in inducing Fas-mediated apoptosis in cultured RA-FLS and reducing synovial hyperplasia in animal models of RA (10). Therefore Romano et al. (11) showed that the pro-apoptotic Fas receptor is highly expressed on HA-FLS and that its stimulation by agonistic anti-Fas IgM mAb is effective in inducing HA-FLS apoptosis, isolated from knee synovial biopsies from six HA patients. Notably, anti-Fas mAb could exert its potent in vitro pro-apoptotic effects also in the presence of the strong proliferative stimuli of TNF-α and bFGF, suggesting that it might also be effective in the treatment of severe HA synovitis *in vivo*.

Connective tissue growth factor (CTGF)

Connective tissue growth factor (CTGF) is a member of the CCN (CYR61-CTGF-NOV)

family of matricellular proteins, which includes six members in vertebrates. Like other members of the CCN family, CTGF/CCN2 has five distinct domains in order: secretory signal peptide, insulin-like growth factor-binding protein, von Willebrand factor type C repeat, thrombospondin type-1 repeat and C-terminal cystine-knot-containing domains. CTGF has been documented as a secreted protein that is required for the development of fibrotic tissues in a variety of organs (12). For persons with hemophilia (PWH), arthrofibrosis is often the most severe and disabling component of their arthropathy and the most refractory to treatment; it routinely occurs rapidly following joint replacement as compared to other patients (13). However, the etiology of arthrofibrosis in hemophilia is not well understood. J. Jang et al (14) showed that CTGF expression is elevated in hemophilia patients with arthrofibrosis and absent in patients with osteoarthritis, examining human synovial tissues obtained from 10 hemophilia and 10 osteoarthritis patients undergoing joint surgery and processed for histology and immunohistochemistry. Additionally, they found that CTGF is always associated with haemosiderin-pigmented macrophage-like cells (HMCs), which suggests that CTGF is produced by synovial A cells following the uptake of blood breakdown products.

Vascular endothelial growth factor (VEGF) in synovium and peripheral blood

Hemophilic Joint Disease (HJD) secondary to recurrent hemarthroses is composed of synovial neovascularization and bony arthropathy.

Vascular endothelial growth factor (VEGF), the principal signaling molecule in angiogenesis, can be induced by hypoxia and certain cytokines through interaction with its receptors, VEGFR1 and VEGFR2. The synovitic reaction in other joint diseases that share histologic similarities with HJD have enhanced oxygen demand and show evidence of de novo blood vessel formation, including endothelialization of the synovium. Endothelialization may occur as a result of mature endothelial cell migration or through the recruitment of bone marrow (BM)–derived endothelial progenitor cells (EPCs) and hematopoietic progenitor cells (HPCs) from the peripheral circulation. Importantly, proliferating synovium can secrete chemocytokines, such as VEGF, that might promote recruitment of endothelial cells (ECs) to sites of active angiogenesis.

S. Acharya et al. (15) provide evidence of local and systemic angiogenic response in hemophilic subjects with recurrent hemarthroses. They observed an elevation in proangiogenic factors (vascular endothelial growth factor-A (VEGF-A), stromal cell–derived factor-1, and matrix metalloprotease-9) and proangiogenic macrophage/monocyte cells (VEGF+/CD68+ and VEGFR1+/CD11b+) in the synovium and peripheral blood of HJD subjects along with significantly increased numbers of VEGFR2+/AC133+ endothelial progenitor cells and CD34+/VEGFR1+ hematopoietic progenitor cells. Sera from HJD subjects induced an angiogenic response in endothelial cells that was abrogated by blocking VEGF, whereas peripheral blood mononuclear cells from HJD subjects stimulated synovial cell proliferation, which was blocked by a humanized anti-VEGF antibody (bevacizumab). Human synovial cells, when incubated with HJD sera, could elicit up-regulation of HIF-1+ mRNA with HIF-1+ expression in the synovium of HJD subjects, implicating hypoxia in the neoangiogenesis process.

Urinary C-terminal telopeptide of type II collagen (u-CTXII)

Type II collagen is the major component of the articular cartilage matrix and is degradated by proteolytic enzymes secreted by chondrocytes and synoviocytes. Therefore, it is possible to identify a specific urinary biomarker, identified as u-CTX II (Urinary C-terminal telopeptide of type II collagen) which allows to quantify the extent of this catabolic process.

In hemophilic patient this biomarker may be related to hemarthrosis (16); in fact, it was possible to observe a statistically significant increase of the biomarker value, five days after the acute event, returning to normal level fourteen days after bleeding.

*Synovial fluid tumor necrosis factor alpha (TNF-**α**)*

TNF-α plays a very important role in the

inflammatory process that occurs in the catabolic action of cartilage and joint tissues. It is activated in its soluble form (s-TNFα) by a protease belonging to the family of disintegrins and metalloproteases (ADAM17, TNFα-converting enzyme) which is in turn modulated by a recently identified enzyme known as iRhom2. It binds to two receptor types, TNF-receptors of type I (TNFR1, TNFRSF1A, CD120a) and type II (TNFR2, TNFRSF1B, CD120b).

Both contribute to triggering the cascade that leads to destruction of cartilage and joint tissues (in particular through type I receptors) and angiogenesis (type II receptors). In hemophilic patient it is possible to observe, a higher basal level of TNF-α at the level of synovial fluid, and an increased iron intracellular concentration in TNF-mediated synovial macrophages. In literature, an increasing role is assumed by the iRhom2 / ADAM17 / TNF-α complex with regard to the development of macrophage invasion and synovitis resulting from hemarthrosis in the hemophilic patient (17).

Recent studies have in fact emphasized that an inactivation of this complex leads to the reduction of the aforementioned processes and, above all, a reduction of osteopenia through reduction of mediated TNF osteoclastogenesis, of synovial hypertrophy and reduction of the expression of calprotectin (18).

DISCUSSION

Validated scoring systems enable universal interpretation and comparison of findings. The World Federation of Hemophilia (WFH) orthopaedic score (Gilbert score) is well known but was never validated. It is based on evaluation of swelling, muscle atrophy, crepitus on motion, range of motion, flexion contracture, instability and axial deformity. Although used worldwide for several decades, the score was designed to monitor relatively advanced arthropathy. To evaluate outcome of prophylactic clotting factor replacement in children with hemophilia, the Haemophilia Joint Health Score (HJHS) was developed aiming at scoring early joint changes in children aged 4-18. The HJHS has been used for adults on long-term prophylaxis but interpretation of small changes remains difficult.

Conventional radiography is the most frequently used method of imaging. Two main radiographic scoring systems have been developed: the Arnold–Hilgartner scale (3) and the Pettersson scale (19). The former is a progressive scale (describing the single most severe change), whereas the more widely used Pettersson scale is additive (determined by totalling points for different changes). However, conventional radiography is unable to detect osteochondral changes early in the development of hemophilic arthropathy, and given the possibility of subclinical joint bleeds, accurate non-invasive imaging tools are required to detect early soft-tissue and cartilage abnormalities.

MRI has the capacity to visualize early soft-tissue changes such as hemosiderin deposition and synovial hypertrophy. It may thus be used to detect prior subclinical hemarthroses. Widely known is the Denver scale, a progressive scale analogous to the Arnold–Hilgartner X-ray scale (20). However, progressive methodology cannot differentiate early from moderate/severe changes, and thus has a 'ceiling' effect.

Compared with MRI, ultrasound has advantages of easy access, lack of radiation, portability, relatively low cost and lack of need for sedation in young patients. Also, ultrasound can differentiate between synovial hypertrophy and hemosiderin deposition, which may not be possible with MRI in cases of severe hemosiderin deposition, given the presence of susceptibility artefacts from extracellular hemosiderin on gradient echo magnetic resonance images. This advantage of ultrasound over MRI is particularly important for evaluating synovial status in PWH who are candidates for radiosynovectomy. However, ultrasound enables visualization only of the joint periphery, limiting its use for assessment of cartilage abnormalities in the inner joint aspect. Several systematic protocols for ultrasound imaging acquisition of hemophilic joints have been developed in recent years (21), but systematization and consensus on protocols and interpretation are required to enable comparison of results.

Another issue favoring the study of biomarkers

in patients with hemophilic arthropathy is the fact that the disease is largely restricted to 3 major joints: ankle, elbow, and knee. The Pettersson score, a radiologic classification of hemophilic arthropathy in which individual scores in the knees, ankles, and elbows are summed to yield a total score, provides a good view of total joint damage in patients with the advanced stages of disease (22,23).

The good correlation of the combined index of biomarkers with radiographic joint damage might be due to the fact that joint damage in patients with hemophilic arthropathy occurs mostly in the elbow, knee, and ankle joints (24). These joints are relatively large joints, and therefore, they contribute significantly to circulating and excreted levels of biomarkers.

Whether and, if so, which (combination of) biomarkers are predictive of radiographic progression of joint damage remains to be studied.

Urinary, serum and synovial biomarkers illustrated could be evaluated in patients with hemophilic arthropathy for early and correct diagnosis of hemophilic arthropaty, because they have important implications in the development of arthrofibrosis, altered inflammatory response and bleeding. Moreover, better knowledge of their biological activity is important to identify possible new biological treatment options. Nevertheless, current literature still has little bearing on clinical practice and the specific characteristics of hemophilic arthropathy might be useful in future evaluations of new biomarkers, with studies on humans patients that assess real effectiveness of them.

REFERENCES

1. Rodriguez-Merchan EC. Orthopaedic problems about the ankle in hemophilia. J Foot Ankle Surg 2012;51:772–6.
2. G.Pasta, R.Vanelli, E.Jannelli, A.Castelli, M.Mosconi, P.S. Preti, C. Ambaglio, F.Benazzo
3. Primary total knee replacement in hemophiliacs: experience of a single institution along fourteen years of surgical procedures. J Biol Regul Homeost Agents 2018; 32(6 Suppl. 1):145-50.
4. Arnold WD, Hilgartner MW. Hemophilic arthropathy. Current concepts of pathogenesis and management. J Bone Joint Surg Am 1977; 59:287-305.
5. Conway EM, Nowakowski B. Biologically active thrombomodulin is synthesized by adherent synovial fluid cells and is elevated in synovial fluid of patients with rheumatoid arthritis. Blood 1993; 81:726-33.
6. Boehme MWJ, Deng Y, Raeth U, Bierhaus A, Ziegler R, Stremmel W. Release of thrombomodulin from endothelial cells by concerted action of TNFa and neutrophils:in vivo and in vitro studies. Immunology 1996; 87:134-40.
7. Van de Wouwer M, Collen D, Conway EM. Thrombomodulin-protein C-EPCR system:integrated to regulate coagulation and inflammation. Arterioscler Thromb Vasc Biol 2004; 24:1374–83.
8. Dargaud Y, Simpson H, Chevalier Y, et al. The potential role of synovial thrombomodulin in the pathophysiology of joint bleeds in haemophilia. Haemophilia 2012; 18(5):818-23.
9. Roosendaal G, Lafeber FP. Pathogenesis of haemophilic arthropathy. Haemophilia 2006; 12(Suppl. 3):117–21.
10. Bartok B, Firestein GS. Fibroblast-like synoviocytes: key effector cells in rheumatoid arthritis. Immunol Rev 2010; 233:233-55.
11. Odani-Kawabata N, Takai-Imamura M, Katsuta O et al. ARG098, a novel antihuman Fas antibody, suppresses synovial hyperplasia and prevents cartilage destruction in a severe combined immunodeficient- HuRAg mouse model. BMC Musculoskelet Disord 2010; 11:221.
12. Romano E, Manetti M, Peruzzi F, Melchiorre D, Milia AF, Bellando-Randone S, Nishioka K, Innocenti M, Carulli C, Linari S, Morfini M, Ibba-Manneschi L, Matucci-Cerinic M, Guiducci S. Agonistic anti-human Fas monoclonal antibody induces fibroblast-like synoviocyte apoptosis in haemophilic arthropathy: potential therapeutic implications. Haemophilia. 2014 Jan;20(1):e32-9. doi: 10.1111/hae.12304. Epub 2013.
13. Kubota S, Takigawa M. Cellular and molecular actions of CCN2/CTGF and its role under physiological and pathological conditions. Clin Sci (Lond) 2015; 128:181-96.
14. Silva M, Luck JV. Long-term results of primary total knee replacement in patients with hemophilia.

J Bone Joint Surg Am 2005; 87:85-91.

15. Jiang J, Leong NL, Khalique U, Phan TM, Lyons KM, Luck JV Jr. Connective tissue growth factor (CTGF/CCN2) in haemophilic arthropathy and arthrofibrosis: a histological analysis. Haemophilia 2016; 22(6):e527-e536
16. Acharya SS, Kaplan RN, Macdonald D, Fabiyi OT, DiMichele D, Lyden D. Neoangiogenesis contributes to the development of hemophilic synovitis. Blood 2011; 117(8):2484-93.
17. Jansen NW, Roosendaal G, Lundin B, et al. The combination of the bio- markers urinary C-terminal telopeptide of type II collagen, serum cartilage oligomeric matrix protein, and serum chon- droitin sulfate 846 reflects cartilage damage in hemophilic arthropathy. Arthritis Rheum 2009; 60:290e8.
18. Coline Haxaire, Narine Hakobyan, Tania Pannellini, Camila Carballo, David McIlwain, Tak W. Mak, Scott Rodeo, Suchitra Acharya, Daniel Li, Jackie Szymonifka, Xiangqian Song, Sebastien Monette, Alok Srivastava, JaneE.Salmon, and Carl P. Blobel, Blood-induced bone loss in murine hemophilic arthropathy is prevented by blocking the iRhom2/ADAM17/TNF-a pathway. Blood 2018; 132(10):1064-74.
19. Issuree PD, Maretzky T, McIlwain DR, et al. iRHOM2 is a critical pathogenic mediator of inflammatory arthritis. J Clin Invest. 2013; 123(2):928-32.
20. Pettersson H, Ahlberg A, Nilsson IM. A radiologic classification of hemophilic arthropathy. Clin Orthop Relat Res 1980; 149:153-9.
21. Nuss R, Kilcoyne RF, Geraghty S et al. MRI findings in haemophilic joints treated with radiosynoviorthesis with development of an MRI scale of joint damage. Haemophilia 2000; 6:162-9.
22. Muca-Perja M, Riva S, Grochowska B, Mangiafico L, Mago D, Gringeri A. Ultra- sonography of haemophilic arthropathy. Haemophilia 2012; 18:364–-8.
23. Pettersson H GM. Diagnostic imaging in hemophilia: musculo- skeletal and other hemorrhagic complications. Berlin: Springer-Verlag 1985; 28–54.
24. Pettersson H, Ahlberg A, Nilsson IM. A radiologic classification of hemophilic arthropathy. Clin Orthop Relat Res 1980; 149:153-9.
25. Fischer K, van Hout BA, van der Bom JG, Grobbee DE, van den Berg HM. Association between joint bleeds and Pettersson scores in severe haemophilia. Acta Radiol 2002; 43:528-32.

Use of synthetic cartilage implant (Cartiva®) for degeneration of the first and second metatarsophalangeal joint: what is the current evidence?

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Polyvinyl alcohol hydrogel implants (also known as Synthetic Cartilage Implant or Cartiva® have been described in the treatment of degeneration of the first and second metatarsophalangeal joint (MTPJ). We reviewed literature to report characteristics of devices on the market and investigate their efficacy and safety. Following the PRISMA checklist, the Medline and Scopus databases were searched, including studies reporting use of Cartiva® for treating joint degeneration of the first and second MPTJ. Studies were searched for surgical technique, postoperative protocol, clinical scores, complications and reoperations. We found that, although some studies suggest that the use of Synthetic Cartilage Implant (Cartiva® is effective in the treatment of hallux rigidus in providing symptoms relief without sacrifice of joint motion, the redundancy of cohorts reported in studies and the frequency of conflict of interest reported by authors weaken the strength of evidence available and warrant further studies. Regarding the treatment of the second MTPJ ailments, no recommendation can be formulated to date due to the lack of primary studies.

The term hallux rigidus (HR) was firstly used by Cotterill in 1887 for describing the arthritic degeneration of the first metatarsophalangeal joint (MTPJ1) (1), which represents one of the most common cause of forefoot pain (2). Over time, various classifications have been proposed. Hallux Rigidus treatment mainly depends on the stage of the disease (3). A nonsurgical approach, mainly based on orthoses and large-toe-box or rocker-bottom shoes, may be adopted in early stages, but in case of failure or advanced painful degeneration surgery is indicated. Options include cheilectomy, decompression phalangeal or metatarsal osteotomy, arthroplasty and MTPJ1 fusion (4, 5). To date, arthrodesis represents the gold standard for most authors in this field (6–9). However, although MTPJ1 fusion rates vary from 88% to 100% in the literature (6–9), non-union still represents one of the most common complications and cause for revision surgery, with revision-fusion reported up to 8% and removal of hardware up to 14% (10).

In tackling advanced HR, several studies have investigated the efficacy of joint replacement.
This operative option aims to preserve range of motion and to some extent a better function. However, complication (such as loosening, malalignment/dislocation, implant fragmentation and bone loss) and revision rates remain globally higher than fusions (6, 7). Interestingly, over the last years new synthetic (polyvinyl alcohol hydrogel) cartilage implant hemiarthroplasty (Cartiva®, Cartiva Inc., Georgia, US) have been proposed in the treatment of HR and lesser toes osteoarthritis with the aim to decrease pain, improve function, and maintain

Key words: CARTIVA; hallux; rigidus; Synthetic Cartilage Implant; MTP joint; second

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motion for advanced joint degeneration.

In this scenario, we performed a review of current literature to outline the evidence provided for or against the use of Synthetic Cartilage Implant (Cartiva®) in the treatment of degeneration of the first and second MTPJ.

MATERIALS AND METHODS

This systematic review was designed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Eligibility criteria

We included studies reporting the use of Synthetic Cartilage Implant or Cartiva® for treating joint degeneration of the first and second MTPJ, designed as technical note, biomechanical study (in-vitro study) and prospective or retrospective clinical study (randomized clinical trials, controlled clinical trials, observational cohort prospective and retrospective studies, case series) in English, French, Spanish and Italian.

Data sources and search

A comprehensive electronic search of the current literature was performed by Medline, Scopus and EMBASE databases, from the earliest records through September 06, 2019. Additional studies were identified by checking the bibliographies of the articles selected. Reviews were excluded. If full texts were not available, authors were contacted. Using Boolean operators, the following search terms were used: Cartiva OR synthetic cartilage implant.

Study selection

Results were managed using Endnote. Duplicates and studies without abstracts were excluded. Titles and abstracts were screened by two authors at different places and times, then eligible studies were selected. Disagreements were solved through discussion and consensus.

Data were extracted about the study design (and the Level of Evidence), demographics (sample size, sex, age), treatment, follow-up, clinical scores, patient satisfaction, success criteria, failure rate, intraoperative and postoperative complications, work and sport activities resumption time. Failure was considered as absence of relief from symptoms or need for further surgery.

Summary measures and synthesis of results

Summarized data are presented as mean value ± standard deviation, ranges and frequencies. All analyses were performed using STATA statistical software package (Version 14.0, StataCorp, 2015). A critical analysis was provided for each outcome even if a formal meta-analysis was not performed due to the lack of data in primary studies.

RESULTS

First metatarsophalangeal joint

Seven studies were identified, all studies performed after 2016 (10–16). There was one level I (11), three level II (10, 12, 13) and three level IV studies (14–16) (Table I and Table II). Six were clinical studies and one was a cost-analysis (10) and in six studies relevant conflict of interest were disclosed with Cartiva Inc. (11–16). Length of follow-up ranged from 1 to 5.8 years. Overall, 216 implants have been assessed, with 5 studies investigating the same cohort (11–13, 15, 16). Three studies were on behalf of Cartiva® MOTION Study Group (11–13) and in one collaborator from the same group where acknowledged (15).

The technique adopted by most authors is the one described by the manufacturer: dorsal or medial incision on the first metatarsophalangeal joint to gain access to the first metatarsal head; resection of osteophytes from the metatarsal head; placement of a guide wire to introduce the cannulated drill bit and then to drill the metatarsal head; placement of appropriately sized CARTIVA® with the implant delivery tube and seated to allow for 1 to 2 mm of the implant to extend beyond the adjacent native cartilage of the metatarsal. Cassinelli et al. have made minor adjustments to main technique, using a freer elevator placed on the metatarsal head to prevent the step drill from advancing fully into the head stopping the reamer 1 to 1.5 mm short of the metatarsal head. The implant is then seated beyond 2-2.5 mm to try to minimize the risk of symptomatic subsidence (14).

Overall, in all clinical studies authors reported good clinical outcomes, with a complication rate estimated between 11% and 20%, as depicted in Table II. At 5-year follow-up implant survivorship

Table I. *Characteristics of studies included in this review dealing with CARTIVA® for first metatarsophalangeal joint degeneration: study design, level of evidence, number of feet, age and sex, bone mass index (BMI), grade, follow-up, conflict of interest and funding.*

Author (year)	Study design	Level of Evidence	N of feet (patients)	Age and sex	BMI	Hallux Rigidus Grade	Follow up	Conflict of interest	Funding
Baumhauer (2016)	Prospective multi centred randomised non-inferiority clinical trial	I	152 (130 patients)	57,4±8,8, 26 males and 104 females	27,2±4,4	N/A	2 years	Yes	No
Daniels (2016)	Prospective case series	IV	27 patients	56,1 (40,1-71,9), 6 males and 26 females	27,1 (19,2-36,8)	N/A	5.4 (4.9-6.4) years	Yes	Yes
Baumhauer (2017)	Retrospective multi-centred randomised non-inferiority clinical trial	II	202 (152 implant + 50 fusions)	Cohort from Baumhauer (2016)	Cohort from Baumhauer (2016)	2: 59 3: 110 4: 33	2 years	Yes	No
Goldberg (2017)	Retrospective randomised clinical trial	II	152 feet (130 patients)	Cohort from Baumhauer (2016)	Cohort from Baumhauer (2016)	2: 36 3: 73 4: 20	2 years	Yes	Yes
Cassinelli (2019)	Prospective case series	IV	64	62 (38-86), 8 males and 52 females	25,9 (17,9-39,4)	2: 18 3: 40 4: 8	12,5 months (1-30); telephone 18,5 months (12-30)	Yes	No
Rothermel (2019)	Cost analysis	II	From literature	N/A	N/A	N/A	1 years	No	No
Glazebrook (2018)	Prospective, randomized, noninferiority clinical trial case series	IV	119 (112 patients)	58,2±8,8, 25 males and 87 females	27,0±4,2	N/A	5.8±0,7 years	Yes	Yes

Table II. *Characteristics of studies included in this review dealing with CARTIVA® for first metatarsophalangeal joint degeneration: outcome, complications and conclusion of the authors.*

Author (year)	Outcome	Complications	Conclusion of the authors
Baumhauer (2016)	**FAAM sports**: 36,9± to 79,5±24,6 **FAAM ADL**: 59,4±16,9 to 90,4±15,0 **VAS:** 68,0±13,9 to 14,5±22,1 **SF-36 PF:** 52,4±22,8 to 83,2±20,9 **ROM peak dorsiflexion:** 22,7±11,2 to 29±11,9	17/152 (11.2%) - 14 conversion to arthrodesis - 1 joint manipulation for motion -1 moberg osteotomy -1 debridement of the joint scars	Implant matched gold standard of fusion
Daniels (2016)	**VAS**: 64,1 to 5,7 **SF-36:** 39,5(22,0-54,0) to 52,2(25,2-61,6) **FAAM sports:** 39,2 to 89,4 **FAAM ADL**: 61,4 to 95,3 **ROM dorsiflexion**: 9,4(0,0-25,0) to 18,2(10,0-30,0) **ROM peak dorsiflexion**: 9,3 (0-18,0) to 20,9(0-50,0)	1/27 (4%) -1 conversion to arthrodesis Not counted as complications: 2 asymptomatic cystis in proximal phalanx	At 5 years, implants improved significantly outcomes with good survivorship
Baumhauer (2017)	*At baseline* **VAS:** *-2:* 70,5±13,9 *-3:* 68,4±14,1 *-4:* 66,3±14,0 **ROM peak dorsiflexion:** *-2:* 23,8±8,9 *-3:* 22,4±12,7 *-4:* 23,7±10,6 **Remaining cartilage proximal phalanx:** *-100%:* 3 *-75%:* 25 *-50%:* 84 *-25%:* 61 *-0%:* 17 **Remaining cartilage on metatarsal head:** *-75%:* 19 *-50%:* 67	Cohort from Baumhauer (2016)	Weak correlation between outcomes. Recommend use of symptoms and signs for treatment. Grade assessment may underestimate arthritic change.

stood at 85% (16). In his cost-analysis, Rothermel et al. demonstrated that significantly higher inclusive costs are associated with the synthetic hydrogel implant when compared to arthrodesis (10).

Second metatarsophalangeal joint

Among the three studies found (17–19), two were level IV clinical studies (17,18) including 11 feet in total and one was a cadaveric analysis (level V) (19). On 10 cadaveric specimens, De Cesar Netto et al. have concluded that the second metatarsal could be safely drilled until 8 mm in 80% of cases, preserving an intact bone rim around (19). In Brandao's clinical study, four out of six implants for the second MTPJ failed requiring revision to Weil's osteotomy at a mean of 15 months after the index procedure (17). In that study, authors used a 6-mm implant that was left at least 3 mm proud on all occasions. Intra-operatively, they aimed to achieve 90 degrees of dorsiflexion in every case (17). In another clinical study, authors used 8-mm implants and reported minimal pain and good ROM documenting good functional outcome at 2 years of follow-up, but without any assessment of preoperative scores (18) (Table III).

DISCUSSION

In the scientific community, Cartiva® implant has been proposed as a viable treatment option to decrease pain, improve function and maintain motion in the treatment of hallux rigidus in various stages (10–16). The main finding of our study is that while the use of this polyvinyl alcohol implant has been documented by multiple authors as leading to good clinical outcome with a reasonable complication rates (11% to 20%) up to 5 years of time (15, 16), many studies have been realised on redundant cohorts and with authors disclosing Cartiva-related possible conflict of interest (11–13, 15, 16), which somehow arises concerns about the generalizability of their conclusions. With regards to the second MTPJ, only two studies with a total of 11 patients are insufficient to gather any recommendation in favour of the use of these implants in tackling joints issues.

Table III. *Characteristics of studies included in this review dealing with CARTIVA® for second metatarsophalangeal joint degeneration.*

Author (year)	*Study design*	*LoE*	*N of feet (patients)*	*Age and sex*	*BMI*	*Outcome*	*Follow up*	*Complications*	*Conflict of interest*	*Funding*	*Conclusion of the authors*
Brandao (2019)	Prospective case series	IV	6 (3 Freiburg's, 2 OA, 1 OCD)	51, all females	N/A	**FAAM ADL:** 65 to 75 **MOXFQ:** 57 to 44	19±10,9 months	4/6 -conversion to Weil osteotomy	No	No	High failure rate cartiva (67%), most commonly due to AVN perhaps linked with Freiberg's.
DeCesarNetto (2019)	Cadaveric study	V	10	48,3 (25-61), 4 males and 6 females	N/A	**Anatomical Height and Width:** 15,4 and 14,0 **CT Height and Width:** 11,2 and 10,6 **Medial and lateral rim after drilling:** *-6mm:* 2,7/2,6 *-7mm:* 1,8/2,2 *-8mm:* 1,0/1,4 *-9mm:* 0,7/1,2 *-10mm:* 0,4/0,9	N/A	-20% failed to accommodate the smallest available CARTIVA implant (8mm) -80% failed to accommodate the secondo smallest available CARTIVA implant (10mm)	Yes	No	8mm min size of implant. Medial and lateral cortex tends to fail first. If it is to be considered an option, a smaller implant is required of approximate 4mm or 6mm diameter
Glazebrook (2019)	Retrospective case series	IV	5	57.1 male and 4 females	N/A	**VAS:** 20 **SF-36 PCS:** 44,4 **SF-36 MCS:** 52,1 **FAAM sports:** 75 **FAAM ADL:** 89	25 months (15-38)	0	Yes	Yes	There are no documented preoperative scores. The sample is too small. The procedure improved pain but there is no objective evidence.

After failure of conservative treatment, various surgical options are advocated for the treatment of hallux rigidus. In early stages (I and II), cheilectomy is a well-studied procedure with success rates of over 90% at 10-year follow-up (20), however its main indication is dorsal pain with metatarsophalangeal impingement but a good preservation of the cartilage layers. The progression of osteoarthritis, sometimes associated with the recurrence of dorsal osteophytes, may warrant further procedures. If some dorsal cartilage damage is already present, a dorsiflexion osteotomy of the first phalanx (also called Moberg osteotomy) may be performed alone or as an adjunct to cheilectomy, with the aim to reduce the load on the diseased area and provide symptoms relief (21). Although this has been proven to provide good symptoms relief, it must be considered that a subsequent arthrodesis may result more difficult as compared to a primary one (5). In severe HR (stage III and IV), joint fusion remains the gold standard (6–9), with fusion rates reported between 77% and 100% (22).

Exactly like for tibiotalar osteoarthritis, where the historical gold standard represented by the joint fusion (23–25) is more and more debated in view of increasing recent evidence in favour of total ankle arthroplasty (26), also the possibility to replace the first MTP joint reducing the pain without sacrificing the motion seems understandably attractive. According to Glaze brook, in case of failure a revision to fusion could be performed without any additional technical difficulty as compared to primary arthrodesis (16). Indeed, the results provided by the overmentioned Level I and II studies (11, 13), together with two mid-terms follow-up studies at over 5 years showing a good survivorship of the implant (15, 16), definitely would encourage the adoption and diffusion of these new implants, nevertheless some considerations must be discussed.

We found three potential biases as significant limitations of the evidence available thus far. First, although eight studies produced only in a few years would demonstrate some interest on behalf of the scientific community towards this new implant, 50% of them actually investigate the same cohort of patients, therefore the total amount of cases followed remains limited at 216. Secondly, a number of studies have been produced in collaboration with the CARTIVA® Motion study group, therefore there is some risk that results in the hands of surgeons who are particularly familiar with the implant might not be reproducible in different sites. Thirdly, the conflict of interest disclosed in most studies raises concerns about a possible publication bias. Apart from that, the cost-analysis from Rothermel et al. (10) suggests that the use of Synthetic Cartilage Implant might not be cost-effective if compared to traditional arthrodesis. This might play a crucial role in the clinician decision-making process in an era where continuous attention is paid to care-related costs.

For what concerns the second MTPJ, a clear evidence is still lacking, and no clear recommendation can be formulated at this stage in favour or against the use of polyvinyl alcohol hydrogel implants to treat metatarsal head joint degeneration.

We acknowledge some limitations for this study. Unfortunately, we were unable to perform a formal meta-analysis, essentially because of the low number of studies and heterogeneity of parameters assessed by primary authors. However, similarly to other published topic reviews about foot and ankle pathologies (27–29), the believe that this critical review will be certianly useful to surgeons who are intrigued by the Cartiva® implant and are keen to understand what is the state-of-the-art about this relatively new procedure. Secondly, only one cohort (assessed in three studies) was compared to a different procedure (arthrodesis), therefore we could not draw any solid conclusion about the superiority of Cartiva® implant with respect to the current gold standard.

Although some studies suggest that the use of Synthetic Cartilage Implant (Cartiva®) is effective in the treatment of hallux rigidus in providing symptoms relief without sacrifice of joint motion, the redundancy of cohorts reported in studies and the frequency of conflict of interest reported by authors weaken the strength of evidence available and make necessary further studies. Regarding the treatment of the second MTPJ ailments, no recommendation can be formulated to date due to the lack of primary studies.

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REFERENCES

1. Cotterill JM. The pathology of hallux rigidus. Br Med J 1903; 2:1400. doi:10.1136/bmj.2.2239.1400.
2. Beeson P, Phillips C, Corr S, Ribbans W. Classification Systems for Hallux Rigidus: A Review of the Literature. Foot Ankle Int 2008; 29:407-14. doi:10.3113/FAI.2008.0407.
3. Maffulli N, Papalia R, Palumbo A, Del Buono A, Denaro V. Quantitative review of operative management of hallux rigidus. Br Med Bull 2011; 98:75-98. doi:10.1093/bmb/ldq041.
4. Yee G, Lau J. Current Concepts Review: Hallux Rigidus. Foot Ankle Int 2008;29:637-46. doi:10.3113/FAI.2008.0637.
5. Ho B, Baumhauer J. Hallux rigidus. EFORT Open Rev 2017; 2:13-20. doi:10.1302/2058-5241.2.160031.
6. Stone OD, Ray R, Thomson CE, Gibson JNA. Long-Term Follow-up of Arthrodesis vs Total Joint Arthroplasty for Hallux Rigidus. Foot Ankle Int 2017; 38:375-80. doi:10.1177/1071100716682994.
7. Raikin SM. Comparison of Arthrodesis and Metallic Hemiarthroplasty of the Hallux Metatarsophalangeal Joint. J Bone Joint Surg Am 2007; 89:1979. doi:10.2106/JBJS.F.01385.
8. Brodsky JW, Baum BS, Pollo FE, Mehta H. Prospective Gait Analysis in Patients with First Metatarsophalangeal Joint Arthrodesis for Hallux Rigidus. Foot Ankle Int 2007; 28:162–5. doi:10.3113/FAI.2007.0162.
9. Bennett GL, Sabetta J. First Metatarsalphalangeal Joint Arthrodesis: Evaluation of Plate and Screw Fixation. Foot Ankle Int 2009; 30:752-7. doi:10.3113/FAI.2009.0752.
10. Rothermel SD, King JL, Tupinio M, Walley KC, Juliano PJ, Aynardi MC. Cost Comparison of Synthetic Hydrogel Implant and First Metatarsophalangeal Joint Arthrodesis. Foot Ankle Spec 2019; 193864001985061. doi:10.1177/1938640019850617.
11. Baumhauer JF, Singh D, Glazebrook M, Blundell C, De Vries G, Le ILD, et al. Prospective, Randomized, Multi-centered Clinical Trial Assessing Safety and Efficacy of a Synthetic Cartilage Implant Versus First Metatarsophalangeal Arthrodesis in Advanced Hallux Rigidus. Foot Ankle Int 2016; 37:457–69. doi:10.1177/1071100716635560.
12. Baumhauer JF, Singh D, Glazebrook M, et al. Correlation of Hallux Rigidus Grade With Motion, VAS Pain, Intraoperative Cartilage Loss, and Treatment Success for First MTP Joint Arthrodesis and Synthetic Cartilage Implant. Foot Ankle Int 2017; 38:1175–82. doi:10.1177/1071100717735289.
13. Goldberg A, Singh D, Glazebrook M, et al. Association Between Patient Factors and Outcome of Synthetic Cartilage Implant Hemiarthroplasty vs First Metatarsophalangeal Joint Arthrodesis in Advanced Hallux Rigidus. Foot Ankle Int 2017; 38:1199–206. doi:10.1177/1071100717723334.
14. Cassinelli SJ, Chen S, Charlton TP, Thordarson DB. Early Outcomes and Complications of Synthetic Cartilage Implant for Treatment of Hallux Rigidus in the United States. Foot Ankle Int 2019:1071100719855049. doi:10.1177/1071100719855049.
15. Daniels TR, Younger ASE, Penner MJ, et al. Midterm Outcomes of Polyvinyl Alcohol Hydrogel Hemiarthroplasty of the First Metatarsophalangeal Joint in Advanced Hallux Rigidus. Foot Ankle Int 2017; 38:243–7. doi:10.1177/1071100716679979.
16. Glazebrook M, Blundell CM, O'Dowd D, et al. Midterm Outcomes of a Synthetic Cartilage Implant for the First Metatarsophalangeal Joint in Advanced Hallux Rigidus. Foot Ankle Int 2019; 40:374–83. doi:10.1177/1071100718815469.
17. Brandao B, Fox A, Pillai A. Comparing the efficacy of Cartiva synthetic cartilage implant hemiarthroplasty vs osteotomy for the treatment of conditions affecting the second metatarsal head. Foot n.d.
18. Glazebrook M, Morash J, Alhadhoud M, Daniels TR. Preliminary Experience With Polyvinyl Alcohol Hydrogel Implant for Pathology of the Second Metatarsal Head. Foot Ankle Int 2019;107110071986670. doi:10.1177/1071100719866700.
19. de Cesar Netto C, Godoy-Santos AL, Cabe TN, Roberts LE, Harnroongroj T, Deland J, et al. The use

of polyvinyl alcohol hydrogel implants in the lesser metatarsal heads. Is it safely doable? A cadaveric study. Foot Ankle Surg 2019; doi:10.1016/j.fas.2018.12.009.

20. Coughlin MJ, Shurnas PS. Hallux Rigidus. J Bone Joint Surg Am 2004;86:119–30. doi:10.2106/00004623-200409001-00003.
21. Ho B, Baumhauer J. Hallux rigidus. EFORT Open Rev 2017; 2:13–20.doi:10.1302/2058-5241.2.160031.
22. Galois L, Hemmer J, Ray V, Sirveaux F. Surgical options for hallux rigidus: state of the art and review of the literature. Eur J Orthop Surg Traumatol 2019. doi:10.1007/s00590-019-02528-x.
23. Mehdi N, Bernasconi A, Laborde J, Lintz F. Comparison of 25 ankle arthrodeses and 25 replacements at 67 months' follow-up. Orthop Traumatol Surg Res 2019; 105:139–44. doi:10.1016/j.otsr.2018.10.014.
24. Bernasconi A, Mehdi N, Laborde J, de Cesar Netto C, Dagneaux L, Lintz F. Joystick of the Talus for Correcting Malalignment During Arthroscopic Ankle Arthrodesis: A Surgical Tip. Arthrosc Tech 2018; 7:e517–22. doi:10.1016/j.eats.2018.01.005.
25. Bernasconi A, Mehdi N, Lintz F. Fibular Intra-articular Resection During Arthroscopic Ankle Arthrodesis: The Surgical Technique. Arthrosc Tech 2017; 6:e1865–70. doi:10.1016/j.eats.2017.07.007.
26. Daniels TR, Mayich DJ, Penner MJ. Intermediate to Long-Term Outcomes of Total Ankle Replacement with the Scandinavian Total Ankle Replacement (STAR). J Bone Jt Surgery-American Vol 2015; 97:895–903. doi:10.2106/JBJS.N.01077.
27. Bernasconi A, Sadile F, Smeraglia F, Mehdi N, Laborde J, Lintz F. Tendoscopy of Achilles, peroneal and tibialis posterior tendons: An evidence-based update. Foot Ankle Surg 24:374–82. doi:10.1016/j.fas.2017.06.004.
28. Bernasconi A, Lintz F, Sadile F. The role of arthroereisis of the subtalar joint for flatfoot in children and adults. EFORT Open Rev 2017; 2:438–46. doi:10.1302/2058-5241.2.170009.
29. Bernasconi A, de Cesar Netto C, Barg A, Burssens A, Richter A; Weight Bearing CT International Study Group LF. AAFD: Conventional radiographs are not enough! I need the third dimension. Tech Foot Ankle Surg 2019.

Foot and ankle measurements on cone beam weightbearing computed tomography

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Over the last years, an increased number of studies have reported the use of cone beam weightbearing computed tomography (WBCT) in the assessment of foot and ankle pathology. This new technology has enabled to overcome the limits inherently related to two-dimensional radiographs (superimposition bias, operator-related bias, rotation bias) and to obtain images reproducing the bones and joints anatomy during physiological standing with a low radiation dose. We performed a review of the current literature to summarize the evidence about the use of 2D or 3D measurements on WBCT images in various foot and ankle conditions. Our aims were to describe measurements proposed so far and to report data on reliability and validity from primary authors.

It is well known that in the study of foot and ankle pathologies the presence of natural force of gravity plays a crucial role for a correct assessment and definition of bony alignment. This is the reason why, historically, plain standing radiographs have represented the gold standard in the first assessment of foot, being a useful complement of physical examination for most of the bone and joint pathologies.

However, several biases inherently related to two-dimensional images has been acknowledged, such as the superimposition, the rotation and the operator-related ones (1, 2). Consequently, multiple attempts have been made in the past aiming to simulate weightbearing conditions during computed tomography, with the advantage to gather precious information on bony lesions, calcifications and joint status (3-5). Unfortunately, those methods are flawed by the lack of active muscle contraction and variability of conditions in which load is applied, and their use has never spread in clinical practice (3). In this scenario, a growing amount of studies has been produced over the last years, dealing with the application of cone beam weightbearing computed tomography (WBCT) in foot and ankle clinical practice (6-11).

The use of cone beam technology, as opposed to fan beam for classical CT, has enabled to obtain tomographic images like standard CT's but in a standing position and with a much lower quantity of radiation (12). Authors have documented advantages in the use of WBCT for several pathologies, such as flatfoot, pes cavovarus, syndesmotic injuries, ankle instability and forefoot conditions. Additionally, new software has allowed us to calculate three-dimensional (3D) measurements (so called 3D biometrics) with the advantage to be defined by a volume rather than a plane (6-11).Bearing this in mind, we have performed a review of the current literature to summarize the evidence about the use of 2D or 3D measurements on WBCT images in various foot and ankle conditions. Our aims were (i) to describe measurements proposed so far and (ii) to report findings from primary authors.

Key words: weightbearing; computed tomography; foot; cone beam; three-dimensional

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MATERIALS AND METHODS

Study design

A retrospective review was carried out of studies dealing with foot and ankle measurements on cone beam WBCT images published over the last decade. The study was compliant with the Health Insurance Portability and Accountability Act (HIPAA) and the Declaration of Helsinki.

Eligibility criteria

Inclusion criteria were: study reporting two- or three-dimensional foot and/or ankle measurements on cone beam WBCT images; study published over the last ten years (2009-2019); review and clinical study (randomized clinical trials, controlled clinical trials, observational cohort prospective and retrospective studies, case series) in English, French, Spanish and Italian. We excluded studies: reporting redundant data with previous publications; adopting simulated-weightbearing techniques; not documenting any measurement; biomechanical study, technical note, *in vitro* study and cadaveric study.

Data sources and search

A comprehensive electronic search of the current literature was performed by Medline (PubMed) from the January 01, 2009, through August 25, 2019, using PRISMA flow diagram. Additional studies were identified by checking the bibliographies of the articles selected. If full texts were not available, authors were contacted. Using Boolean operators, the following search terms were used: weight AND bear* AND computed AND tomograph* AND foot.

Study selection and data organization

Results were managed using Endnote. Duplicates and studies without abstracts were excluded. Titles and abstracts were screened by two authors at different places and times. After applying exclusion criteria, eligible studies were selected. Disagreements were solved through discussion and consensus.

Data was extracted about pathology investigation, type of two- or three-dimensional measurements taken, assessment of intra-observer and inter-observer reliability or validity, comparisons between non-standing and standing tomographic imaging. Results have been organised based on anatomical areas, i.e. ankle, hindfoot, midfoot and forefoot. Summarized data (reliability of measurements) are presented as mean value ± standard deviation with ranges, as reported by primary authors.

RESULTS

Twenty eight studies were included in this systematic review, of which 6 were dealing with the ankle (13–18), 19 with the hindfoot (6,8–10,12,19–29), 5 with the midfoot (19,20,30,31) and 12 with the forefoot (12, 19, 21, 28, 31-36) (Table I).

Ankle

Topographic measurements of the distal tibiofibular syndesmosis have been reported by Hamard et al., Patel et al. and Malhotra et al. (Table II) (14, 17, 18). Burssens et al. and Haleem et al. investigated the talar tilt, which was found at 2.4° ± 0.84 (ICC: 0.86 and 0.81 for intra and inter-observer reliability, respectively) and 0.91°± 1.12 (ICC: 0.52 for inter-observer reliability) (13, 19). Lepojarvi et al. studied the weight-bearing translation of the fibula, analyzing the difference between maximum extrarotation and maximum intrarotation (16). Kim et al. reported values about the Talus Rotation Ratio (TRR), comparing Varus-osteoarthritic ankles with a control group: in the Varus-osteoarthritic group TRR was 2.40 ± 1.32 (ICC: 0.91 intra-observer and 0.83 inter-observer reliability) whereas in the control group it stood at 1.06 ± 0.65 (ICC: 0.94 intra-observer and 0.86 inter-observer reliability) (15).

Hindfoot

A few studies have investigated recently and introduced measurements concerning the hindfoot, also known as 3D biometrics, calculated through a dedicated software, such as the Foot and Ankle Offset (FAO), the Hindfoot Alignment Angle (HAA), and the Calcaneal Offset (CO) (Lintz et al., Zhang et al. Bernasconi et al. and others) (Table III) (6–11).

On the other side, in 2016 Burssens et al. performed an analysis of three other methods to measure the hindfoot alignment (25):

- assessing the relationship between the bisector of the Achilles tendon and the calcaneum (HAA CL)

Table I: *Main characteristics of the studies included in this review.*

Author	LoE	Anatomical district	N	Age	Measurements
Bernasconi 2019	III	Hindfoot	51 (17 control, 34 varus)	Control: 46.1±17 Varus: 45.5±16.1	FAO CO HAA
Burssens 2016	III	Hindfoot	60 (30 varus, 30 valgus)	N/A	HAA ATT TT TA TI SVA
Burssens 2018	III	Ankle. Hindfoot	48	39.6±13.2	HAA TC TA TCr TI TT SVA
Cheung 2018	II	Forefoot	50	52.2	HVA IMA
Cody 2016	III	Hindfoot	62 (45 flatfloot, 15 control)	Control: 52 Flatfoot: 57	ISA IHA
Colin 2014	III	Hindfoot	59	45	SVA
Collan 2013	III	Forefoot	15 (5 control, 10 hallux valgus)	55.7±13.6 hallux valgus 57.4±6.4 control	HVA IMA MTP
De Cesar Netto 2019	III	Hindfoot Midfoot Forefoot	54 (NBA players)	24.4	FAO CO HAA ISA IHA FAA NtFd MCtFd
Ellis 2010	III	Hindfoot Midfoot Forefoot	20 (10 control, 10 flatfoot)	55.5±13.9 flatfoot 61.0±8.6 control	TMT TN HAA FAA CPA
Haleem 2014	II	Hindfoot Midfoot Forefoot	33 (10 control, 23 flatfoot)	Control: 48.5±14.3 Flatfoot: 63.0±8.3	TMT TC TT TN
Hamard 2019	III	Ankle	33	46.09	A B C
Hirschmann 2014	III	Hindfoot Midfoot	22	46.0±17.1	HAA FCd TCd LTCd NCd
Kang 2017	III	Hindfoot Midfoot Forefoot	53	49.5 (20 to 74)	HVA IMA TMT TN CPA
Kim 2017	III	Ankle	148 (52 control, 96 varus)	Control: 26 Varus: 60	TRR
Kimura 2017	III	Hindfoot Forefoot	20 (10 control, 10 hallux valgus)	58±14.2 hallux valgus 56±5.0 control	HVA IMA TMT CPA
Kimura 2018	III	Forefoot	22 (11 control, 11 hallux valgus)	57±13.2 hallux valgus 56±4.7 control	HVA IMA
Krahenbuhl 2016	III	Hindfoot	60 (20 control, 40 case)	47 control 60 case	SVA
Kunas 2018	III	Hindfoot	58 (20 control, 38 flatfoot)	Control: 36±13 Flatfoot: 57±12	ISA
Lepojarvi 2016	III	Ankle	64	36 ankles: 26-36 years 28 ankles: 60-64 years	ST AW PW TFCS RO
Lintz 2017	III	Hindfoot	135 (57 control, 38 varus, 40 valgus)	N/A	FAO
Lintz 2019	III	Hindfoot	34 chronic ankle instability	45.6±14.1	FAO CO HAA
Malhotra 2019	III	Ankle	26	48.2±14.01	A B C D E F α
Ota 2019	III	Hindfoot Forefoot	28 (14 male, 14 female)	29.9±2.8 male 28.2±5.1 female	MTP
Patel 2019	III	Ankle	50	47.1 male 57.8 female	A B C D E F α
Richter 2014	III	Hindfoot Forefoot	30	N/A	IMA TMT HAA CPA
Richter 2015	III	Hindfoot Forefoot	50	48.4±15.1	CPA TMT HMT
Yoshioka 2016	III	Forefoot	40 (20 control, 20 flatfoot)	35.5±9.5 control 34.9±13.7 flatfoot	M1R M5R CR
Zhang 2019	II	Hindfoot	249 (115 control, 78 valgus, 56 varus)	N/A	FAO HAA

*Abbreviations: LoE: level of evidence; N: number of patients: **A**: distance between the most anterior point of tibia and fibula nearest to the incisura; **B**: distance between the most posterior point of the tibia and fibula nearest to the incisura; **C**: shorter distance between tibia and fibula at the midpoint of incisura; **D**: shortest distance from the bisector of the line between most anterior and posterior points of the incisura to the most anterior point on the fibula; **E**: shortest distance from the bisector of the line between most anterior and posterior points of the incisura to the most posterior point on the fibula; **F**: shortest distance from the perpendicular of the line between most anterior and posterior points of the incisura, drawn at the most anterior point of the incisura to the most anterior point on the fibula; α: angle between the line between most anterior and posterior points of the incisura and the axis of the fibula; **TT**: Talar Tilt; **STT**: subtalar tilt; **ST**: Sagittal Translation of the fibula; AW: Anterior Width of the distal tibiofibulatr syndesmosis; PW: Posterior Width of the distal tibiofibular syndesmosis; TFCS: TibioFibular Clear Space; RO: Rotation of the fibula; FAO: Foot and Ankle Offset; **CO**: calcaneal offset; **HAA**: hindfoot angle alignment; **TRR**: Talus Rotation Ratio; **TA**: Tibial Axis; **TC**: talocalcaneal axis; **TCr**: Talocrural angle; **TI**: inclination of tibial joint; **SVA**: subtalar vertical angle; **ISA**: inf-tal-sup-tal angle; **IHA**: inf-tal horizontal angle; **FAA**: forefoot arch angle; **NtFd**: navicular to floor distance; **MCtFd**: medial cuneiform to floor distance; **IMA**: intermetatarsal angle; **TMT**: talometatarsal angle; **TN**: talonavicular angle; **FCd**: fibular-calcaneal distance; **TCd**: talo-calcaneal distance; **HVA**: hallux valgus angle; **CPA**: calcaneal pitch angle; **MTP**: metatarsal pronator angle; **M1R**: first metatarsal rotation; **M5R**: fifth metatarsal rotation; **CR**: calcaneal rotation; **HMT**: high of metatarsal head.*

Table II: *Topographic measurements of the syndesmosis with inter and intra-observer reliability.*

Author	A (mm)	B (mm)	C (mm)	D (mm)	E (mm)	F (mm)	α (°)
Hamard 2017	3.0 ± 0.2	4.8 ± 0.2	2.6 ± 0.2	N/A	N/A	N/A	N/A
Patel 2017	2.9 ± 0.94	5.17 ± 1.37	3.25 ± 1.01	10.34 ± 1.43	7.61 ± 1.70	0.98 ± 1.23	-12.78 ± 5.45
Malhotra 2019	3.8 ± 1.2	5.9 ± 1.8	4.8 ± 1.9	9.7 ± 1.6	7.1 ± 1.6	1.4 ± 1.4	-15.0 ± 6.7
	ICC A	**ICC B**	**ICC C**	**ICC D**	**ICC E**	**ICC F**	**ICC α**
Hamard 2017	0.83 inter	0.84 inter	0.89 inter	N/A	N/A	N/A	0.64 inter
Patel 2017	0.84 intra	0.81 intra	0.84 intra	0.77 intra	0.71 intra	0.64 intra	0.69 intra
	0.75 inter	0.73 inter	0.69 inter	0.94 inter	0.77 inter	0.66 inter	0.72 inter
Malhotra 2019	0.83 inter	0.90 inter	0.96 inter	0.85 inter	0.85 inter	0.90 inter	0.66 inter

Abbreviations: ***ICC****: intraclass correlation coefficient;* ***Intra****: intraobserver reliability;* ***Inter****: Interobserver reliability;* ***A****: distance between most anterior point of tibia and fibula nearest the incisura;* ***B****: distance between the most posterior point of tibia and fibula nearest to the incisura;* ***C****: shorter distance between tibia and fibula at the midpoint of incisura;* ***D****: shortest distance from the bisector of the line between most anterior and posterior points of the incisura to the most anterior point on the fibula;* ***E****: shortest distance from the bisector of the line between most anterior and posterior points of the incisura to the most posterior point on the fibula;* ***F****: shortest distance from the perpendicular of the line between most anterior and posterior points of the incisura, drawn at the most anterior point of the incisura to the most anterior point on the fibula;* ***α****: angle between the line between most anterior and posterior points of the incisura and the axis of the fibula.*

Table III: *3D biometrics (FAO, HAA and CO) with relative values and inter and intra-observer reliability.*

Author	FAO (%)	ICC FAO	HAA (°)	ICC HAA	CO (mm)	ICC CO
Lintz 2017	2.3 ± 2.9	0.96 intra (0.92-1.00) 0.95 inter (0.99-1.00)	N/A	N/A	N/A	N/A
Lintz 2019	-2.2 ± 5.4 (CLAI) 2.6 ± 4.7 normal	N/A	N/A	N/A	-3.2 ± 8.5 (CLAI) 6.7 ± 9.8 normal	N/A
Zhang 2019	1.2 ± 2.8	0.98 intra (0.98-0.99) 0.98 inter (0.98-0.99)	3.2 ± 3.1	0.80 intra (0.93-0.96) 0.75 inter (0.93-0.96)	N/A	N/A
Bernasconi 2019	0.5 ± 3.0	0.91 intra (0.69-1.00) 0.97 inter (0.94-0.99)	1.8 ± 9.5	0.91 intra (0.72-1.00) 0.97 inter (0.94-0.99)	0.9 ± 5.9	0.89 intra (0.71-1.00) 0.97 inter (0.94-0.99)

Abbreviations: ***FAO****: foot and Ankle Offset;* ***HAA****: hindfoot alignment angle;* ***CO****: calcaneal offset; ICC: intraclass correlation coefficient; Intra: intraobserver reliability; Inter: Interobserver reliability.*

- setting up images to obtain a 50-degree view to simulate the long axial view (HAA LA)
- assessing the relationship between the inclination of the tibia (anatomical axis) and inclination of the talus and calcaneum (talocalcaneal angle).

In a further study, the authors also analysed other measurements, such as the HAA (composed out of the intersection between the anatomical tibia axis and the talocalcaneal axis both in 2D and in 3D), tibial axis (TA), talo-calcaneal axis (TC), talo-crural angle (TCr), tibial joint inclination (TI), talar tilt (TT) and, subvertical talar angle (SVA) (Table IV) (13). Further measurements reported in literature are the inftal-suptal angle (ISA), inftal-hor angle (IHA), subvertical talar angle (SVA) and calcaneal pitch angle (CPA) (Table IV) (26, 37).

Midfoot

Different authors reported measurements focused on the navicular bone and the rest of the midfoot:

- De Cesar Netto et al: Navicular to floor distance: 38.30 mm (36.19 to 40.42); medial cuneiform to floor distance: 26.79 mm (25.30 to 28.28) (30);
- Haleem et al.: (ICC inter-observer: > 0.8 except navicular-cuneiform angle < 0.8): talo-navicular coverage and uncoverage angle: 17.28° ± 13.05 and 0.9° ± 0.74; navicular-cuneiform angle: 6.54° ± 5.91 (19);
- Hirschmann et al. (ICC inter-observer: > 0.70, except the fibular-calcaneal distance < 0.70): fibular-calcaneal distance, tibial-calcaneal distance and navicular-calcaneal distance: 0.3 mm ± 6.0, 20.6 mm ± 4.2 and 15.3 mm ± 4.7; lateral talo-calcaneal space: 2.2 mm ± 1.1; talo-calcaneal overlap: 1.4 mm ± 3.9 (20);
- Ellis et al.: (ICC inter-observer: > 0.51): talo-navicular angle and talo-navicular coverage angle: 10.8° with pain and 10.7° with no pain and 34.3° with pain and 33.2° with no pain (31).

Forefoot

Regarding the forefoot, the most diffused measurements are certainly the Hallux Valgus Angle (HVA) and Inter Metatarsal Angle (IMA)

Table IV: *Assessment of the inftal-suptal angle (ISA), inftal-hor angle (IHA), subvertical talar angle (SVA) and calcaneal pitch angle (CPA) with relative values and inter and intra-observer reliability.*

Author	ISA (°)	ICC ISA	IHA (°)	ICC IHA	SVA (°)	ICC SVA	CPA (°)	ICC CPA
Kunas 2018	5 ± 4 cont. 22 ± 7 FF	> 0.70	N/A	N/A	N/A	N/A	N/A	N/A
Burssens 2018	N/A	N/A	N/A	N/A	98.4 ± 8.1	N/A	N/A	N/A
De Cesar Netto 2019	5.31 (3.50-7.12)		4.04 (2.56-5.51)	N/A	N/A	N/A	N/A	N/A
Cody 2016	10.7 ± 6.4 cont 21.2 ± 6.7 FF	> 0.80 intra > 0.80 inter	5.7 ± 6.7 cont. 15.9 ± 5.7 FF	> 0.80 intra > 0.80 inter	N/A	N/A	N/A	N/A
Krahenbuhl 2016	N/A	N/A	N/A	N/A	98 cont. 91 varus 109 valgus	0.97 intra (0.95-0.98) 0.98 inter (0.98-0.99)	N/A	N/A
Colin 2014	N/A	N/A	N/A	N/A	103.9 ± 4.4 flat facet 97.4 ± 6.2 concave facet		N/A	N/A
Richter 2014	N/A	N/A	N/A	N/A	N/A	N/A	17.8 ± 5.4	> 0.9 inter
Ellis 2010	N/A	N/A	N/A	N/A	N/A	N/A	3.5 pain 2.5 no pain	0.79 inter (0.45-0.91)
Kimura 2018	N/A	N/A	N/A	N/A	N/A	N/A	20.1 ± 3.4 cont. 15.3 ± 3.6 HV	
Kang 2017	N/A	N/A	N/A	N/A	N/A	N/A	19.3 ± 4.16	0.81 intra (0.77-0.86) 0.87 inter (0.82-0.94)
Richter 2015	N/A	N/A	N/A	N/A	N/A	N/A	18.1 ± 5.4	> 0.8

Other abbreviations: ***ICC****: intraclass correlation coefficient;* ***Intra****: intraobserver reliability;* ***Inter****: Interobserver reliability;* **Cont***: control;* ***FF****: flatfoot;* ***HV****:hallux valgus.*

(12,21,32–35). Is some study authors have tried to define normal and pathological values (in condition like hallux valgus or hallux rigidus) (Table V). In 2014, Richter et al. reported the height of the medial sesamoids of the foot and the height of metatarsal heads (HMT) with an inter-observer reliability > 0.8: H1MT was 16.4 mm ± 2.9; H2MT was 19.1 mm ± 2.5; H3MT was 18.2 mm ± 2.1; H4MT was 17.5 mm ± 2.1; H5MT was 16.0 mm ± 2.2 (12).

Other authors studied the metatarsal rotation instead:

- Collan et al. analyzed the first proximal phalanx pronation angle and first metatarsal bone pronation angle; they respectively measured 4° ± 4 and 2° ± 3 in the control group and 33° ± 3 and 8° ± 2 in the hallux valgus group (33);
- Yoshioka et al. studied the rotation of the first and fifth metatarsal bone in the different movement plans (dorsal/plantar flexion, eversion/inversion, and abduction/adduction); they respectively measured 1.1°, 2°, and 2.3° for first metatarsal bone and 0.1°, 2.7° and 3.1° for fifth metatarsal bone (36);
- Ota et al. analyzed the weight-bearing pronation angle of the first metatarsal bone; it measured 1.8° ± 5.1 in males and 3.1° ± 2.5 in females (35).

DISCUSSION

Over the last years cone beam weight-bearing computed tomography (WBCT) has become progressively more diffused in foot and ankle practices (3, 38): this is the main reason why we performed this review. Our main finding was that there is a multitude of measurements that have been documented so far in literature and that have shown an excellent intra and inter-observer reliability in a vast majority of cases. We also faced an increasing

Table V: *Assessment of the hallux valgus angle (HVA) and inter metatarsal angle (IMA), with relative values and inter and intra-observer reliability.*

Author	HVA (°)	ICC HVA	IMA (°)	ICC IMA
Kimura 2018	14 ± 2.6 control 43 ± 9.2 HV	N/A	9 ± 1.1 control 22 ± 3.8 HV	N/A
Cheung 2018	15 control 11 HR	0.95 intra 0.90 inter	12 control 13 HR	0.94 intra 0.91 inter
Kimura 2017	14.1 ± 2.8 control 43.2 ± 10.1 HV	N/A	9.3 ± 1.3 control 22.1 ± 4.1 HV	N/A
Richter 2014	N/A	N/A	9.3 ± 3.5	> 0.9 inter
Collan 2013	15 ± 4 control 35 ± 3 HV	0.95 inter	11 ± 1 control 17 ± 1 HV	0.72 inter
Kang 2017	19.9 ± 11.0	0.86 intra (0.82-0.90) 0.84 inter (0.81-0.88)	10.9 ± 3.61	0.85 intra (0.82-0.89) 0.81 inter (0.76-0.85)

*Abbreviations: **HV**: hallux valgus; **HR**: hallux rigidus; **ICC**: intraclass correlation coefficient; **Intra**: intraobserver reliability; **Inter**: Interobserver reliability.*

interest toward three-dimensional measurements (6-11), that may take full advantage from this new cone beam technology and allow to assess the foot as a volume rather than two-dimensional planes, inherently biases by rotation issues, superimposition of bones and operator-related variability.

There is good consensus on the analysed parameters at the level of the ankle, as showed by Hamard et al., Patel et al. and Malhotra et al. In particular, the topographic measurements of the syndesmosis have demonstrated high inter-observer reliability (ICC > 0.7) (17,18,39). A secondary role is represented by talar tilt, studied by Burssens et al. and Haleem et al. and reported as having a lower reliability (ICC inter-observer > 0.5) (13,19). Certainly further studies are needed to analyse the ankle in condition of maximum stress, deformity or pathology, as done by Lepojarvi et al. and Kim et al. (15, 16); in our opinion, although these papers reported good inter-observer reliability, they might not be considered a true reference for the clinical practice because of the insufficient evidence they provide.

Regarding the hindfoot, there are several studies focusing on the assessment of the alignment (Varus or valgus). The Foot and Ankle Offset may vary from 0,6% to 2% in normally aligned feet, with an excellent reliability in all papers (ICC inter-observer and intra-observer > 0.90) (8-10). It is interesting to note that the hindfoot alignment angle or HAA might be calculated in two ways (namely a two-dimensional technique and a three-dimensional one) giving different type of results (9, 10, 13, 28, 31). Although in all cases but one (31) authors document good reliability (ICC inter-observer > 0.75), we recommend caution when reading manuscripts dealing with this measurement since the method of assessment may vary (25).

The calcaneal pitch angle, which is widely used on traditional radiographs, has also been assessed on 3D WBCT images, demonstrating uniformity of values among studies and an excellent inter and intra-observer reliability (12, 34, 35) except in one study (ICC < 0.8) (31). For what concerns the morphology of the subtalar joint, a good inter and intra-observer reliability (ICC > 0.70) (both in normal and in flatfoot groups) has been proven for measurements of the inclination of the joint relatively to the talus (inftal-suptal angle) or to the floor (inftal-hor angle) (26, 37).

Interestingly, on the midfoot and navicular bone there is no clear consensus about which measurement would be superior to another one (19, 20, 28, 29). Conversely, for the assessment of forefoot, the most used and reliable measurements seem to be the HVA and the IMA (12, 21, 32-35), which in the majority of studies have been investigated and characterized by an excellent inter and intra-observer reliability. Richter et al. also analysed the height of metatarsal heads, with good reliability as well (12). The assessment of the rotation of the metatarsal, performed by Collan et al. Yoshioka et al. and Ota et al. hasn't provided yet a clear answer to define what should be considered true bone rotation and what bone torsion (33, 35, 36).Further studies will shed more light on this matter.

We acknowledge some limitations for this study. At first, its retrospective design without any formal statistical analysis. As a matter of fact, when planning surgery on complex deformity like flatfoot, being them conservative (joint-sparing procedures (7) also including tendoscopy (40, 41) or subtalar arthroereisis (42) and joint-sacrificing (such as fusion or replacements (43–45), is necessary to obtain measurements as objective as possible in order to assess both the starting point and the quality of the outcome achieved (30). As such, considering the growing evidence of studies dealing with WBCT measurements, we believe that this study might serve as a summary of the available evidence for the clinician keen to perform these complex procedures. Another limitation is certainly the lack of direct comparison between measurements, that we estimate, was the result of the heterogeneity of primary studies.

The study of ankle and foot with weight-bearing CT may benefit from multiple measurements in the different anatomical districts. Over the last years, many authors have reported excellent reliability for two-dimensional assessments, however, only the introduction of three-dimensional tools has allowed to overcome biases related to conventional

radiography. We advocate comparative studies between various measurements for each anatomical area (ankle, hindfoot, midfoot and forefoot), to shed some light on the potential superiority of one in relation to one other.

REFERENCES

1. Beam Computed Tomography. Foot Ankle Int 2019; 107110071985830. doi:10.1177/1071100719858309.
2. Bernasconi A, de Cesar Netto C, Barg A, Burssens A, Richter A; Weight Bearing CT International Study Group LF. AAFD: Conventional radiographs are not enough! I need the third dimension. Tech Foot Ankle Surg 2019.
3. Lintz F, Welck M, Bernasconi A, Thornton J, Cullen NP, Singh D, et al. 3D Biometrics for Hindfoot Alignment Using Weightbearing CT. Foot Ankle Int 2017; 38:684-9. doi:10.1177/1071100717690806.
4. Zhang JZ, Lintz F, Bernasconi A, Zhang S. 3D Biometrics for Hindfoot Alignment Using Weightbearing Computed Tomography. Foot Ankle Int 2019; 40:720–6. doi:10.1177/1071100719835492.
5. Bernasconi A, Cooper L, Lyle S, Patel S, Cullen N, Singh D, et al. Intraobserver and interobserver reliability of cone beam weightbearing semi-automatic three-dimensional measurements in symptomatic pes cavovarus. Foot Ankle Surg 2019. doi:10.1016/j.fas.2019.07.005.
6. De Cesar Netto C, Bernasconi A, Roberts L, Pontin PA, Lintz F, Saito GH, Roney A, Elliott AJ OM. Foot Alignment in Symptomatic National Basketball Association Players Using Weightbearing Cone Beam Computed Tomography. Orthop J Sport Med 2019. doi:10.1177/2325967118824149.
7. Richter M, Seidl B, Zech S, Hahn S. PedCAT for 3D-imaging in standing position allows for more accurate bone position (angle) measurement than radiographs or CT. Foot Ankle Surg 2014; 20:201-7. doi:10.1016/j.fas.2014.04.004.
8. Burssens A, Vermue H, Barg A, Krähenbühl N, Victor J, Buedts K. Templating of Syndesmotic Ankle Lesions by Use of 3D Analysis in Weightbearing and Nonweightbearing CT. Foot Ankle Int 2018; 39:1487-96. doi:10.1177/1071100718791834.
9. Hamard M, Neroladaki A, Bagetakos I, Dubois-Ferrière V, Montet X, Boudabbous S. Accuracy of cone-beam computed tomography for syndesmosis injury diagnosis compared to conventional computed tomography. Foot Ankle Surg 2019. doi:10.1016/j.fas.2019.03.006.
10. Kim J-B, Yi Y, Kim J-Y, Cho J-H, Kwon M-S, Choi S-H, et al. Weight-bearing computed tomography findings in varus ankle osteoarthritis: abnormal internal rotation of the talus in the axial plane. Skeletal Radiol 2017;46:1071–80. doi:10.1007/s00256-017-2655-0.
11. Lepojärvi S, Niinimäki J, Pakarinen H, Leskelä H-V. Rotational Dynamics of the Normal Distal Tibiofibular Joint With Weight-Bearing Computed Tomography. Foot Ankle Int 2016;37:627-35. doi:10.1177/1071100716634757.
12. Patel S, Malhotra K, Cullen NP, Singh D, Goldberg AJ, Welck MJ. Defining reference values for the normal tibiofibular syndesmosis in adults using weight-bearing CT. Bone Joint J 2019; 101-B:348–52. doi:10.1302/0301-620X.101B3.BJJ-2018-0829.R1.
13. Malhotra K, Welck M, Cullen N, Singh D, Goldberg AJ. The effects of weight bearing on the distal tibiofibular syndesmosis: A study comparing weight bearing-CT with conventional CT. Foot Ankle Surg 2018. doi:10.1016/j.fas.2018.03.006.
14. Haleem AM, Pavlov H, Bogner E, Sofka C, Deland JT, Ellis SJ. Comparison of Deformity with Respect to the Talus in Patients with Posterior Tibial Tendon Dysfunction and Controls Using Multiplanar Weight-Bearing Imaging or Conventional Radiography. J Bone Jt Surgery-American Vol 2014; 96:e63-1–8. doi:10.2106/JBJS.L.01205.
15. Hirschmann A, Pfirrmann CWA, Klammer G, Espinosa N, Buck FM. Upright Cone CT of the hindfoot: Comparison of the non-weight-bearing with the upright weight-bearing position. Eur Radiol 2014; 24:553–8. doi:10.1007/s00330-013-3028-2.
16. Kimura T, Kubota M, Taguchi T, Suzuki N, Hattori A, Marumo K. Evaluation of First-Ray Mobility in Patients with Hallux Valgus Using Weight-Bearing CT and a 3-D Analysis System. J Bone Joint Surg 2017; 99:247–55. doi:10.2106/JBJS.16.00542.
17. Krähenbühl N, Tschuck M, Bolliger L, Hintermann B, Knupp M. Orientation of the Subtalar Joint. Foot Ankle Int 2016; 37:109–14. doi:10.1177/1071100715600823.

18. Kunas GC, Probasco W, Haleem AM, Burket JC, Williamson ERC, Ellis SJ. Evaluation of peritalar subluxation in adult acquired flatfoot deformity using computed tomography and weightbearing multiplanar imaging. Foot Ankle Surg 2018; 24:495–500. doi:10.1016/j.fas.2017.05.010.
19. Ota T, Nagura T, Yamada Y, Yamada M, Yokoyama Y, Ogihara N, et al. Effect of natural full weight□ bearing during standing on the rotation of the first metatarsal bone. Clin Anat 2019; 32:715–21. doi:10.1002/ca.23385.
20. Burssens A, Peeters J, Buedts K, Victor J, Vandeputte G. Measuring hindfoot alignment in weight bearing CT: A novel clinical relevant measurement method. Foot Ankle Surg 2016; 22:233–8. doi:10.1016/j.fas.2015.10.002.
21. Cody EA, Williamson ER, Burket JC, Deland JT, Ellis SJ. Correlation of Talar Anatomy and Subtalar Joint Alignment on Weightbearing Computed Tomography With Radiographic Flatfoot Parameters. Foot Ankle Int 2016; 37:874–81. doi:10.1177/1071100716646629.
22. Colin F, Horn Lang T, Zwicky L, Hintermann B, Knupp M. Subtalar Joint Configuration on Weightbearing CT Scan. Foot Ankle Int 2014; 35:1057–62. doi:10.1177/1071100714540890.
23. de Cesar Netto C, Shakoor D, Dein EJ, Zhang H, Thawait GK, Richter M, et al. Influence of investigator experience on reliability of adult acquired flatfoot deformity measurements using weightbearing computed tomography. Foot Ankle Surg 2018. doi:10.1016/j.fas.2018.03.001.
24. Ellis SJ, Yu JC, Johnson AH, Elliott A, O'Malley M, Deland J. Plantar pressures in patients with and without lateral foot pain after lateral column lengthening. J Bone Joint Surg Am 2010; 92:81–91. doi:10.2106/JBJS.H.01057.
25. de Cesar Netto C, Schon LC, Thawait GK, da Fonseca LF, Chinanuvathana A, Zbijewski WB, et al. Flexible Adult Acquired Flatfoot Deformity. J Bone Joint Surg 2017; 99:e98. doi:10.2106/JBJS.16.01366.
26. Ellis SJ, Yu JC, Williams BR, Lee C, Chiu Y-L, Deland JT. New radiographic parameters assessing forefoot abduction in the adult acquired flatfoot deformity. Foot Ankle Int 2009; 30:1168–76. doi:10.3113/FAI.2009.1168.
27. Cheung ZB, Myerson MS, Tracey J, Vulcano E. Weightbearing CT Scan Assessment of Foot Alignment in Patients With Hallux Rigidus. Foot Ankle Int 2018; 39:67-74. doi:10.1177/1071100717732549.
28. Collan L, Kankare JA, Mattila K. The biomechanics of the first metatarsal bone in hallux valgus: a preliminary study utilizing a weight bearing extremity CT. Foot Ankle Surg 2013; 19:155–61. doi:10.1016/j.fas.2013.01.003.
29. Kimura T, Kubota M, Suzuki N, Hattori A, Marumo K. Comparison of Intercuneiform 1-2 Joint Mobility Between Hallux Valgus and Normal Feet Using Weightbearing Computed Tomography and 3-Dimensional Analysis. Foot Ankle Int 2018; 39:355–60. doi:10.1177/1071100717744174.
30. Ota T, Nagura T, Yamada Y, Yamada M, Yokoyama Y, Ogihara N, et al. Effect of natural full weight□ bearing during standing on the rotation of the first metatarsal bone. Clin Anat 2019; 32:715–21. doi:10.1002/ca.23385.
31. Yoshioka N, Ikoma K, Kido M, Imai K, Maki M, Arai Y, et al. Weight-bearing three-dimensional computed tomography analysis of the forefoot in patients with flatfoot deformity. J Orthop Sci 2016; 21:154–8. doi:10.1016/j.jos.2015.12.001.
32. Probasco W, Haleem AM, Yu J, Sangeorzan BJ, Deland JT, Ellis SJ. Assessment of Coronal Plane Subtalar Joint Alignment in Peritalar Subluxation via Weight-Bearing Multiplanar Imaging. Foot Ankle Int 2015; 36:302–9. doi:10.1177/1071100714557861.
33. Richter M, Lintz F, de Cesar Netto C, Barg A, Burssens A. Results of more than 11,000 scans with weightbearing CT — Impact on costs, radiation exposure, and procedure time. Foot Ankle Surg 2019. doi:10.1016/j.fas.2019.05.019.
34. Hamard M, Neroladaki A, Bagetakos I, Dubois-Ferrière V, Montet X, Boudabbous S. Accuracy of cone-beam computed tomography for syndesmosis injury diagnosis compared to conventional computed tomography. Foot Ankle Surg 2019. doi:10.1016/j.fas.2019.03.006.
35. Bernasconi A, Sadile F, Welck M, Mehdi N, Laborde J, Lintz F. Role of Tendoscopy in Treating Stage II Posterior Tibial Tendon Dysfunction 2018; 39:433–42. doi:10.1177/1071100717746192.
36. Bernasconi A, Sadile F, Smeraglia F, Mehdi N,

Laborde J, Lintz F. Tendoscopy of Achilles, peroneal and tibialis posterior tendons: An evidence-based update. Foot Ankle Surg 24:374–82. doi:10.1016/j.fas.2017.06.004.

37. Bernasconi A, Lintz F, Sadile F. The role of arthroereisis of the subtalar joint for flatfoot in children and adults. EFORT Open Rev 2017; 2:438–46. doi:10.1302/2058-5241.2.170009.
38. Mehdi N, Bernasconi A, Laborde J, Lintz F. Comparison of 25 ankle arthrodeses and 25 replacements at 67 months' follow-up. Orthop Traumatol Surg Res 2019;1 05:139-44. doi:10.1016/j.otsr.2018.10.014.
39. Bernasconi A, Mehdi N, Lintz F. Fibular Intra-articular Resection During Arthroscopic Ankle Arthrodesis: The Surgical Technique. Arthrosc Tech 2017; 6:e1865–70. doi:10.1016/j.eats.2017.07.007.
40. Bernasconi A, Mehdi N, Laborde J, de Cesar Netto C, Dagneaux L, Lintz F. Joystick of the Talus for Correcting Malalignment During Arthroscopic Ankle Arthrodesis: A Surgical Tip. Arthrosc Tech 2018; 7:e517-22. doi:10.1016/j.eats.2018.01.005.

Ultrasound-guided collagen injections in the treatment of supraspinatus tendinopathy: a case series pilot study.

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Aim of the present pilot study was to verify, for the first time ever, the effects of collagen injections in patients with chronic supraspinatus tendinopathy. Eighteen patients with chronic supraspinatus tendinopathy were treated with a series of 4 type I porcine collagen ultrasound-guided injections, at weekly intervals. The effects were verified at 2-week, 1-month and 3-month follow-up by means of shoulder scoring systems and sonography. A very strong evidence ($p<0.001$) of a statistically significant main effect amongst the multiple clinical observation was found. Ultrasound imaging highlighted improvement in the structural integrity of the tendon. Compared to other injection therapies, collagen injections proved to be at least equally effective, faster acting and safer.

Supraspinatus (SSP) is one of the four muscles that comprise the rotator cuff of the shoulder, the others being subscapularis, infraspinatus, and teres minor. The rotator cuff muscles work as stabilizers of the glenohumeral joint. SSP has its origin from the supraspinous fossa of the scapula and inserts into the greater tuberosity of the humerus. SSP together with the deltoid muscle adducts the arm at the shoulder by fixing the head of the humerus firmly against the glenoid fossa. SSP functions as an abductor for the initial 30° of abduction.

Rotator cuff syndrome (RCS) constitutes a spectrum of disease across a wide range of pathologies associated with injury or degenerative conditions affecting the rotator cuff. RCS is a frequent cause of pain in the shoulder and often brings to functional and labour disabilities. Within RCS, the most common muscle affected is SSP (1).

The definitive cause of SSP tendinopathy remains uncertain. Proposed mechanisms include intrinsic, extrinsic, or combined mechanisms. Extrinsic mechanisms potentially involve attrition of the tendon from contact with bone structures. Intrinsic mechanisms relate to factors that directly influence tendon health and quality, including aging, genetics, postural imbalances, vascular changes, altered loading, and surgery (2, 3). Excessive tissue load remains the most substantial causative factor in the development of SSP tendinopathy. Indeed, the prevailing pathogenesis model suggests that SSP tendinopathy occurs from a primary response of the tendon cells to overload, which results in tendon cells activation and proliferation, increase in proteoglycans, that in their turn cause collagen matrix disruption, and increased vascularisation (4).

Symptoms of RCS include pain at rest and at night, particularly if lying on the affected shoulder, and pain and weakness when lifting heavy objects or rotating the arm. Tenderness or deformity can be detected at physical examination. There is limited evidence for

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any of the tests commonly used in diagnosing SSP tendinopathy as being very sensitive or specific. The empty can test (Jobe's test) and the full can test (Neer test) are the most commonly employed. Patients with SSP tendinopathy may also experience a painful arc of movement between 60° and 120° of abduction, which was found to carry the highest likelihood ratio compared with other provocative tests (5).

There are three imaging options in the evaluation of SSP tendinopathy: plain radiography (X-ray), ultrasound (US), and Magnetic Resonance (MR) with or without arthrography (MRA). US, and US elastography is increasingly gaining in importance for the study of muscles and tendons (6-8). US is an excellent tool for evaluating rotator cuff: it is less expensive than MR and it allows to assess dynamic movements of the shoulder. US may be helpful to detect signs of tendinopathy and to predict improvement or worsening of the tendon health at the tissue level (9). For the shoulder there is a lack of clinically relevant, standardized and reliable US methods for assessing tendinopathy. Since US is highly influenced by clinician experience and technique, standardized US procedures for assessment of structural changes in relation to tendinopathy need to be defined. Based on the literature, consensus was made on definitions of relevant structural changes related to SSP tendinopathy, including thickening, fibrillar disruption and calcifications (10).

There are several treatment options for SSP tendinopathy. Conservative treatment may include rest, activity modification, non-steroidal anti-inflammatory drugs (NSAIDs), and physical therapy, focused on both core and scapular muscles strengthening (11). In about 80% of patients, nonsurgical treatment relieves pain and improves function. If rest, medications, and physical therapy do not relieve pain, patients can undergo injection therapy. Several injection therapy options are available, including injection of corticosteroids, hyaluronic acid (HA), platelet-rich plasma (PRP), and natural irritants (prolotherapy). These injection treatments have shown variable effectiveness and have some criticalities. The combination of injection therapies with physical exercise can reduce recovery time (12).

Type I porcine collagen injections represent a new and refined tool in prevention and therapy of ageing of intra-articular structures, as well as of periarticular ones and of those concerning mesodermic supporting tissues (13-16). Collagen injections can stimulate synthesis, maturation and secretion of endogenous type I collagen, which is always deficient in inflammatory and/or degenerative diseases concerning the musculokeletal system and other anatomical structures of mesodermic origin (17).

Aims of this prospective pilot study were (a) to evaluate the effects of a series of 4 porcine type I collagen US-guided injections (once a week) on pain and disability in a group of patients who have been suffering from SSP tendinopathy for at least 6 months, and, (b) to verify the effects of this injection therapy on the ultrasonographic tendon structure.

MATERIALS AND METHODS

This is a prospective observational pilot study and was carried out at Federico II University Hospital in Naples, Italy. The subjects were all outpatients and we enrolled them from October 2018 to May 2019. All the patients who referred shoulder pain and disability were evaluated to verify the criteria for the enrollment and underwent ultrasound and X-ray. The inclusion criteria were: age >18 years, symptomatic SSP tendinopathy of at least 6 months of duration, pain triggered by overhead activities, positive impingement sign (Neer test), pain with supraspinatus testing (Jobe's test), ultrasound evidence of SSP tendinopathy, and lack of therapy in the last 6 months. The exclusion criteria were; previous shoulder surgery, rotator cuff tears greater than 50% of the tendon thickness, adhesive capsulitis, inflammatory arthritis, acromioclavicular joint pain, X-ray evidence of glenohumeral osteoarthritis, and previous fractures/bone tumors/osteonecrosis of the humerus. After a full and clear description of the study protocol, all patients enrolled were invited to sign the informed consent. The study was carried out in accordance with the principles of the Declaration of Helsinki and met the ethical standards of the local ethics committee.

We selected 20 patients but 2 refused to take part in the trial. Finally, we enrolled 18 patients, of which 11

males and 7 females, with an average age of 52 ± 15 years. For the treatment we planned 4 US-guided injections of 2 ml porcine type I collagen, once a week. Ultrasound-guided injections for SSP tendinopathy have proved to be superior to blind interventions (18). All injections were performed by a single doctor with over 10 years of experience. Injections were performed using an anterior approach. The patients were seated on a chair with the arm in internal rotation to expose as much of the SSP tendon as possible. This position was best achieved by placing the patient's arm behind his back. A 22-gauge needle was directed towards the main hypoechoic/anechoic area of the supraspinatus tendon as guided by US until the tip of the needle was seen in the correct position and then the collagen was injected slowly. Patients were invited to keep the shoulder at rest until the day after. No other treatment was associated with collagen injections.

Patients were evaluated at the time of enrollment (T0), right before the third injection (T0), one month (T2) and three months (T3) after the last injection by means of the Constant-Murley (CM) score and the disability of the arm, shoulder and hand (DASH) questionnaire. An ultrasound evaluation of the rotator cuff was performed by a radiologist with over 20 years of experience at T0 and T3. An ordinal grading scale was assessed. The scale ranged from 0 to 5 (0 = normal tendon; 1 = thickening; 2 = disruption without calcifications; 3 = disruption with microcalcifications; 4 = disruption with macrocalcifications; 5 = partial rupture) (10).

Statistical analysis

Analysis of variance (ANOVA) for repeated measures was used to compare both CM and DASH mean scores with each other at different time points (T0, T1, T2, T3). Afterwards, Bonferroni post-hoc test was employed to perform pairwise comparisons by time points (T0/T1, T0/T2, T0/T3, T1/T2, T1/T3, T2/T3). The confidence interval was established at 95% ($p < 0.05$). With regards to US evaluation, a simple comparison between means ± standard deviation was performed at two different time points (T0 and T3).

CM and DASH mean scores and standard deviations at different time points are listed in Tables I and II respectively. For repeated measures ANOVA provided very strong evidence ($p < 0.001$) of a statistically significant main effect amongst the multiple observation, both as regards to CM score and DASH questionnaire (Fig. 1). The multiple-comparison post-hoc correction (Bonferroni method) highlighted statistically significant differences between CM and DASH mean scores for each pair of time points ($p < 0.05$) except for the pair T2/T3.

US mean scores and standard deviation at T0 and T3 are listed in Table III. We observed a 27.5% reduction in the US mean score between the two time points (Fig. 2).

No adverse event has been described after collagen

Table I. *Descriptive statistics of CM score at different time points.*

	Mean	Std. Deviation
T0	53,11	12,700
T1	62,89	10,775
T2	72,17	10,450
T3	75,00	12,916

Table II. *Descriptive statistics of DASH score at different time points.*

	Mean	Std. Deviation
T0	37,72	19,078
T1	28,89	15,080
T2	19,72	10,063
T3	18,67	13,002

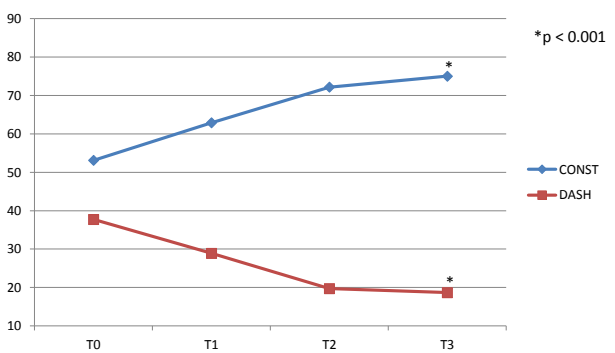

Fig. 1. *Constant score and DASH questionnaire multiple observation at different time points.*

injections, except for some cases of burning sensation at the injection site which resolved spontaneously in a few hours.

SSP tendinopathy is a frequent cause of shoulder pain but its pathophysiology is not fully understood. Treatment of SSP tendinopathy is a challenge for physicians, physical therapists and all the healthcare professionals. The current literature suggests a multidisciplinary approach: NSAIDs, exercise rehabilitation, physical therapy modalities, shock wave therapy, injection therapies, and surgery (19).

In this pilot study we wanted to evaluate the collagen injection therapy in a cohort of 18 subjects affected by SSP tendinopathy (4 US-guided injections, once a week, of type I porcine collagen). The results were evaluated by administering CM score and DASH questionnaire, before the first and the third injections, and one month and three months after the last injection. All the selected patients underwent US evaluation of SSP tendon at the time of enrollment and at 3-month follow-up. At the end of the treatment we observed a statistically significant improvement on pain and function. The positive findings were registered both in objective (CM score) and subjective (DASH questionnaire) outcome measures. Three-month post-treatment US evaluation showed reduced tendon thickness and a trend towards normalization in the tendon sonographic features.

At this stage there are not literature studies about collagen injections in the treatment of SSP tendinopathy. Several injection therapies with substances different from collagen are used in a variety of shoulder conditions and RCS. Most of the literature on injection therapies for RCS focuses on corticosteroids. Although some studies have reported efficacy in reducing pain and improving function, there is little reproducible evidence. In a 2017 meta-analysis on corticosteroid injections in rotator cuff tendinosis, Mohamadi et al. highlighted that corticosteroid injections provide minimal transient pain relief in a small number of

Table III. *Descriptive statistics of US grading score at different time points*.

3h	T0	T3	ΔT0-T3	%ΔT0-T3
Totale score	51	37	-14	-27,5
Mean	2,8	2	-0,8	
Standard deviation	1,5	1,9		

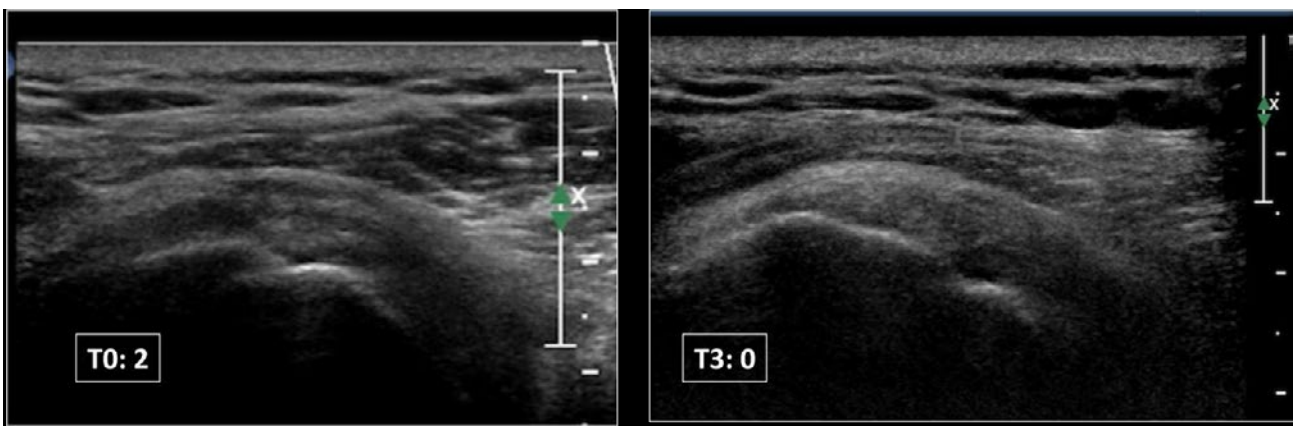

Fig. 2. *Sonographic assessment of a patient with supraspinatus tendinopathy who switched from a pre-treatment score of 2 to a post-treatment score of 0.*

patients, that they cannot modify the natural history of the disease, and that, given the potential to accelerate tendon degeneration associated with corticosteroids, they have limited appeal (20). Another injection therapy that has been described for the treatment of chronic painful rotator cuff tendinopathy is prolotherapy or hypertonic dextrose injection. The literature on prolotherapy in the shoulder is limited to small retrospective series. A recent prospective, randomized, double blinded clinical trial by Cole et al. aimed to compare glucose prolotherapy injection into the SSP tendon with corticosteroid injection into the subacromial bursa for treatment of SSP tendinopathy. Authors concluded that glucose prolotherapy offers no additional benefit over subacromial corticosteroid injection (21). The use of PRP for the treatment of RCS has been extensively studied through multiple RCTs and meta-analyses.

The variability on the composition of PRP produced make it difficult to draw any definitive conclusions on the efficacy of PRP treatment of RCS. In 2019 Hurley et al. performed a systematic review of the literature on the use of PRP for non-operative treatment of RCS. The authors stated that the currently limited available evidence suggests that in the short term PRP injections may not be beneficial and that interpretation of the literature is confounded by the lack of reporting of the cytology and characteristics of PRP (22). The peritendinous administration of hyaluronic acid (HA) has shown promising results in clinical trials including patients with various disorders involving tendons in the rotator cuff. However, the superiority of HA over other interventions in scales assessing pain is controversial, and few studies have evaluated the efficacy of HA in the treatment of lesions affecting a tendon. In their 2017 multicenter, randomized, controlled trial, Flores et al. found that combined treatment with peritendinous 2% HA injections and physical therapy promotes faster recovery in patients with SSP tendinopathy (23). Recently mesenchymal stem cells (MSCs) derived from bone marrow and adipose have garnered the most attention for use in RCS. Nevertheless, only a few studies have examined the effect of augmentative MSC therapy on RC repair in humans, with early results suggesting a possible improvement in repair site healing (24).

Eventually, several newer injection therapies have gained popularity in the treatment of SSP tendinopathy. However, the existing evidence for each type of therapy is currently limited and some of them have shown a lack of safety due to their potential side effects (25). Another limitation of several injection therapies for tendinophaties is the high cost, which make them accessible only to a limited number of patients.

The present study has some limitations: (a) a small sample, (b) the lack of a control group, and (c) the short follow-up time. However, it should be stated that this is a pilot study and that it is currently the only study in the literature on the effectiveness of collagen injection therapy in SSP tendinopathy.

In conclusion, this pilot study has shown that a series of 4 type I porcine collagen US-guided injections, at weekly intervals, is able to reduce significantly pain symptoms and improve the function in a group of 18 patients with chronic SSP tendinopathy. Moreover, the positive clinical findings have been confirmed by ultrasonographic features. Finally, we can state that there are grounds for carrying out an RCT to confirm our preliminary data.

REFERENCES

1. Sambandam SN, Khanna V, Gul A, Mounasamy V. Rotator cuff tears: An evidence based approach. World J Orthop. 2015; 6(11):902-18
2. Corrado B, Ciardi G. Facioscapulohumeral distrophy and physiotherapy: a literary review. J Phys Ther Sci 2015; 27(7):2381-5. doi: 10.1589/jpts.27.2381.
3. Corrado B, Ciardi G, Servodio Iammarrone C, Arpino G. Home Exercise Program is an effective tool in improving upper limb function and quality of life in breast cancer survivors: A retrospective observational study. Journal of Human Sport and Exercise. 2018; 13(4)926-39. doi: https://doi.org/10.14198/jhse.2018.134.19
4. Cook J, Purdam C. Is compressive load a factor in the development of tendinopathy? Br J Sports Med 2012; 46(3):163e8
5. Hermans J, Luime JJ, Meuffels DE, et al. Does this patient with shoulder pain have rotator cuff disease?: the rational clinical examination systematic review. JAMA 2013; 310:837-47.
6. Domenichini R, Pialat JB, Podda A, Aubry S. Ultrasound elastography in tendon pathology: s tate of the art. Skeletal Radiol. 2017; 46(12):1643-1655. doi: 10.1007/s00256-017-2726-2.

7. Vola EA, Albano M, Di Luise C, Servodidio V, Sansone M, Russo S, Corrado B, Servodio Iammarrone C, Caprio MG, Vallone G. Use of ultrasound shear wave to measure muscle stiffness in children with cerebral palsy. J Ultrasound. 2018; 21(3):241-247. doi: 10.1007/s40477-018-0313-6.
8. Corrado B, Albano M, Caprio MG, Di Luise C, Sansone M, Servodidio V, Russo S, Vallone G, Vola EA, Servodio Iammarrone C. Usefulness of point shear wave elastography to assess the effects of extracorporeal shockwaves on spastic muscles in children with cerebral palsy: an uncontrolled experimental study. MLTJ 2019; 9(1):124-130. doi: 10.32098/mltj.01.2019.04
9. Vasishta A, Kelkar A, Joshi P, Hapse R. The value of sonoelastography in the diagnosis of supraspinatus tendinopathy-a comparison study. Br J Radiol. 2019; 92(1095):20180951. doi: 10.1259/bjr.20180951.
10. Ingwersen KG, Hjarbaek J, Eshoej H, Larsen CM, Vobbe J, Juul-Kristensen B. Ultrasound assessment for grading structural tendon changes in supraspinatus tendinopathy: an inter-rater reliability study. BMJ Open. 2016; 6(5):e011746. doi: 10.1136/bmjopen-2016-011746
11. Lewis J. Rotator cuff related shoulder pain: Assessment, management and uncertainties. Man Ther 2016; 23:57-68. doi: 10.1016/j.math.2016.03.009.
12. Lin MT, Chiang CF, Wu CH, Huang YT, Tu YK, Wang TG. Comparative effectiveness of injection therapies in rotator cuff tendinopathy: a systematic review, pairwise and network meta-analysis of randomized controlled trials. Archives of Physical Medicine and Rehabilitation. Arch Phys Med Rehabil. 2019; 100(2):336-349.e15. doi: 10.1016/j.apmr.2018.06.028.
13. Furuzawa-Carballeda J, Lima G, Llorente L, et al. Polymerized-type I collagen downregulates inflammation and improves clinical outcomes in patients with symptomatic knee osteoarthritis following arthroscopic lavage: a randomized, double-blind, and placebo-controlled clinical trial. ScientificWorldJournal. 2012; 2012:342854. doi: 10.1100/2012/342854
14. Martin LS, Massafra U, Bizzi E, Migliore A. A double blind randomized active-controlled clinical trial on the intra-articular use of Md-Knee versus sodium hyaluronate in patients with knee osteoarthritis ("Joint"). BMC Musculoskelet Disord. 2016; 17:94. doi: 10.1186/s12891-016-0948-4
15. Nitecka-Buchta A, Walczynska-Dragon K, Batko-Kapustecka J, Wieckiewicz M. Comparison between collagen and lidocaine intramuscular injections in terms of their efficiency in decreasing myofascial pain within masseter muscles: a randomized, single-blind controlled trial. Pain Res Manag. 2018; 2018:8261090. doi: 10.1155/2018/8261090
16. Corrado B, Mazzuoccolo G, Liguori L, Chirico VA, Costanzo M, Bonini I, Bove G, Curci L. Treatment of lateral epicondylitis with collagen injections: a pilot study. MLTJ 2019; 9(4):584-589. DOI: 10.32098/mltj.04.2019.14
17. Randelli F, Menon A, Giai Via A, et al. Effect of a collagen-based compound on morpho-functional properties of cultured human tenocytes. Cells. 2018; 7(12). pii: E246. doi: 10.3390/cells7120246
18. Abat F, Campos J, Torras J, Madruga M, Planells G, Rodriguez-Baeza A. Comparison of ultrasound-guided versus blind interventions for supraspinatus tendinopathy: a cadaveric study. MLTJ 2019; 9(3):328-337. doi: 10.32098/mltj.03.2019.06
19. Andres BM, Murrell GAC. Treatment of tendinopathy: what works, what does not, and what is on the horizon. Clin Orthop Relat Res 2008; 466(7):1539–1554.
20. Mohamadi A, Chan JJ, Claessen FM, Ring D, Chen NC. Corticosteroid injections give small and transient pain relief in rotator cuff tendinosis: a meta-analysis. Clin Orthop Relat Res. 2017; 475(1):232-243. doi: 10.1007/s11999-016-5002-1.
21. Cole B, Lam P, Hackett L, Murrell GAC. Ultrasound-guided injections for supraspinatus tendinopathy: corticosteroid versus glucose prolotherapy - a randomized controlled clinical trial. Shoulder Elbow. 2018; 10(3):170-178. doi: 10.1177/1758573217708199
22. Hurley ET, Hannon CP, Pauzenberger L, Fat DL, Moran CJ, Mullett H. Nonoperative treatment of rotator cuff disease with platelet-rich plasma: a systematic review of randomized controlled trials. Arthroscopy. 2019; 35(5):1584-1591. doi: 10.1016/j.arthro.2018.10.115.
23. Flores C, Balius R, Álvarez G, Buil MA, Varela

L, Cano C, Casariego J. Efficacy and Tolerability of Peritendinous Hyaluronic Acid in Patients with Supraspinatus Tendinopathy: a Multicenter, Randomized, Controlled Trial. Sports Med Open. 2017; 3(1):22. doi: 10.1186/s40798-017-0089-9.

24. Kim YS, Sung CH, Chung SH, Kwak SJ, Koh YG. Does an Injection of Adipose-Derived Mesenchymal Stem Cells Loaded in Fibrin Glue Influence Rotator Cuff Repair Outcomes? A Clinical and Magnetic Resonance Imaging Study. Am J Sports Med. 2017; 45(9):2010-2018. doi: 10.1177/0363546517702863.
25. Lin KM, Wang D, Dines JS. Injection Therapies for Rotator Cuff Disease. Orthop Clin North Am. 2018; 49(2):231-239. doi: 10.1016/j.ocl.2017.11.010.

Heterotopic ossification around the lesser trochanter of the femur simulating a malignant lesion. A case report with long-term follow-up and revision of literature.

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We report the case of a 28-year-old female who complained of groin pain and restricted range of motion of the hip for the previous two months. A plain radiograph, CT scan and MRI of the pelvis showed a bone mass of uncertain origin around the lesser trochanter, simulating malignancy. An open biopsy was performed to obtain a correct diagnosis. The histological examination excluded a malignant lesion. Two months later, the mass was surgically excised and at follow-up, 9 years after surgery, the patient was completely asymptomatic, without any radiographic sign of recurrence. This is a rare case of heterotopic ossification of the proximal part of the femur, that appeared without any significant trauma or other predisposing risk factors; because the lesion led us to suspect a malignant disease, an open biopsy was needed to make the diagnosis. From an accurate review of the literature, heterotopic ossifications mimicking a malignant lesion that appeared without any predisposing factors are extremely rare.

Heterotopic ossification is characterized by the formation of mature, lamellar bone, in the extra-skeletal soft tissue. The pathophysiology of heterotopic ossification is still debated. The function of pro-angiogenic and osteoinductive factors, hypoxia of the surrounding tissue and mechanical stimuli are possible predisposing factors (1). Generally, the diagnosis is simple, as it is often related to the patient's clinical history. Clinical and radiographic examinations are usually sufficient to diagnose this pathological condition, and only in some cases it is necessary to perform a bone scan, CT scan and/or MRI, especially for planning the surgical excision.

This disorder generally occurs after traumatic brain injury, spinal cord injury, elbow and acetabular fractures, hip joint replacement and thermal injury (predisposing factors) (2-5). The diagnosis may be difficult, as well as in other benign lesions, that look like malignant tumors (6-8). Differential diagnosis includes also osteochondroma, fibrodysplasia ossificans progressiva (9), calcium metabolism disorders and bizarre parosteal osteochondromatous proliferation (10).

Nonsteroidal anti-inflammatory drugs and radiation are commonly used in the prophylaxis of heterotopic ossification, in some cases associated with continuous passive motion (11). Surgical excision is indicated in patients with functional limitations (12-14). In this study, we report the case of a 28-year-old female with a large symptomatic heterotopic ossification localized around the lesser trochanter, simulating a malignant tumor.

Case report

A 28-year-old female was admitted to our institution with left groin pain, which had lasted for the previous two months. The pain in the left groin increased on weight-bearing and walking and

Key words: heterotopic ossification, lesser trochanter, hip, tumor.

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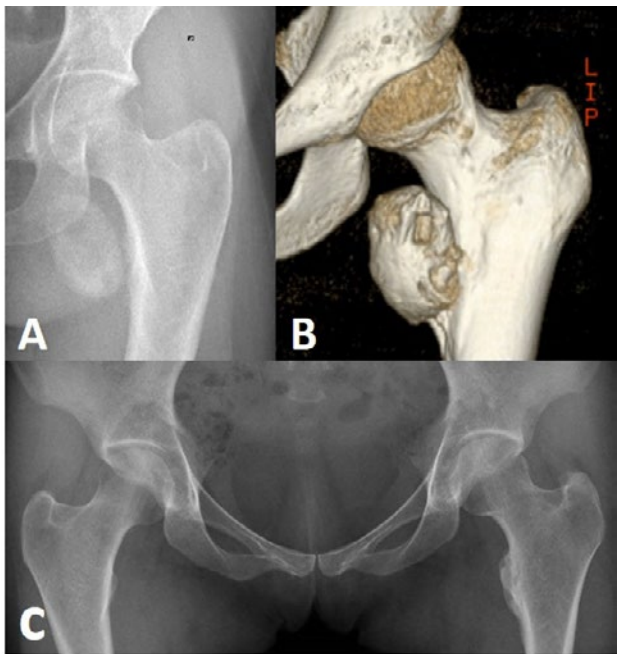

Fig. 1. *Radiographic examination in AP view and CT scan with 3D reconstruction of the left hip showed a bone mass in the soft tissue around the lesser trochanter (A, B). At follow-up, 9 years after the surgical excision, the radiographic examination of the pelvis did not show any recurrence of the heterotopic ossification (C).*

decreased at bed rest and after taking nonsteroidal anti-inflammatory drugs. During the physical examination, moderate pain was reported at groin palpation, associated with a restricted range of motion of the left hip and mild limping. The patient had already had a radiographic examination of the pelvis (Fig. 1A), a CT scan (Fig. 1B) and an MRI (Fig. 2) that revealed a bone mass around the lesser trochanter. Bone scan was not performed. The laboratory tests were normal, including the alkaline phosphatase. Since her clinical history did not reveal any predisposing factor for heterotopic ossification and the radiological investigations suggested a possible malignancy of the lesion, an open biopsy was performed through a mini open medial approach.

At the histological examination, the mass was formed by bone trabeculae separated by loose hypocellular fibro-vascular tissue (transmitted light); the view of the same fields by polarized light demonstrated the coexistence of both woven (wb) and lamellar bone (lb) (Fig. 3). Two months later, the mass was excised with a medial surgical approach described by Ludloff without any perioperative complication.

To prevent postoperative recurrence of ossification, 100 mg of indomethacin was administered daily after surgery for 6 weeks, associated with an early fully active rehabilitation program. The patient was examined for the first two years after surgery clinically and radiographically at regular intervals, but no recurrence was observed.

At the final follow-up, nine years after the surgical excision, the patient was completely asymptomatic with a full range of motion of the affected hip; she was involved in sports activities. The radiographic examination of the pelvis showed no recurrence of the mass (Fig. 1C).

DISCUSSION

Heterotopic ossification represents a pathological condition whose etiology and pathogenesis are still unknown (1); it generally occurs after trauma, brain injuries, spinal cord injuries, elbow and acetabular fractures, hip arthroplasty and thermal injuries (2-5), that represent the main predisposing factors. Heterotopic ossification may cause pain and severe

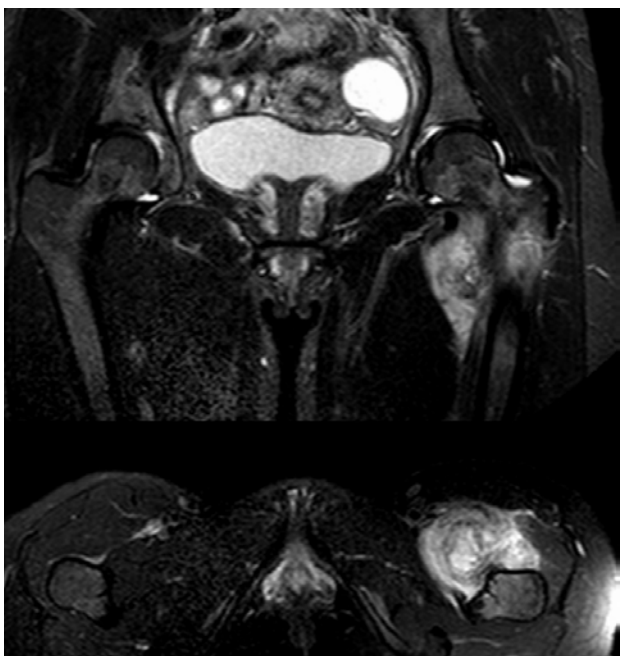

Fig. 2. *MRI of the pelvis in coronal and axial sections showed the lesion in the soft tissue around the left lesser trochanter, mimicking malignancy.*

restriction of the range of motion of the affected joint. Diagnosis in most cases is simple, based on a radiographic examination. Surgical excision of the heterotopic bone may be indicated in some cases, but recurrence may occur over time (12-14).

In our case, the patient did not report any significant trauma before the onset of symptoms; therefore, we excluded a neglected avulsion fracture of the lesser trochanter that generally occurs in adolescent athletes during growth, as a result of a sudden violent contraction of the iliopsoas muscle, and represents the most common condition which generates a heterotopic ossification around the lesser trochanter (15). Moreover, our patient was fully grown (28-years-old), and in adult patients, avulsion fractures of the lesser trochanter are extremely rare whereas they are often associated with traumatic intertrochanteric or subtrochanteric fractures (16). Other pathological conditions should be also considered in differential diagnosis, as osteochondroma, fibrodysplasia ossificans progressive (9), calcium metabolism disorders and bizarre parosteal osteochondromatous proliferation (10). However, the most serious pathology to be excluded, is an undiagnosed primitive or metastatic malignant disease (17-19). The biopsy of the mass, performed to exclude a malignant lesion and the other suspected pathologies, demonstrated the coexistence of both normal woven and lamellar bone, thus allowing the final diagnosis of a benign heterotopic ossification. At this point, a successful surgical excision was performed, with no recurrence at the 9-year follow-up.

To the best of our knowledge, only a few studies reports heterotopic ossifications mimicking malignant lesion in patients without predisposing factors (20, 21). On the contrary, some cases of myositis ossificans simulating sarcomas have been

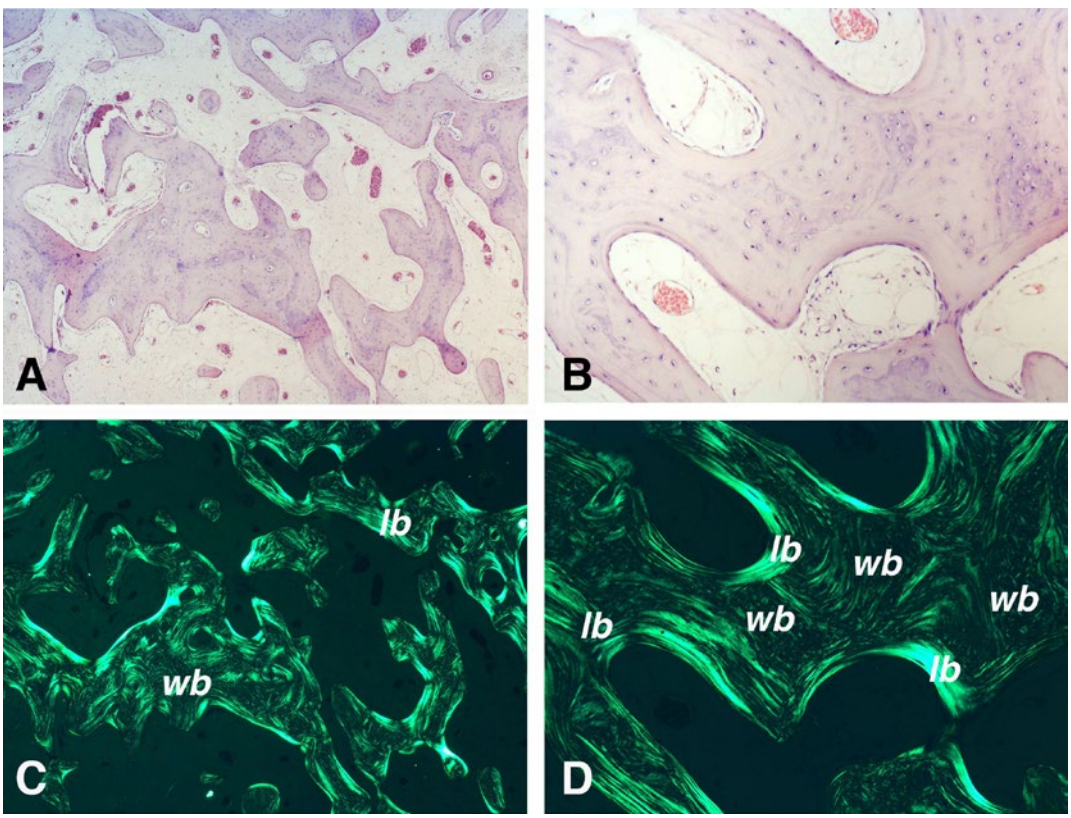

Fig. 3. *Transmitted (A, B) and polarized (C, D) light views of the same microscopic fields of the mass at low and high-power magnification. By transmitted light, the mass was formed by bone trabeculae separated by loose hypocellular fibro-vascular tissue; polarized light demonstrated the coexistence of both woven (wb) and lamellar bone (lb).*

reported (22-25). Botchu *et al.* (20) reported five cases of heterotopic ossification of distal tibia and fibula which had initially been referred as a suspected surface osteosarcoma. In all cases, there was a history of prior ankle trauma, but the significance was not recognized at the time of referral to the specialist orthopedic oncology center. Only two cases had an excision biopsy of the suspected lesion, but histological examination showed no signs of neoplasia. The remaining three cases were treated conservatively, after MRI and CT scans. More recently, O'Callaghan *et al.* (21) reported a heterotopic ossification of the proximal aspect of the femur in a 19-year-old girl without any significant traumatic event, other than a fall down the stairs occurred 4 months before. Radiographs revealed a mineralizing soft-tissue mass of the proximal aspect of the thigh, related with the anterior femoral cortex. A CT-guided core needle biopsy of the mass was inconclusive and, subsequently, an open biopsy was performed that excluded malignancy. They stated that their case may well be the only report that describes heterotopic ossification associated with a minor trauma without any risk factors.

Heterotopic ossification in soft tissue that simulated sarcomas are also reported in myositis ossificans by several authors (22-25). In the last 12 years, four case reports have been published on myositis ossificans mimicking malignant bone lesions. In two cases the mass was localized in the thigh, in one case in the shoulder and in another case in the elbow. No patients had history of trauma or other predisposing factors for heterotopic ossification. In all cases the diagnosis was made with a biopsy which showed a typical histological aspect of myositis ossificans.

After an accurate review of the literature, we can conclude that our case is very rare, because the heterotopic ossification that simulated a malignant lesion had formed without any significant trauma or other risk factors and only an open biopsy allowed a correct diagnosis.

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This study was approved by the ethics committee of Policlinico Tor Vergata, Rome; the patient was informed about the study and consented to participate. The data of the manuscript are available. The authors declare that there is no conflict of interest regarding the publication of this paper. No funds have been received by the authors.

REFERENCES

1. Ranganathan K, Loder S, Agarwal S, et al. Heterotopic ossification: basic-science principles and clinical correlates. J Bone Joint Surg Am 2015; 97:1101-11.
2. Kaplan FS, Glaser DL, Hebela N, Shore EM. Heterotopic ossification. J Am Acad Orthop Surg 2004; 12:116-25.
3. Cipriano CA, Pill SG, Keenan MA. Heterotopic ossification following traumatic brain injury and spinal cord injury. J Am Acad Orthop Surg 2009; 17:689-97.
4. Chen HE, Yang JY, Chuang SS, Huang CY, Yang SY. Heterotopic ossification in burns: our experience and literature reviews. Burns 2009; 35:857-62.
5. Barfield WR, Holmes RE, Hartsock LA. Heterotopic ossification in trauma. Orthop Clin North Am 2017; 48:35-46.
6. De Maio F, Caterini A, Marsiolo M, Farsetti P. Pubic osteolysis simulating a malignant lesion. A case report with long-term follow-up. J Biol Regul Homeost Agents 2019; 33(2 Suppl.1)183-6.
7. Ippolito E, Farsetti P, Boyce A, Corsi A, De Maio F, Collins M. Radiographic classification of coronal plane femoral deformities in polyostotic fibrous dysplasia. Clin Orthop 2012, 472:1558-67.
8. Ippolito E, Farsetti P, Valentini MB, Potenza V (2015). Two-stage surgical treatment of complex femoral deformities with severe coxa vara in polyostotic fibrous dysplasia. J Bone Joint Surg 2015; 97A:119-25.
9. Pignolo RJ, Shore EM, Kaplan FS. Fibrodysplasia ossificans progressiva: diagnosis, management, and therapeutic horizons. Pediatr Endocrinol Rev 2013; 10 (Suppl 2):437-44.
10. Takahashi R, Matsuo T, Kawanami K, Takata T, Takahashi E, Deie M. Bizarre parosteal osteochondromatous proliferation of the femur: A

case report. J Orthop 2018; 15: 606-09.
11. Vavken P, Castellani L, Sculco TP. Prophylaxis of heterotopic ossification of the hip: systematic review and meta-analysis. Clin Orthop Relat Res 2009; 467:3283-9.
12. Ippolito E, Formisano R, Caterini R, Farsetti P, Penta F. Resection of elbow ossification and continuous passive motion in postcomatose patients. J Hand Surg Am 1999; 24:546-53.
13. Ippolito E, Formisano R, Caterini R, Farsetti P, Penta F. Operative treatment of heterotopic hip ossification in patients with coma after brain injury. Clin Orthop Relat Res 1999; 365: 130-8.
14. Arduini M, Mancini F, Farsetti P, Piperno A, Ippolito E. A new classification of peri-articular heterotopic ossification of the hip associated with neurological injury: 3D CT scan assessment and intra-operative findings; Bone Joint J 2015; 97B: 899-904.
15. Homma Y, Balba T, Ishii S, Matsumoto M, Kaneko K. Avulsion fracture of the lesser trochanter in a skeletally immature freestyle footballer. J Pediatr Orthop B 2015; 24:304-7.
16. Singh P, Kumar A, Shekhawat V, Singh P. Nonpathological lesser trochanter fracture in adult: case report and brief review of literature. J Clin Diagn Res 2015; 9:04-5.
17. Phillips CD, Pope TL Jr, Jones JE, Keats TE, MacMillan RH 3rd. Nontraumatic avulsion of the lesser trochanter: a pathognomonic sign of metastatic disease? Skeletal Radiol 1988; 17:106-10.
18. Afra R, Boardman DL, Kabo JM, Eckardt JJ. Avulsion fracture of the lesser trochanter as a result of a preliminary malignant tumor of bone. A report of four cases. J Bone Joint Surg Am 1999; 81:1299-304.
19. Kumar P, Agarwal S, Rajhish RK, Kumar V, Jindal K. Isolated spontaneous atraumatic avulsion of lesser trochanter of femur. A pathognomonic sign of malignancy in adults? A case report and review of literature. J Orthop Case Rep 2017; 7:16-19.
20. Botchu R, Douis H, Davies AM, James SL, Puls F, Grimer R. Post-traumatic heterotopic ossification of distal tibiofibular syndesmosis mimicking a surface osteosarcoma. Clin Radiol 2013; 68:676-9.
21. O'Callaghan PK, Carter E, Walton Z, Chapin R, Brumer E. Heterotopic ossification formation following a simple concussion: a case report. JBJS Case Connect 2018; 8:26.
22. Yamaga K, Kobayashi E, Kubota D et al. Pediatric myositis ossificans mimicking osteosarcoma. Pediatr Int 2015; 57: 996-9. Ragunanthan N, Sugavanam C. Pseudomalignant myositis ossificans mimicking osteosarcoma: a case report. J Orthop Surg (Hong Kong) 2006; 14:219-21.
23. Munoz-Mahamud E, Poggio D, Combalia A. Myositis ossificans mimicking parosteal osteosarcoma: a case report amd literature review. Acta Orthop Belg 2011; 77:274-9.
24. Yamaga K, Kobayashi E, Kubota D et al. Pediatric myositis ossificans mimicking osteosarcoma. Pediatr Int 2015; 57:996-9.
25. Espinosa Munoz E, Ramirez Ocana D, Martin Garcia AM, Puentes Zarzuela C. Myositis ossificans in elbow mimicking soft tissue sarcoma: similar clinical and radiological findings. Reumatol Clin 2017; 15:57-9.

Infection rate of intramedullary nailing for treatment of lower limb polyostotic fibrous dysplasia.

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Polyostotic fibrous dysplasia (PFD) generally cause deformities and fractures of femur and tibia and surgery is often required. The current surgical treatment for deformities is based on single or multiple osteotomies followed by stabilization with intramedullary nails, which are commonly used also for fractures. One of the most common surgical complications of intramedullary nailing is represented by surgical site infection with possible extension to the whole skeletal segment. In the present study we evaluated the incidence of surgical site infections in 44 patients affected by PFD in which 91 femurs or tibiae underwent intramedullary nailing to treat deformities or fractures. We never observed any infection of the operated femurs or tibiae until the final follow-up. The only post surgical infection was present in a patient with monomelic involvement at the contralateral non affected limb, which was surgically treated for limb length inequality, by femur shortening osteotomy stabilized by an intramedullary nail. The most likely hypothesis to explain the complete absence of infections in these patients may be related to the high local concentration of prophylactic antibiotic in the highly vascularized fibrodysplastic bone.

Polyostotic fibrous dysplasia (PFD) and McCune-Albright Syndrome (MAS) commonly affect the femur and tibia, causing deformities and fractures. These deformities are treated by single or multiple osteotomies and stabilized by intramedullary nails, which are generally preferred to the peripheral plates. Similarly, pathological fractures caused by the weakness of the affected bone are treated by reduction and stabilization with intramedullary nail (1-3).

Surgical infection related to intramedullary nailing represent a severe and difficult to treat complication which may cause delayed consolidation or nonunion and limb function impairment.

The incidence of surgical infection related to intramedullary nailing in femurs and tibiae, recently reported in a prospective study which included closed and open fractures, is 11.8% (4). However, other authors, in a current concept review, reported a lower incidence of infection rates in closed femoral shaft fractures treated with intramedullary nailing, ranging from 1% to 3.8% (5). Similar infection rates (3.6%) are reported when intramedullary nails are used in femoral and tibial limb lengthening (6).

In the last 20 years, we developed a high experience in surgical treatment of deformities and fractures involving femurs and tibiae in polyostotic fibrous dysplasia.

In the present study we report the incidence rate of surgical infection in a large series of patients affected by lower limb deformities or fractures caused by polyostotic fibrous dysplasia or McCune-Albright syndrome, surgically treated and stabilized by a rigid intramedullary nail.

Key words: polyostotic fibrous dysplasia, intramedullary nailing, surgical site infection

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MATERIALS AND METHODS

Fortyfour consecutive patients with either polyostotic fibrous dysplasia or McCune Albright syndrome who had undergone femoral and tibial intramedullary nailing between 1998 and 2016 were included in the study. At the admission to our hospital, 5 patients were wheel-chair bound, 24 had a limp, whereas 15 were fractured (8 femurs and 7 tibiae). Twentythree patients were male and 21 female. The mean age at intramedullary nailing was 18.8 years (range from 4 to 38.8 years). Seventeen patients had bimelic involvement and 27 monomelic, whereas in 5 the pelvis was diffusely involved. A total of 91 skeletal segments (femurs or tibiae) were surgically treated by intramedullary nailing; 64 had an intramedullary nailing of the femur and 37 of the tibia.

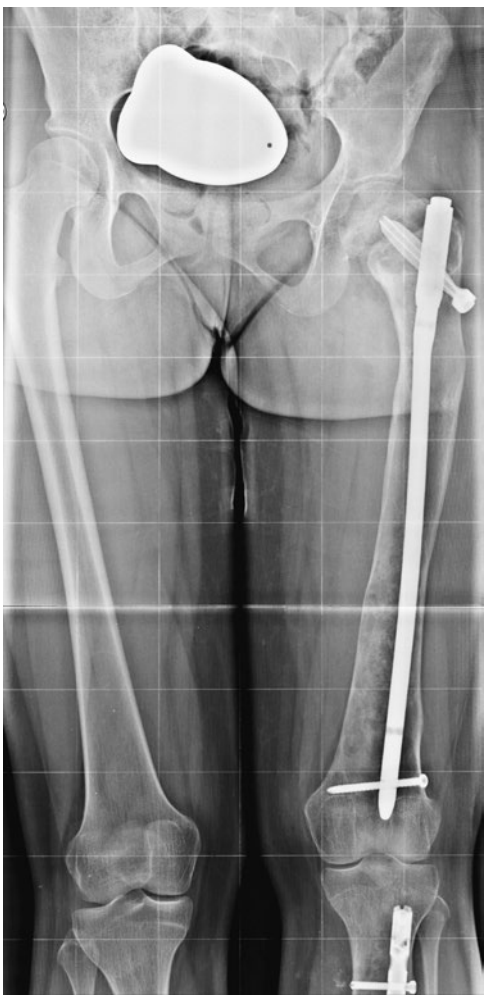

Fig. 1: *Radiographic examination of a 13-year-old patient affected by polyostotic fibrous dysplasia with monomelic involvement of the left femur and tibia. A limb length inequality is present. She was treated by shortening osteotomy of the right unaffected femur stabilized with intramedullary nail. A surgical site infection was observed during the first month after surgery. The patient was successfully treated by accurate surgical debridement plus pulse irrigation and antibiotic therapy.*

Prophylactic antibiotic was administered before all surgeries. According to our classification of the femoral deformities (7, 8) nine were type 1, two type 3, twentyfive type 4, four type 5 and sixteen type 6. For femoral fixation a cervicodiaphyseal nail with diameter from 9 to 11 mm with a spiral blade for femoral neck stabilization was used whereas interlocking nails ranging in diameter from 8 to 10 mm were used for tibial fixation. Either TENS or humeral nails were used in younger children according to their femoral and tibial size. Femoral and tibial deformities were corrected by a minimum of one to a maximum of three osteotomies, and 14 of the 16 type 6 femoral deformities had a two-stage procedure (9). Estimated blood loss (EBL) for femoral intramedullary nailing ranged from 500 to 3000 ml, while from 200 to 600 ml for tibial nailing.

All the patients gave us their informed consent to be included in the study. Thirty-two patients came to the hospital for clinical and radiographic follow-up evaluation. Twelve patients were contacted by e-mail. In all patients we checked for possible post surgical site and late infections until the final follow-up examination.

RESULTS

The mean age at follow-up was 31.2 years, while the mean length of follow-up was 7.6 years. All but 3 femurs and 2 tibiae were fully grown at the time of the last follow up. Twenty-four patients had a normal gait; sixteen a mild to moderate limp; three a severe limp whereas one patient was unable to walk. Pain was absent in 34 patients and still present in 10. ROM limitation was present in 18 hips; 5 knees, and 4 ankles. Leg-length discrepancy ranging from 1 to 4.5 cm was present in 21 patients but only 12 of them used a shoe lift. Of the 91 surgical procedures, we observed the following complications: 3 femoral non-unions, 5 delayed unions, 6 extrusions of the spiral blade, 3 re-fractures and 3 common peroneal

nerve palsies in tibial varus osteotomies, 2 of which recovered spontaneously.

We never observed any post surgical infective complication; none of the patients developed any late infection till the latest follow-up. We observed a post surgical infection in a patient with monomelic involvement at the contralateral non affected limb, which was surgically treated for a limb length inequality, by femur shortening osteotomy stabilized by an intramedullary nail. The patient was successfully treated by surgical debridement plus pulse irrigation (10) and antibiotic therapy (Fig. 1-3).

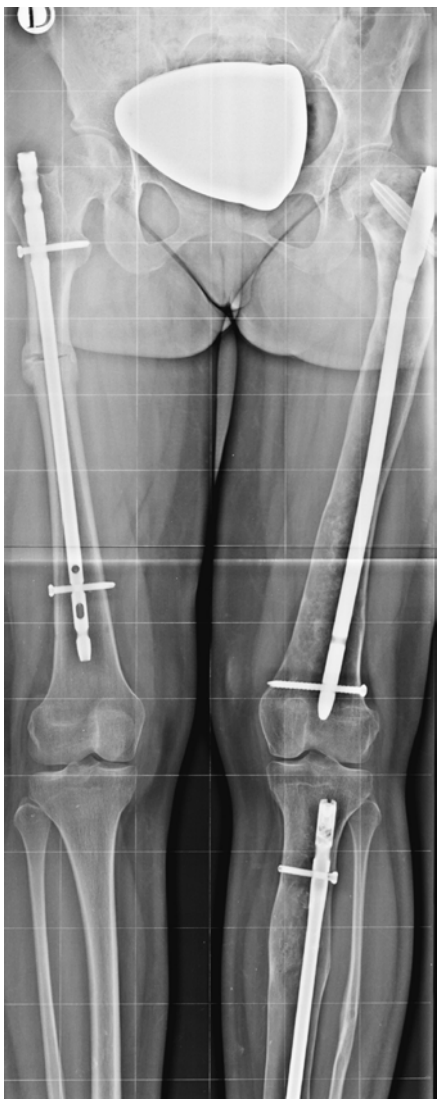

Fig. 2. *Radiograpghic examination of the same patient, three months after surgery. The osteotomy is still healing.*

DISCUSSION

Intramedullary nailing is the surgical procedure of choice for stabilizing corrected deformities and fractures in patients with polyostotic fibrous dysplasia. Rigid intramedullary nails are generally preferred in adults and adolescents because they provide a more stable fixation, while elastic nails are used in childhood to avoid damage of the physes. This method of treatment generally allows high union rates and low complications related to the complexity of the surgical treatment (11, 12).

Surgical site infection in intramedullary nailing as well as in prosthetic infection (13, 14) is considered a serious and difficult to eradicate complication that in the majority of the cases (chronic infections) requires hardware or prosthetic implant removal. On the contrary, early infections may be resolved without nail or implant removal, but by performing an accurate debridement and specific intravenous antibiotic treatment (4, 5). Moreover, infections in orthopaedic surgery require a very expensive treatment and pose an important economic impact for the healthcare system (15).

The reported incidence of infection after intramedullary nailing performed in femur and tibia fractures ranges from 0,9% to 23%, including patients with open fractures (16, 17). Some of these fractures were previously temporary stabilized with an external fixator. A recent study reported an incidence of surgical site infection in femoral and tibial closed and open fractures of 11.8% (4). On the contrary, the infection rate reported in large series of only closed femoral shaft fractures treated by intramedullary nails is much lower, ranging from 1% to 3,8% (5, 18). Duan et al (19) in a systematic review (Cochrane database) reported an incidence of surgical site infection in reamed intramedullary nailing for tibial shaft fractures of 3.8%. This value was slightly lower (3.2%) in unreamed nailing.

To the best of our knowledge, only few papers reported the incidence of surgical site infection in patients affected by polyostotic fibrous dysplasia or McCune-Albright syndrome (20-25). Freeman et al (20) reported no infections in 4 cases of polyostotic fibrous dysplasia surgically treated by osteotomies

stabilized with Zickel nail, followed up for an average of 34.5 months after surgery. Jung et al (21) reported no infections in 7 intramedullary nail stabilized osteotomies, followed-up 30 months after surgery. Yang et al (22) reported a retrospective study conducted on 13 patients operated on for Shepherd's crook deformity caused by fibrous dysplasia (14 femurs), stabilized after valgus osteotomy with an intramedullary nail.

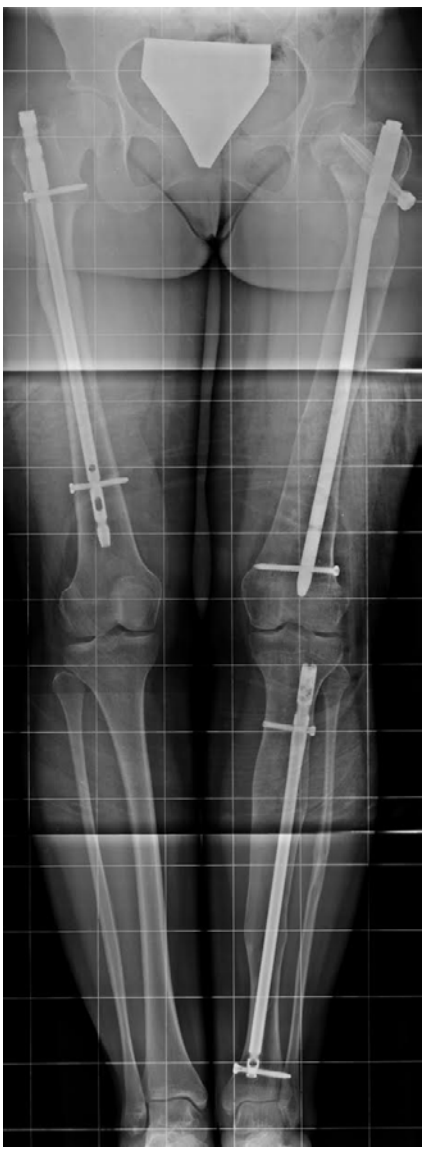

Fig. 3. *Radiograpghic examination of the same patient, at the last follow-up, two years after surgery. The osteotomy is completely healed with an acceptable rebalance of the leg length discrepancy. No signs of infection are present.*

The authors did not report a single case of surgical site infection. Hefty et al (23) reported a new technique for a special intramedullary nail performed in 15 cases followed up 54.2 months after surgery, without any surgical site infection. Kushare et al (24) reported 24 cases surgically treated for deformities or fractures in patients affected by polyostotic fibrous dysplasia. They performed intramedullary nailing in 15 cases and no infection was observed; however they reported only one surgical infection in a patient treated by curettage and bone grafting. Infections are uncommon also in patients with fibrous dysplasia that undergo maxillo facial surgery; Valentini et al (25) reported only one infection in a large series of 95 patients who underwent 68 surgical procedure for craniomaxillofacial fibrous dysplasia. The infection resolved with antibiotics.

We report a very large series of intramedullary nailing of femur and tibia in patients affected by polyostotic fibrous dysplasia, some of them with McCune Albright syndrome, without never observing any surgical site infection. The patients were followed up for an average of 7.6 years and we never observed any late infection either. We believe that the absence of surgical or late infection in intramedullary nailing performed in patients with this disease could be explained by the rich blood supply of fibrodysplastic bone.

This high vascularization of the fibrodysplastic tissue may provide some degree of protection from infection by increasing the local concentration of antibiotic administered for prophylaxis before surgery. It is surprising that no infections were observed in this kind of patients, expecially those that underwent corrective osteotomy, which needs a large surgical exposure and a long time of surgery, that represent two important risk factors for infection.

It is equally surprising that the only post surgical infection in our series was observed in a patient with monomelic involvement at the contralateral non affected limb, which was surgically treated by femur shortening osteotomy stabilized by an intramedullary nail.

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This study was approved by the ethics committee

of Policlinico Tor Vergata, Rome; the patient was informed about the study and consented to participate. The data of the manuscript are available.The authors declare that there is no conflict of interest regarding the publication of this paper. No funds have been received by the authors.

REFERENCES

1. Ippolito E, Bray EW, Corsi A, et al, European Pediatric Orthopaedic Society. Natural history and treatment of fibrous dysplasia of bone: a multicenter clinicophatologic study promoted by the European Pediatric Orthopaedic society. J Pediatr Orthop B.2003; 12:1848-64.
2. Di Caprio MR, Enneking WF. Fibrous dysplasia. Pathophysiology, evaluation, and treatment. J Bone Joint Surg Am. 2005; 87:1848-64.
3. Leet AI, Collins MT. Current approach to fibrous dysplasia of bone and McCune-Albright syndrome. J Child Orthop. 2007; 1:3-17.
4. Oliveira PR, Leonhardt MC, Carvalho VC, Kojima KE, Silva JS, Rossi F, Lima ALL. Incidence and risk factors associated with infection after intramedullary nailing of femoral and tibial diaphyseal fractures: Prospective study. Injury. 2018; 49:1905-11.
5. Ricci WM, Gallagher B, Haidukewych GJ. Intramedullary nailing of femoral shaft fractures: current concepts. J Am Acad Orthop Surg. 2009; 17:296-305.
6. Farsetti P, De Maio F, Potenza V, et al. Lower limb lengthening over an intramedullary nail: a long-term follow-up study of 28 cases. J Orthop Traumatol. 2019; 10:20-30.
7. Ippolito E, Farsetti P, Boyce AM, Corsi A, De Maio F, Collins MT. Radiographic classification of coronal plane femoral deformities in polyostotic fibrous dysplasia. Clin Orthop Relat Res. 2014; 472:1558-67.
8. Ippolito E, Valentini MB, Lala R, De Maio F, Sorge R, Farsetti P. Changing Pattern of Femoral Deformity During Growth in Polyostotic Fibrous Dysplasia of the Bone: An Analysis of 46 Cases.J Pediatr Orthop. 2016; 36:488-93.
9. Ippolito E. Farsetti P, Benedetti Valentini M, Potenza V. Two-stage surgical treatment of complex femoral deformities with severe coxa vara in polyostotic fibrous dysplasia. J Bone Joint Surg Am 2015; 97:119-25.
10. De Luna V, Mancini F, De Maio F, Bernardi G, Ippolito E, Caterini R. Intraoperative Disinfection by Pulse Irrigation with Povidone-Iodine Solution in Spine Surgery. Adv Orthop 2017; 2017:7218918.
11. Ippolito E, Caterini R, Farsetti P, Potenza V. Surgical treatment of fibrous dysplasia of bone in McCune–Albright Syndrome. J Pediatr Endocrinol Metab 2002; 15:939-44.
12. Benedetti Valentini M, Ippolito E, Catellani F, Farsetti P. Internal fixation after fracture or osteotomy oft he femur in young children with polyostotic fibrous dysplasia. J Pediatr Orthop B. 2015; 24:291-5.
13. Ascione T, Pagliano P, Balato G, Mariconda M, Rotondo R, Esposito S. Oral Therapy, microbiological Findings, and comorbidity influence the outcome of Prosthetic Joint Infections undergoing 2-stage exchange. J Arthroplasty 2017; 32: 2239-43.
14. Balato G, Franceschini V, Ascione T, Lamberti A, Balboni F, Baldini A. Diagnostic accuracy of synovial fluid, blood markers, and microbiological testing in chronic knee prosthetic infections. Arch Orthop Trauma Surg 2018; 138:165-71.
15. Efremov K, Benedetti Valentini M, De Maio F, Potenza V, Caterini R, Farsetti P. Periprosthetic hip and knee infections: comparison of etiology, perioperative management and costs. Eur Rev Med Pharmacol Sci. 2019; 23 (suppl 2):217-223
16. Winquist RA, Hansen ST, Clawson DK. Closed intramedullary nailing of femoral fractures. A report of five hundred and twenty cases. J Bone Joint Surg Am 1984; 66: 529-39.
17. Galvin JW, Dannenbaum JHT, Tubb CC, Poepping TP, Grassbaugh JA, Arriongton ED. Infection rate of intramedullary nailing in closed fractures of the femoral diaphysis after temporizing external fixation in an austere environment. J Orthop Trauma 2015; 29: e316-20.
18. Malik MH, Harwood P, Diggle P, Khan SA: Factors affecting rates of infection and non union in intramedullary nailing. J Bone Joint Surg Br. 2004; 86:556-560.
19. Duan X, Al-Qwbani M, Zeng Y, Zhang W, Xiang Z. Intramedullary nailing for tibial shaft fractures

in adults. Cochrane Database Syst Rev. 2012; 1:CD008241.
20. Freeman BH, Bray EW and Meyer LC. Multiple osteotomies with Zickel nail fixation for polyostotic fibrous dysplasia involving the proximal part of the femur. J Bone Joint Surg Am. 1987; 69:691-98.
21. Jung S.T, Chung J.Y, Seo H.Y, Bae B.H and Lim K.Y. Multiple osteotomies and intramedullary nailing with neck cross-pinning for shepherd's crook deformity in polyostotic fibrous dysplasia.Acta Orthopaedica 2006; 77:469-73.
22. Yang L, Jing Y, Hong D, Chong-Qi T. Valgus osteotomy combined with intramedullary nail for Shepherd's crook deformity in fibrous dysplasia: 14 femurs with a minimum of 4 years follow-up. Arch Orthop Trauma Surg 2010; 130:497-502.
23. Hefti F, Donnan L, Krieg AH. Treatment of shepherd's crook deformity in patients with polyostotic fibrous dysplasia using a new type of custom made retrograde intramedullary nail: a tecnical note. J Child Orthop 2017; 11:64-70.
24. Kushare IV, Colo D, Bakhshi H, Dormans JP. Fibrous dysplasia of the proximal femur: surgical management options and outcomes. J Child Orthop 2014; 8:505-11.
25. Valentini V, Cassoni A, Marianetti TM, Terenzi V, Fadda MT, Iannetti G. Craniomaxillofacial fibrous dysplasia: conservative treatment or radical surgery? A retrospective study on 68 patients. Plast Reconstr Surg. 2009; 123:653-60.

Staphylococcus Aureus Panton-Valentine Leukocidin causing hip osteomyelitis, thrombophlebitis and necrotizing pneumonia in an immuocompetent child

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Panton-Valentine leukocidin (PVL) represents an important virulence factor for many strains of Staphylococcus aureus. PVL is an esotoxin causing leucocyte destruction and tissue necrosis. We report on a case of osteomyelitis involving the hip joint with thromblophlebitis complicated by necrotizing pneumonia and life-threatening septic shock. The child required advance respiratory support for 14 days with circulatory support for 7 days in ICU (intensive care unit), surgical draninage via arthrotomy of hip joint and second-line antibiotic treatment for 1 month. Among a wide literature, in Europe over half of Panton-Valentine St. Aureus (PVL-SA) is MSSA. Investigations for PVL are not always available determining an under-recognition of the episodes. Data on prevalence of PVL-SA in Italy are scarce. With this clinical report, we emphasize the recognition of clinical features that must lead to suspect PVL-SA osteomyelitis in children, providing their adequate management.

Panton-Valentine leucocidin (PVL) is a pore-forming heptameric toxin composed of two components, LukS-PV and LukF-PV, leading to lysis of neutrophil, monocytes, and macrophages. PVL gene (lukS/F-PV) can be expressed both by community-acquired methicillin-resistant and methicillin-sensible St. Aureus (MRSA, MSSA) (1,2). In the United States, PVL positive S. aureus (PV-SA) accounted for up to two-thirds of S. aureus related acute pediatric hematogenous osteomyelitis, mostly MRSA stains (3). Moreover, PVL toxin is linked strongly with community-aquired staphylococcal disease, mainly meticillin-resistant associated with a PVL-producing clone, ST8/USA300.

In Europe instead, despite low rate of acquired MRSA described, PVL producing S. aureus isolates are increasingly reported (4). Concerning SA soft tissue and skin paediatric infections, Barrios Lopez et al. reported an incidence of PV-SA of 32% and only 9% of which were MRSA (5). Prevalence of PV-SA is debated in Italy. Recently Chiappini et al. described PVL producing stains in two cases out of a total of 121 children (6). It has been reported that PLV-positive Staphilococcus Aureus (SA) can cause more severe and more susceptible of serious complications diseases and needs most frequently surgical treatment. A severe course of the disease must lead to suspect PLV production.

We report on a case of osteomyelitis involving the hip joint with concomitant external iliac vein thromblophlebitis complicated by necrotizing pneumonia and life-threatening septic shock. The child required advance respiratory support for 14 days with circulatory support for 7 days in ICU (intensive

Key words: osteomyelitis, child, Staphylococcus Aureus infection

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care unit), surgical drainage via arthrotomy of the hip joint, treatment of deep venous thrombosis and advance antibiotic treatment for 1 month.

Recognition of clinical features related to PVL-SA pediatric osteomyelitis and testing for such toxin, can enhance the quality of management, including deep vein thrombosis study, with a better outcome.

Case report

A previously healthy three years old child of Kenyan origin was admitted to the emergency department of our hospital. He complained of hip pain after accidentally falls off the slide and was initially discharge to the home with anti-inflammatory therapy. Due to the onset of hyperpyrexia (body temperature > 39 °C), the child was again led to hospital. At the physical examination the child was suffering and tachypneic, the left coxo-femoral joint appeared swelled with pain on active and passive mobilization. Blood examination revealed anemia (Hemoglobin = 8.6 g/dl), leucopenia (L 1.730/mmc, N 780/mm3), thrombocytopenia (Platelet count of 113.000/mmc), markedly increased flogosis markers (CRP was 210 mg/l, n.v.<5) and increased D-dimer. An X-ray of the affected joint and the chest were performed. These demonstrated phlogosis with irregularity and thickening of the femoral metaphysis, and a bilateral reticulo-nodular pattern in the lungs with a consolidation in the left apical site. He was admitted with a diagnosis of septic arthritis, so empirical antibiotic therapy was started with Vancomycin and Gentamicin.

One day after admission, the general clinical conditions worsened with onset of lethargy, paralytic ileus and metabolic acidosis. So, with the diagnosis of suspected septic shock, the child was transferred to the Intensive Care Unit where inotropic and vasopressor treatments and invasive ventilation were required.

A total body CT scan highlights presence of: a fluid collection (12 x 5 mm) anterior to the left femoral head with thrombosis of the homolateral external iliac vein, extended up to the common femoral vein upstream of the sapheno-femoral cross extended; some areas of confluent parenchymal consolidations in the superior lobe of the left lung and in the inferior lobe of the right lung and widespread nodules compatible with pneumatocele. Anticoagulant therapy with enoxaparin sodium has been started. It was therefore decided to modify the antibiotic therapy, replacing Gentamicin with Amikacin and starting Piperacillin-Tazobactam, with the continuation of Vancomycin, considering the positivity of blood culture for Staphylococcus aureus MSSA received in the meantime.

In the following days, there was a further worsening of the clinical conditions, such as to require ventilation in HFOV, administration of endotracheal surfactant and iNO. It was therefore decided to further modify the antibiotic therapy, replacing Piperacillin-Tazobactam and Amikacin with Clindamycin. Furthermore, given the critical conditions and the absence of improvement, despite an appropriate antibiotic therapy, according to the antibiogram, it was decided to research the Toxin Panton-Valentine-Leukocidin on peripheral blood sample, with a positive result. Vancomycin and Clindamycin were suspended and Meropenem, Linezolid, Oxacillin were started, with a good response and progressive improvement of clinical conditions.

The child was subsequently subjected to surgical drainage via arthrotomy and joint washing of ankle joint. Two days after the surgery the CRP was decreased from the previous value of 50.8 mg/l to 18.5 mg/l and it turned negative in the next 20 days. Three months after the diagnosis the MRI and radiography of the hip bone showed a noticeable improvement with conserved articular relationships. The ultrasound exam of the iliac and femoral vessels demonstrates the disappearance of the previously described thrombus.

DISCUSSION

Shallcross et al in a meta-analysis including 76 studies evidenced a higher need for surgery in skin infection by PVL producer stains respect to PVL-negative infections (4). In PVL-positive osteomyelitis, a more frequent resort to surgery has been explained in a study by Pannaraj PS el al (14 of 17 PVL-positive *vs* 2 of 7 PVL-negative,

p=0·02) (7). Our case demonstrates that the most important reduction of CRP (a main marker of therapeutic efficacy) can be achieved only after surgical debridement. Surgical treatment could not be possible at the beginning, due to lung involvement and the general conditions. Generally, a major risk of systemic complication and evolution in ARDS (Acute respiratory distress syndrome) and septic shock is well known in this disease and intensive care assistance must be considered.

In our patient, immediately on admission, a picture of septic shock appeared with concurrent diagnosis of septic arthritis. Therefore, suspecting the presence of septic embolism, blood colture and second-line imaging (CT) was performed. The result of the blood colture, considering the critical condition of the patient without any antibiotic efficacy on the fever, the lung involvement and the thrombosis of the homolateral external iliac vein made suspect the presence of a PVL-SA strain.

Martínez-Aguilar also evaluated a higher incidence of complications in these patients (such as orthopedic complications needing much surgical procedures and deep vein thrombosis). Respect to this late aspect, in his article is reported that ten of 33 PVL-positive cases vs none of 23 PVL-negative cases, (p=0·002) developed deep vein thrombosis (8).

Thrombosis is thought to be connected to lysis of neutrophils, able to activate platelets with the liberation of cytokines and HOCL. Moreover, PV toxin induce eterotipic aggregates between neutrophils and platelets, with a role in the multiorgan failure in septic shock. Recently Niemann et al studied the role of alfa-defensin, secreted by lysis of neutrophils, capable of activate platelets (9).

Enhanced inflammation with exalted cytokines production and altered coagulation allows the disease to become systemic (3).

Pathogenetic explanation of such mechanism is setting new therapy based upon antioxidants and resveratrol. Antimicrobic therapy is well known for β-lactams that could lead to an enhancement of PVL secretion, so Piperacillin administration was interrupted. Therefore, an antimicrobic therapy with molecules inhibiting protein synthesis is preferable. If MSSA is documented Oxacillin in association with Clindamycin, also for her good penetration in the lung, must be considered (10).

Linezolid in combination with Clindamycin represented in our report the successful antimicrobic strategy. Linezolid could represent a good solution, considering efficacy upon PVL-strains, bone penetration of the molecule and the possibility of orally administration after discharge to go home.

REFERENCES

1. Bakthavatchalam YD, Nabarro LEB, Ralph R, Veeraraghavan B. Diagnosis and management of Panton-Valentine leukocidin toxin associated Staphylococcus aureus infection: an update. Virulence 2017; 0. doi:10.1080/21505594.2017.1362532.
2. Takadama S, Nakaminami H, Sato A, Shoshi M, Fujii T, Noguchi N. Dissemination of Panton-Valentine leukocidin-positive methicillin-resistant Staphylococcus aureus USA300 clone in multiple hospitals in Tokyo, Japan. Clin Microbiol Infect 2018; 24(11):1211e1-1211.e7. doi:10.1016/j.cmi.2018.02.012.
3. Bocchini C. E, Hulten K G, Mason E. O. Jr, et al. Leukocidin genes are associated with enhanced inflammatory response and local disease in acute hematogenous Staphylococcus aureus osteomyelitis in children. Pediatrics 2006; 117(2):433-40. doi:10.1542/peds.2005-056654850.
4. Shallcross LJ, Fragaszy E, Johnson AM, Hayward AC. The role of the Panton-Valentine leucocidin toxin in staphylococcal disease: a systematic review and meta-analysis. Lancet Infect Dis 2013; 13(1):43-54. doi:10.1016/S1473-3099(12)70238-4.
5. Barrios López M, Gómez González C, Orellana MÁ, Chaves F, Rojo P. Staphylococcus aureus abscesses: methicillin-resistance or Panton-Valentine leukocidin presence? Arch Dis Child. 2013; 98(8):608-10. doi:10.1136/archdischild-2012-302695.
6. Chiappini E, Camposampiero C, Lazzeri S, Indolfi G, De Martino M, Galli L. Epidemiology and Management of Acute Haematogenous Osteomyelitis in a TertiaryPaediatric Center. Int J Environ Res Public Health. 2017; 14(5)E47. doi:10.3390/

ijerph14050477.

7. Pannaraj PS, Hulten KG, Gonzalez BE, Mason EO, Jr, Kaplan SL. Infective pyomyositis and myositis in children in the era of community-acquired, methicillin-resistant Staphylococcus aureusinfection. Clin Infect Dis. 2006; 43:953–960.
8. Martinez-Aguilar G, Avalos-Mishaan A, Hulten K, et al. Community-acquired, methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* musculoskeletal infections in children. Pediatr Infect Dis J. 2004; 23:701–706.
9. Niemann S, Bertling A, Brodde MF, et al. Panton-Valentine Leukocidin associated with *S. aureus* osteomyelitis activates platelets via neutrophil secretion products. Sci Rep. 2018; 8(1):2185. doi:10.1038/s41598-018-20582-z.
10. Hot Topic /Panton–Valentine leukocidin-positive Staphylococcus aureus: a position statement from the International Society of Chemotherapy International Journal of Antimicrobial Agents 51 2018; 16-25.

Diluted povidone-iodine irrigation prior to wound closure in primary and revision total joint arthroplasty of hip and knee: a review of the evidence

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Periprosthetic Joint Infection (PJI) of the Hip and of the Knee is a tremendous complication associated with high patient morbidity, cost, and increased health care resource utilization. Over the last few years, several perioperative strategies have been developed in the hopes of reducing the risk of early superficial and deep surgical site infection (SSI). One of the most performed intraoperative treatments to reduce the risk of SSI in total joint arthroplasty is the use of dilute povidone-iodine (DPI) irrigation prior to wound closure. For this reason, we believed a systematic review of the literature was needed to better understand the current literature on the efficacy of dilute betadine in reducing PJI. The search terms for this systematic review was performed for keywords "betadine", "povidone-iodine", "lavage", "irrigation" and "arthroplasty". A total of six studies were included, four of these reported the outcome of primary total joint arthroplasty, and two of these reported the outcome of revision total joint arthroplasty. Some studies reported that the use of DPI is effective to reduce the incidence of infective complications, meanwhile other studies did not find differences when DPI was used. More studies must be addressed to provide the efficacy of DPI irrigation.

Periprosthetic Joint Infection (PJI), represents a devasting complications after total knee arthroplasty (TKA) and total hip arthroplasty (THA). While the incidence of failure secondary to dislocation, osteolysis, and aseptic loosening have gradually declined, the burden of PJI at both hip and knee remains constant and increasing in overall number each year (1).

Between 2001 and 2009 in the United States, using the International Classification of Disease (ICD-9), 2.4% of TJA patients develop PJI at an annual cost of more than 300 million dollars per year (1 ,2). Recent guidelines (The Second International Consensus Meeting on orthopedic infections and Global Guidelines for the Prevention of Surgical Site Infection), including recommendations following the International Consensus on Orthopedic Infections, suggest that the use of intraoperative irrigation with antiseptic solution could potentially reduce the risk of post-operative infection (4, 5).

As highlighted by the international consensus meeting on PJI, the use of dilute povidone-iodine (DPI) irrigation before wound closure is well studied in other medical and surgical specialties (5), but only few studies have been were performed in Orthopedic surgery, and more specifically, arthroplasty. (6, 7). These studies concluded that when DPI irrigation is performed before wound closure there is a significant reduction in the rate of early PJI (8).

For the prevention of PJI, many authors (9, 10), suggest to prepare the DPI solution by mixing 30 mL

Keywords: betadine lavage, povidone-iodine lavage

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of povidone-iodine with 1 L of 0.9% saline solution in a sterile splash basin, and apply the DIP before the fascial closure for up to 3 minutes. After that time, the remaining the soak must be cleaned with 1 L of normal saline solution to remove the remnants of the PDI solution.

Currently, only few clinical studies were reported on the outcome of patients that underwent total joint arthroplasty of the hip and of the knee using the DPI irrigation protocol (10-15). Four studies reported the outcome, with post-operative infection as the primary endpoint of patients that underwent primary TKA and THA (10-13), while two studies (14, 15), reported the outcome of patients that underwent revision TKA and THA.

MATERIALS AND METHODS

The search was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria (16) on the Unites State National Library of Medicine (PubMed/MEDLINE), for studies published from January 2000 to September 2019. The terms "betadine", "povidone-iodine", "lavage", "irrigation" and "arthroplasty" were utilized in various combinations using AND/OR Boolean operators.

Inclusion criteria were any original research study in which povidone-iodine was used prior to wound closure after implantation of primary or revision total joint replacement of the hip and of the knee. Case reports, surgical technique reports, *in vitro* studies, book chapter, and abstracts from scientific meetings were not included.

Two independent reviewers (GC and IDM) separately conducted the articles search by initially screening title and abstract. If the title and abstract provided sufficient information about the appropriateness to be included in the review, the full text was analyzed. In addition, a cross-reference check was performed looking for any additional studies. In case of disagreement between the two-authors a third author (SPK) was consulted and consensus was reached. The following information were collected from each study: first author, year of publication, study design, if there were included primary or revision total joint replacement and the number of patients.

Table I. *studies that reported reoperation due to infection as endpoint of patients in which diluted povidone-iodine irrigation was used.*

First Author	Year of Pub.	Study Design	Primary or Revision	n° of patients	Evidence
Brown et al.	2012	Retrospective	Primary	688	Higher infection Incidence in Non Povidone-Iodine group
Frisch et al.	2017	Retrospective	Primary	386	No differences for for non-surgical site infection, for suoperficial site infection and deep infection
Hernandez et al.	2019	RCT	Primary	11738	Higher infection reoperation rate after 1 year in the Povidone-Iodine group
Calkins et al.	2019	RCT	Revision	457	Lower incidence of postoperative infection at 90 days in the povidone-iodine group
Hart et al.	2019	RCT	Revision	2884	No differences between the two groups
Driesman et al.	2019	Retrospective	Primary	2386	No differences between the two groups

RESULTS

The search resulted in 48 abstract that were examined to determine the efficacy of using povidone-iodine lavage before wound closure in primary and revision TKA and THA. Following duplicate articles elimination, and after applying inclusion and exclusion criteria, a total of six studies were included for the final analysis. Four of these reported the efficacy of povidone-iodine lavage in primary total joint arthroplasty (15198 primary total joint arthroplasty) and two of these reported the efficacy of povidone-iodine lavage in revision total joint arthroplasty (3341 revision total joint arthroplasty).

Evidence of using Dilute Povidone-Iodine Lavage in primary total joint arthroplasty

Brown et al. 2012 (10), have evaluated the efficacy of dilute betadine solution (0.35%) lavage for three minutes after implantation of the prosthetic component, followed by pulsatile lavage with 1L of saline solution. They compared a group of 688 TJA (272 THA and 414 TKA) in which the Dilute Povidone-Iodine (DPI) Lavage protocol was used, with a group of 1862 TJA (630 THA and 1232 TKA) in which the Povidone-Iodine Lavage protocol was not used. They documented that the non-DPI group of patients showed a significant higher rate of acute post-operative deep infection (0.97% vs 0.15%, $p = 0.04$) compared with the group in which the Povidone-Iodine solution was used.

The most frequent micro-organism isolated in the Non-Dilute Povidone group was *S. Aureus* (eleven of eighteen cases) in both knee and hip patients. Frisch et al. 2017 (11), performed a retrospective review on prospectively collected data of 906 TJA. In 664 THA underwent an intraoperative irrigation with 0.9% saline solution followed by a 2-minute soak with < 2% dilute povidone-iodine solution which was washed out before wound closure. In 386 TJA the intraoperative washout was performed with 0.9% saline and periodic 0.05% CHG solution (Irrisept, Irrimax Corporation, Innovation Technologies, Inc. Lawrenceville, GA) followed by a final 1-minute soak in CHG with immediate closure afterward.

They found no statistically significant differences between the groups for non-surgical site infection ($p = 0.125$), superficial surgical site infection ($p = 0.913$) and deep surgical site infection ($p = 0.534$). Hernandez et al 2019 (12), analyzed a cohort of 11.738 TJA (5.534 THA and 6.204 TKA), looking for the difference in rate of reoperation after 3 months and 1 year. In 3732 cases (31.8%, 1322 THA and 2410 TKA) prior to closure the wound was irrigated with 1L of 0.25% Povidone-Iodine solution.

They discovered a similar reinfection rate either after 3 months for hip and knee ($p = 0.7$ for primary THA, $p = 0.06$), and found no significant difference regarding the reoperation rate for infection at 1 year that resulted similar between those who received dilute PI irrigation (0.7%) and those who did not (0.9%) ($p=0.06$). Driesman et al (13), evaluated 2386 patient who underwent TJAs operation between 2017 and 2018. A total of 1159 primary TKAs and THAs were performed with chlorhexidine gluconate (Irresept) for all intraoperative antiseptic lavages while 1227 TKAs and THAs with the new sterile betadine wash. No significant difference was reported among the general characteristics of the two groups. PJI was diagnosed in 4 patients in the chlorhexidine gluconate was cohort compared to 7 patients in the betadine was cohort in the first 3 months (0.35% compared to 0.57%; $p= 0.61$). This trend was reported also at 1-year follow-up with 0.78% in the chlorhexidine group and 1.14% in the betadine group ($p= 0.48$). According to the results of this paper PJI rates were not affected when intraoperative washes used chlorhexidine gluconate instead of betadine.

Evidence of using Dilute Povidone-Iodine Lavage in revision total joint arthroplasty

Calkins et al. 2019 (14), performed a randomized controlled trials (RCT) of 457 revision TJA (297 revision TKA and 160 revision THA). The dilute Povidone-Iodine solution was prepared mixing 17.5 mL of betadine mixed with 500 mL of normal saline solution. After components implantation, the surgical wound was soaked with the dilute betadine solution for three minutes, followed by pulsatile lavage with 1 L of saline solution before wound closure.

In addition, they used 10% povidone-iodine solution to paint the wound edges. They found a significant lower incidence of post-operative infections after 90 days from the index arthroplasty in the Dilute Povidone-Iodine group (respectively 8 patients in the saline group and 1 patient in the betadine group, $p = 0.037$.

No significant difference for major wound complications in the two groups (respectively 3 patients in the saline group and 0 in the betadine group, $p = 0.248$). Hart et al. 2019 (15), performed a retrospective analysis of a single institution total joint registry, identifying 2884 revision TJA (1402 revision THAs and 1482 revision TKAs).

In 27% of revision THAs and in 35% of revision TKAs cases a three-minute wash of the wound with dilute povidone-iodine after components implant was used. No benefit with the use of dilute povidone-iodine solution was found, neither for the rate of reoperation for infection at 3 months ($p = 0.58$ for revision THA, and $p = 0.06$ for revision TKA) nor for reoperation for infection at 12 months ($p = 0.78$ for revision THA, and $p = 0.06$ for revision TKA).

DISCUSSION

Our review of the literature suggests that the use of dilute povidone-iodine during primary and revision TKA and THA could be an effective prophylactic procedure to reduce the risk of SSI and of PJI. Not all the reported studies founded a significant reduction in the post-operative development of septic complications, and more studies need to be performed to obtain a major consensus.

The estimated average hospital costs for the treatment of PJI is $31.753 and $25.692 for hip and knee respectively (17). Kerbel et al. (18), performed an economic model for determining cost effectiveness, based on a break-even analysis. This model defines the point when the cost of the infection preventing protocol is overcome by the cost of a new PJI. They considered the costs reported above as the cost of each revision, and $2.54 the cost of 17.5 mL of 10% povidone-iodine diluted solution and 500 mL of normal saline solution. Considering these costs, this protocol became effective for an infection rate of 1.10 for TKA and 1.62 for THA with an absolute risk reduction of 0.01% (cost effectiveness is justified if dilute povidone-iodine solution prevent one infection out 10 thousand surgeries).

PJI of the hip and knee is associated with a high incidence of mortality and morbidity (19-21). Often, PJI occurs within the first year from the index arthroplasty, and in 85% of cases within the first 30 days (19). Many studies have reported that intraoperative contaminations of the surgical wound are common (22). In the majority of cases, the most frequent micro-organism isolated is *Staphylococcus aureus* (23). Povidone-iodine solution at 10% has been used since many years as pre-operative antiseptic; Its mechanism of action involves the gradual release of free iodine when it comes at contact with tissues. Free iodine enters within the cell and expresses its oxidized power and bactericidal effects (24). Different concentration of Povidone-Iodine solutions has demonstrated an excellent broad-spectrum effect, and, against *Staphylococcus Aureus* either in vitro (24) and in vivo studies (25). DIP demonstrated to have a very low cytotoxicity for human tissues, compared to other antiseptics as chlorhexidine, ethanol and polyexhanide (26).

There are only few studies that report the outcomes of patients that underwent primary and revision TJA of hip and of knee using a DPI irrigation protocol. DPI irrigation is a cost-effective and safe procedure to prevent PJI. However, while the use of DPI irrigation has reduced the incidence of post-operative infections in some studies, other studies have demonstrated that there were no differences after DPI. More studies with a higher level of evidence must be addressed to demonstrate the true efficacy of DPI irrigation in prevention of PJI of hip and of knee reconstruction surgery.

REFERENCES

1. Kurtz SM, Lau E, Watson H, Schmier JK, Parvizi J. Economic burden of periprosthetic joint infection in the United States. J Arthroplasty. 2012; 27(8 Suppl):61-5.e1.
2. Kurtz SM, Lau E, Watson H, Schmier JK, Parvizi J. Economic burden of periprosthetic joint infection

in the United States. J Arthroplasty. 2012; 27(8 Suppl):61-5.e1..
3. Global Guidelines for the Prevention of Surgical Site Infection. Geneva: World Health Organization; (2018).
4. Blom A, Cho J, Fleischman A, Goswami Ket al. General Assembly, Prevention, Antiseptic Irrigation Solution: Proceedings of International Consensus on Orthopedic Infections. J Arthroplasty. 2019; 34(2S):S131-S138.
5. De Luna V, Mancini F, De Maio F, et al. Intraoperative Disinfection by Pulse Irrigation with Povidone-Iodine Solution in Spine Surgery. Adv Orthop. 2017; 2017:7218918.
6. Goswami K, Austin MS. Intraoperative povidone-iodine irrigation for infection prevention. Arthroplast Today. 2019; 5(3):306-8.
7. Chundamala J, Wright JG. The efficacy and risks of using povidone-iodine irrigation to prevent surgical site infection: an evidence-based review. Can J Surg. 2007; 50(6):473-81.
8. Ruder JA, Springer BD. Treatment of Periprosthetic Joint Infection Using Antimicrobials: Dilute Povidone-Iodine Lavage. J Bone Jt Infect. 2017; 2(1):10-14.
9. Brown NM, Cipriano CA, Moric M, Sporer SM, Della Valle CJ. Dilute betadine lavage before closure for the prevention of acute postoperative deep periprosthetic joint infection. J Arthroplasty. 2012; 27(1):27-30.
10. Frisch NB, Kadri OM, Tenbrunsel T, Abdul-Hak A, Qatu M, Davis JJ. Intraoperative chlorhexidine irrigation to prevent infection in total hip and knee arthroplasty. Arthroplast Today. 2017; 3(4):294-97.
11. Hernandez NM, Hart A, Taunton MJ, et al. Use of Povidone-Iodine Irrigation Prior to Wound Closure in Primary Total Hip and Knee Arthroplasty: An Analysis of 11,738 Cases. J Bone Joint Surg Am. 2019; 101(13):1144-50.
12. Driesman A, Shen M, Feng JE, Waren D, Slover J, Bosco J, Schwarzkopf R. Preioperative Chlorhexidine Gluconate Wash During Joint Arthroplasty has Equivalent Periprosthetic Joint Infection Rates in Comparison to Betadine Wash. J Arthroplasty. 2019; In press
13. Calkins TE, Culvern C, Nam D, Gerlinger TL, et al. Dilute Betadine Lavage Reduces the Risk of Acute Postoperative Periprosthetic Joint Infection in Aseptic RevisionTotal Knee and Hip Arthroplasty: A Randomized Controlled Trial. J Arthroplasty. 2019; S0883-5403(19)30843-5.
14. Hernandez NM, Hart A, Taunton MJ, et al. Use of Povidone-Iodine Irrigation Prior to Wound Closure in Primary Total Hip and Knee Arthroplasty: An Analysis of 11,738 Cases. J Bone Joint Surg Am. 2019; 101(13):1144-50.
15. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Medicine (Internet). 2009; 6(7):e1000097.
16. Kamath AF, Ong KL, Lau E, Chan V, Vail TP, Rubash HE, et al. (2015) Quantifying the burden of revision total joint arthroplasty for periprosthetic infection. J Arthroplasty 2015; 30:1492e7.
17. Kerbel YE, Kirchner GJ, Sunkerneni AR, Lieber AM, Moretti VM. The Cost Effectiveness of Dilute Betadine Lavage for Infection Prophylaxis in Total Joint Arthroplasty. J Arthroplasty. 2019; 34(7S):S307-S311.
18. Lamagni T. Epidemiology and burden of prosthetic joint infections. J Antimicrob Chemother. 2014; 69 Suppl:i5-10.
19. Lum ZC, Natsuhara KM, Shelton TJ, Giordani M, Pereira GC, Meehan JP. Mortality During Total Knee Periprosthetic Joint Infection. J Arthroplasty. 2018; 33(12):3783-3788.
20. Ascione T, Pagliano P, Balato G, Mariconda M, Rotondo R, Esposito S. Oral Therapy, Microbiological Findings, and Comorbidity Influence the Outcome of Prosthetic Joint Infections Undergoing 2-Stage Exchange. J Arthroplasty. 2017; 32(7):2239-43
21. Jonsson EÖ, Johannesdottir H, Robertsson O, Mogensen B. Bacterial contamination of the wound during primary total hip and knee replacement. Median 13 years of follow-up of 90 replacements. Acta Orthop. 2014; 85(2):159-64.
22. Wang FD, Wang YP, Chen CF, Chen HP. The incidence rate, trend and microbiological aetiology of prosthetic joint infection after total knee arthroplasty: A 13 years' experience from a tertiary medical center in Taiwan. J Microbiol Immunol Infect. 2018; 51(6):717-22.
23. Oduwole KO, Glynn AA, Molony DC, et al. Anti-biofilm activity of sub-inhibitory povidone-iodine concentrations against Staphylococcus epidermid-

is and Staphylococcus aureus. J Orthop Res. 2010; 28(9):1252-6.
24. Anderson MJ, David ML, Scholz M, Bull SJ, Morse D, Hulse-Stevens M, Peterson ML. Efficacy of skin and nasal povidone-iodine preparation against mupirocin-resistant methicillin-resistant Staphylococcus aureus and S. aureus within the anterior nares. Antimicrob Agents Chemother. 2015; 59(5):2765-73.
25. Bigliardi PL, Alsagoff SAL, El-Kafrawi HY, Pyon JK, Wa CTC, Villa MA. Povidone iodine in wound healing: A review of current concepts and practices. Int J Surg. 2017; 44:260-8.

Intramedullary antibiotic coated nail in tibial fracture: a systematic review

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Implant-associated infections remain one of the main problems in trauma surgery, particularly for treatment of open tibial fractures. The role of systemic antibiotic prophylaxis is now established and accepted, but recent literature also seems to emphasize the importance of local antibiotic prophylaxis. Antibiotic coated nails play a crucial role, allowing at the same time the prevention of infections and favoring the stabilization of fractures. These devices appear to be a clinically effective and safe solution. The purpose of the study was to investigate the role of antibiotic coated nails in the treatment of tibia fractures. A literature review was performed on MEDLINE through PubMed to identify scientific publications relevant to the use of antibiotic coated nails in tibial fractures. Primary outcomes were infection rate and bone union rate. This review present numerous limits due primarily to the small number and different nature of studies published, the heterogeneity of the devices used.

Implant-associated infections, fracture fixation devices and total joint prostheses, remain one of the major problems in orthopedic and trauma surgery. Often requires multiple aggressive treatment, such as removal of implant, surgical debridement and long-term antibiotic therapy with long in-hospital stay and subsequent social and healthcare costs (1).

In consideration of tremendous consequences for the patient quality of life, there is a strong need to improve the prevention and treatment of infections, above all in traumatology. Indeed, rate infection in elective orthopedic surgery is usually low (0,7-4,2%), (2), but it increases in patients with fractures and especially in those with open fractures. Among all long bones fractures, open tibia fractures showed the highest rate of infection (8,8%) compared to closed fracture (2%), due to more extensive comminution, segmental bone loss and poorer vascularization (3, 4).

Risk factors associated with an high infection rate are: severity of soft tissue injury up to 14,4% in Gustilo-Anderson (GA) III grade (31% in GA IIIB&C type) (5, 6), trauma mechanism, polytrauma and primary external fixation, obesity, diabetes mellitus, smoking and chronic disease (7).

Intramedullary nailing is the gold standard for stabilization of tibia shaft fractures, with lower infection rate reported compared to external fixation or plating (8). Systemic administration of antibiotics is now widely accepted, which reduces the absolute risk of early wound infections of 60% (9). Nevertheless, systemic antibiotics administration may have limited efficacy in decreasing the risk of infection associated with the use of foreign metal-implant. In fact, bacteria can colonize the surface of the implant, forming a biofilm (glycocalyx) that protects them from the action of systemic antibiotic. In addition, systemically delivered antimicrobials may not reach adequate concentration at the desired site due to vascular damage.

Hence the idea and the development of alternative

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therapeutic approaches to implement systemic prophylaxis with a local administration of antibiotic. Several strategies for local antibiotic delivery have been developed: e.g. polymethylmethacrylate (PMMA) bone cement, PMMA beads, antibiotic-impregnated collagen sponges, polyglycolic acid, poly-DL-lactide (PDLLA) coated implants or hydroxyapatite coatings (10-12).

Recently systematic review and meta-analysis by Craig et al (5) has shown the benefit of local prophylactic antibiotic therapy, in addition to systemic antibiotics, to reduce infection rates in open tibia fractures treated with intramedullary nailing. The purpose of this study is to analyze, based on available literature, the use of antibiotic-coated intramedullary nails in the treatment of tibial fractures (open or closed).

MATERIALS AND METHODS

A literature review was performed on MEDLINE through PubMed (from inception to March 2019) to identify scientific publications relevant to the use of antibiotic coated nails in tibial fractures. There were no restrictions on the date of publication or language. To minimize the number of missed studies, no filters were applied to the search strategy. From title and abstracts, two authors independently selected studies for inclusion.

Studies with levels of evidence I, II, III and IV and all articles that recruit people of any age with tibia fractures treated with intramedullary antibiotic nail were included. No restrictions on surgical approach to nailing were applied. Exclusion criteria were studies on intramedullary nailing of other bone than the tibia, studies using antibiotic nails only in revision cases (e.g. osteomyelitis, bone defects, post-traumatic infected nonunions) and studies performed on animal models. Titles of journals, names of authors or supporting institutions were not masked at any stage. No attempt was made to contact authors for obtaining individual patient data.

Two authors independently extracted available data from the full text of all eligible studies using a piloted form. Information gathered included the following study characteristics: authors and year of publication, number of patients included and treated, demographic characteristics of the patients, number of patients with fresh fracture and/or revision case, type of fracture, type of implant used and duration of follow-up.

The following outcomes were considered as primary outcomes: infection rate and bone union rate. Each other outcome reported by every single study was considered as secondary outcome. Descriptive statistics was used to summarize findings across all included studies.

RESULTS

The electronic search resulted in 18 hits. Following the PRISMA flow chart (13), 5 studies were finally included in the review (7, 14–17) (Fig. 1).

Studies' characteristics and outcomes are reported in Table I. The included studies analysed 146 tibia fracture (fresh fractures and revision cases). The included studies are 2 retrospective case series, 2 prospective non-randomized case series and 1 case report. The length of follow-up ranged from 6 to 18 months across the studies. Different implant was used: an unreamed tibial nail (UTN) coated with PDLLA and gentamicin in 3 studies (14,15,17) and an expert tibia nail (ETN) coated with PDLLA and gentamicin in 2 studies (7,16). In all the studies the follow-up was conducted through clinical, radiographic and laboratory tests (markers of inflammation and infection).

Primary outcomes were evaluated as follows: for rate of infections, only two studies clearly show the classification used to define infections, that of Centers for Disease Control and Prevention (CDC) (7, 16). The Johnson method (18) was used to evaluate fracture healing in the 3 most recent studies included (7, 14, 16). Consolidated fracture healing was defined as the bridging of at least three of the four cortices in the anterior-posterior and lateral view on the tibia X-Ray.

Secondary outcomes included: clinical findings, subjective and objective functional evaluation scores, quality of life scores and revision surgery.

The first clinical data available are those of the pilot study of Schmidmaier et al (15). Eight patients with open tibia fractures have been treated with an unreamed tibial nail (UTN) coated with PDLLA and gentamicin.

At the one-year follow-up there were no signs of infection (in clinical, laboratory and radiographic examinations) and all fractures consolidated in

6 months. No further surgical procedures were required and no serum gentamicin levels were detected. Gentamicin was chosen as the antibiotic for its broad antimicrobial spectrum, covering most bacteria commonly involved in osteomyelitis and its bactericidal effect.

Also, Raschke et al (17), in their case report, have used a gentamicin coated nail (UTN-Protect) in a severe tibial fracture (GA grade IIIC). In this case, a gentamicin coated nail allowed limb salvage in 17-year-old man involved in a motor-scooter accident. This approach has avoided amputation or prolonged external fixation. Thirteen months after the initial injury, follow up X-ray shown complete bone consolidation and the patient's leg was free of any infectious sign. Obviously, the young age and good general clinical condition of the patient contributed to the success of this approach to his multiple injuries.

In a prospective, non-randomized case series, Fuchs et al (14) investigated the use of the UTN Protect in the surgical treatment of closed or open tibial fracture and in revision surgeries, for a total of 21 patients (12 with open fractures, of which 7 GA grade III).

No deep wound infections were observed in the 19 patients who completed follow-up at 6 months, only one patient had a superficial wound healing problem that required surgical debridment. Eleven of the 19 patients showed healed fractures. The authors also measured the SF-36 physical and mental score at 6 months after surgery, finding a physical score of 42.55 (range 19.35-56.68) and a mental score of 50.45 (range 27.48-64.98). A SF-36 of 50 ± 10 (mean ±standard deviation) is considered normal. The authors concluded that the use of gentamicin coated nail was associated with good clinical, radiological and laboratory outcomes after 6 months and this offered new options for the prevention of infections including revision cases.

Another study, by Metsemakers et al (7), has been the first retrospective evalution on a single-centre experience about the use of ETN Protect. Sixteen

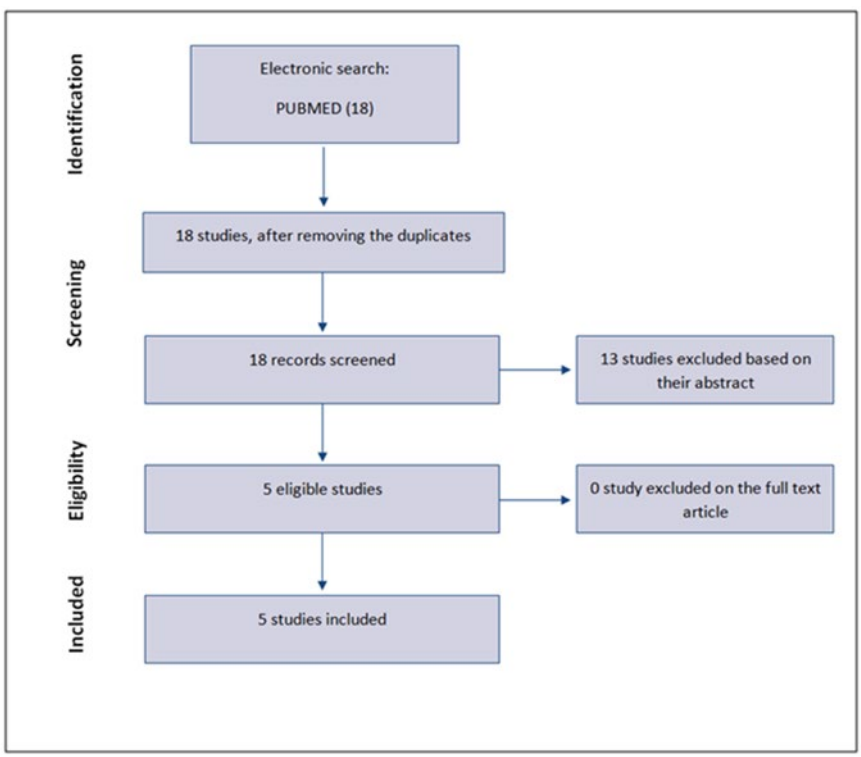

Fig. 1. *PRISMA flow chart.*

patients, 11 (68.8%) with acute open or closed tibia fractures and 5 complex revision cases in infected non-union (31.2%) with a mean of three prior surgical interventions, were treated with a gentamicin-coated intramedullary nail. In the group of acute fractures 9 of 11 (81.2%) were open tibia fracture classified according to GA classification (4 grade II, 2 grade IIIA, 3 IIIB). At 18 months follow-up, in both groups there were no patients diagnosed with a deep infection. On the other hand, 4 patients (3 acute fractures and 1 revision case) had a nonunion and other surgical procedure were necessary. Of these 4 patients 3 underwent a Masquelet procedure (19) and bony healing occurred without signs of infection.

Schmidmaier et al (16) prospectively were enrolled one hundred patients (99 treated with a gentamicin-coated nail) at four different centers in Germany. Sixty-eight suffered from a fresh fracture (33 closed fracture and 35 open fracture, of which 15 GA type III -3 IIIA; 9 IIIB; 3 IIIC) and 31 have undergone surgery for revision purposes (non-union due to infection). Infection was classified according to the Centers for

Table I. *data from the full text of all eligible studies.*

Author and year	Type of study	Implant	Treatment indications	Number of patients	Follow-up (months)	Infection rate	Bone union rate
Schmidmaier et al (2006) [15]	Retrospective case series	PDLLA and gentamicin-coated nails (UTN Protect)	Open tibial fractures	8	12	No infection	8/8
Raschke et al (2010) [17]	Case report	PDLLA and gentamicin-coated nails (UTN Protect)	Severe open tibial fracture (GA IIIC grade)	1	13	No infection	1/1
Fuchs et al (2011)[14]	Prospective case series	PDLLA and gentamicin-coated nails (UTN Protect)	Closed or open tibial fractures and tibia revision cases	21	6 (19 of 21 patients, 1 lost to follow-up and another patient underwent amputation per other reason)	No infection	11/19 complete healed, 8/19 partial union
Metsemakers et al (2015)[7]	Retrospective case series	PDLLA and gentamicin-coated nails (ETN Protect)	Acute tibia shaft fractures (11) or complex tibia fracture revision cases (5)	16	18	No infection	12/16 complete healed; 4 patients non-union: 1 infected non union, 2 GA IIIb , 1 GA II
Schmidmaier et al (2017)[16]	Prospective case series	PDLLA and gentamicin-coated nails (ETN Protect)	Acute open or closed tibia fractures (68) or non-union revision surgery (31)	100 (99 treated)	-87% at 12 months -82% at 18 months	- 4,5% for fresh fracture - 6,5% for revision cases	At 12 months: - 83,1% for fresh fracture -73,7% for revision cases

Disease Control and Prevention (CDC) (20).

During the period of the study 14 infections at the surgical site were reported, but most of these were superficial, instead deep infection or osteomyelitis occurred in six patients (4 of which in patients with fresh fracture and 2 in revision cases). Of the 4 infections in patients with fresh fractures, one occurred in an open GA type III B fracture in a patient who had alcohol abuse during the study (protocol violation) and therefore excluded from the study. At 12 months follow-up, based on available radiographic data, union was observed in 49 (83.1%) patients with fresh fracture and in 14 (73.7%) patient with revision surgery. The percentage of delayed healing was 11.9% in the first group and 21.1% in the second group, while the percentage of non-union was 5.1% and 5.3% respectively.

The EQ-5D and the SF-12 physical component score were used to evaluate the patient's quality of life and the WOMAC score and Iowa Ankle score to evaluate the functional outcome at 3 and 18 months after surgery. The EQ-5D overall score increased by 0.1 point between the 3 and the 18 months visit, and the SF-12 physical score improved by 10.5 points.

DISCUSSION

The present study has several limitations. Only few reliability studies were found. Some other limitations are the design of the included studies (one study is a case report) and the lack of use of the same classification system for the diagnosis of infections. The management of deep infections associated with implants remains an important challenge in the orthopedic and, above all, trauma surgery. The risk of deep wound infection is particularly elevated in fractures with severe soft tissue injury and vascular disruption (according with GA classification).

It seems clear the role of local prophylaxis in fracture fixation to prevent bacterial colonization and biofilm formation on the surface of implants. In recent years, the first clinically usable technologies for the local release of antibiotic substances have been made available, from bone cements with antibiotics, to collagen sponges or antibiotic-impregnated PMMA beads, up to antibiotic-coated nails. Some studies have investigated the use of PMMA bead chains impregnated with antibiotics, these were placed directly on the fracture site but required surgical removal after healing.

A PDLLA loaded with gentamicin offers sustained release kinetics and biodegradability, on the contrary of PMMA beads which must be removed after 4-6 weeks and collagen sponges which do not allow a continuous and controlled release of antibiotic (2).

Antibiotic coated nails allow at the same time the prevention/treatment of infections and the stabilization of fractures. As shown by the above studies the use of tibia nails coated with antimicrobial substances is associated with good clinical, laboratory and radiological results and represents a new option for infection prevention in fresh fracture and in revision cases.

Antibiotic nails allow the release and achievement of high doses of antibiotic at the fracture site, without interfering with the bone healing and consolidation (21). Moreover, they are associated with good systemic biocompatibility and safety and no reports in literature of documented allergies against gentamicin or PDLLA. All these studies showed no signs of local and/or systemic toxicity by gentamicin or other antibiotic used (22).

These coated implants may offer the advantage of a prompt release of antimicrobial agent (burst release with 80% of gentamicin within the first 48h) (23), with the achievement of elevated local concentrations of antibiotic for prolungated time. This reduce the exposure to sub-inhibitory concentrations with favorable effects on the develompment of resistance.

Metsemakers et al (7) published the first study with a cannulated intramedullary nail (ETN), unlike the historically solid-core nail (UTN). The advantages of the ETN are that reaming can be used before the introduction of the nail and the multiple options for proximal and distal locking. The disadvantage compared to solid-core nails is the greater "dead-space" which can increase the risk of infection, as shown by previous studies(24), but the "dip coating process" will also coated the inside of the nail and in this protect against biofilm formation. Moreover, reaming which can facilitate the introduction of larger more stable implants could

also have a negative influence on infection rates (25), but this seems to be prevented by the ETN in carefully selected patients.

In the present study, examined studies that focused on the use of tibia antibiotic-coated nails in fractures. A low rate of infection and a good rate of consolidation with the use of antibiotic nails in tibia fractures was found. These devices appear to be a clinically effective and safe solution, demonstrating their effect especially in patients suffering from fractures with severe soft tissue impairment.

REFERENCES

1. Poultsides LA, Liaropoulos LL, Malizos KN. The socioeconomic impact of musculoskeletal infections. J Bone Joint Surg Am 2010; 92:e13. https://doi.org/10.2106/JBJS.I.01131.
2. Fuchs T, Schmidmaier G, Raschke MJ, Stange R. Bioactive-Coated Implants in Trauma Surgery. Eur J Trauma Emerg Surg 2008; 34:60-8. https://doi.org/10.1007/s00068-006-6110-5.
3. Giannoudis PV, Papakostidis C, Roberts C. A review of the management of open fractures of the tibia and femur. J Bone Joint Surg Br 2006; 88:281–9. https://doi.org/10.1302/0301-620X.88B3.16465.
4. Struijs PAA, Poolman RW, Bhandari M. Infected nonunion of the long bones. J Orthop Trauma 2007; 21:507–11. https://doi.org/10.1097/BOT.0b013e31812e5578.
5. Craig J, Fuchs T, Jenks M, et al. Systematic review and meta-analysis of the additional benefit of local prophylactic antibiotic therapy for infection rates in open tibia fractures treated with intramedullary nailing. Int Orthop 2014; 38:1025–30. https://doi.org/10.1007/s00264-014-2293-2.
6. Gustilo RB, Anderson JT. JSBS classics. Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones. Retrospective and prospective analyses. J Bone Joint Surg Am 2002; 84:682. https://doi.org/10.2106/00004623-200204000-00029.
7. Metsemakers WJ, Reul M, Nijs S. The use of gentamicin-coated nails in complex open tibia fracture and revision cases: A retrospective analysis of a single centre case series and review of the literature. Injury 2015; 46:2433–7. https://doi.org/10.1016/j.injury.2015.09.028.
8. Lillo M, Ezzo OE, Cauteruccio M, Ziranu A, Santis VD, Maccauro G. Infections in primary intramedullary nailing of open tibial fractures: a review article. Eur Rev Med Pharmacol Sci. 2019; 23(2 Suppl):195-200.
9. Gosselin RA, Roberts I, Gillespie WJ. Antibiotics for preventing infection in open limb fractures. Cochrane Database Syst Rev 2004:CD003764. https://doi.org/10.1002/14651858.CD003764.pub2.
10. Aviv M, Berdicevsky I, Zilberman M. Gentamicin-loaded bioresorbable films for prevention of bacterial infections associated with orthopedic implants. J Biomed Mater Res A 2007; 83:10–9. https://doi.org/10.1002/jbm.a.31184.
11. McKee MD, Li-Bland EA, Wild LM, Schemitsch EH. A prospective, randomized clinical trial comparing an antibiotic-impregnated bioabsorbable bone substitute with standard antibiotic-impregnated cement beads in the treatment of chronic osteomyelitis and infected nonunion. J Orthop Trauma 2010; 24:483-90. https://doi.org/10.1097/BOT.0b013e3181df91d9.
12. Zhao L, Chu PK, Zhang Y, Wu Z. Antibacterial coatings on titanium implants. J Biomed Mater Res Part B Appl Biomater 2009; 91:470–80. https://doi.org/10.1002/jbm.b.31463.
13. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaborat... - PubMed - NCBI n.d. https://www.ncbi.nlm.nih.gov/pubmed/19622552 (accessed, 2019).
14. Fuchs T, Stange R, Schmidmaier G, Raschke MJ. The use of gentamicin-coated nails in the tibia: preliminary results of a prospective study. Arch Orthop Trauma Surg 2011; 131:1419–25. https://doi.org/10.1007/s00402-011-1321-6.
15. Schmidmaier G, Lucke M, Wildemann B, Haas NP, Raschke M. Prophylaxis and treatment of implant-related infections by antibiotic-coated implants: a review. Injury 2006; 37 Suppl 2:S105-112. https://doi.org/10.1016/j.injury.2006.04.016.
16. Schmidmaier G, Kerstan M, Schwabe P, Südkamp N, Raschke M. Clinical experiences in the use of a gentamicin-coated titanium nail in tibia fractures. Injury 2017; 48:2235–41. https://doi.org/10.1016/j.

injury.2017.07.008.

17. Raschke M, Vordemvenne T, Fuchs T. Limb salvage or amputation? The use of a gentamicin coated nail in a severe, grade IIIc tibia fracture. Eur J Trauma Emerg Surg 2010; 36:605–8. https://doi.org/10.1007/s00068-010-0017-x.
18. Repair of segmental defects of the tibia with cancellous bone grafts augmented with human bone morphogenetic protein. A preliminary report. - PubMed - NCBI n.d. https://www.ncbi.nlm.nih.gov/pubmed/3052977.
19. Careri S, Vitiello R, Oliva MS, Ziranu A, Maccauro G, Perisano C. Masquelet technique and osteomyelitis: innovations and literature review. Eur Rev Med Pharmacol Sci 2019; 23:210–6. https://doi.org/10.26355/eurrev_201904_17495.
20. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 2008; 36:309–32. https://doi.org/10.1016/j.ajic.2008.03.002.
21. Alt V. Antimicrobial coated implants in trauma and orthopaedics-A clinical review and risk-benefit analysis. Injury 2017; 48:599–607. https://doi.org/10.1016/j.injury.2016.12.011.
22. Moghaddam A, Graeser V, Westhauser F, Dapunt U, Kamradt T, Woerner SM, et al. Patients' safety: is there a systemic release of gentamicin by gentamicin-coated tibia nails in clinical use? Ther Clin Risk Manag 2016; 12:1387–93. https://doi.org/10.2147/TCRM.S107398.
23. Schmidmaier G, Wildemann B, Stemberger A, Haas NP, Raschke M. Biodegradable poly(D,L-lactide) coating of implants for continuous release of growth factors. J Biomed Mater Res 2001; 58:449–55.
24. Horn J, Schlegel U, Krettek C, Ito K. Infection resistance of unreamed solid, hollow slotted and cannulated intramedullary nails: an in-vivo experimental comparison. J Orthop Res 2005; 23:810–5. https://doi.org/10.1016/j.orthres.2004.11.006.
25. Schemitsch EH, Bhandari M, Guyatt G, Sanders DW, Swiontkowski M, Tornetta P, et al. Prognostic factors for predicting outcomes after intramedullary nailing of the tibia. J Bone Joint Surg Am 2012; 94:1786–93. https://doi.org/10.2106/JBJS.J.01418.

Ankle fracture and necrotizing fasciitis: a common fracture and a dreadful complication

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Necrotizing fasciitis is a dreadful complication of the soft tissue. This pathology could be triggered by many factors, such as a fracture. We present a case of case of a necrotizing fasciitis in ankle fracture.

Clostridium perfringens is an anaerobic, spore-forming, gram-positive rod responsible of approximately 80% of post-traumatic gas gangrene cases (1), which is found ubiquitously in the soil and sewage. Post-traumatic clostridial myonecrosis is a diffuse, progressive invasion of healthy muscle tissue. Wounds with vascular compromise (such as deep penetrating injuries or crash wounds) create the ideal environment for clostridial germination and proliferation. After the inoculation, necrosis progresses within 24 to 36 hours from the traumatic injury (2). On a tissue level, production of alpha-toxin has been identified as an essential factor for the development of the characteristic widespread muscle necrosis. *C. perfringens* bacteraemia is a rare but severe complication, with a reported mortality ranging from 27 to 58% (3). Here, were report a case of traumatic clostridial myonecrosis with septicaemia in a 23-years old male patient.

Case presentations

A 23 years-old male suffering from epilepsy, was admitted to our emergency department after a traumatic traffic injury during a rainstorm involving his left lower limb. On admission, his physical examination revealed an open fracture-dislocation of the left ankle (Gustilo type 1; 44A2.3 AO/OTA) and stable vital parameters (Fig. 1).

Laboratory data on admission showed marked leukocitosis, with a white blood cell count of 17.980 cells/mm3 and 88,6% of neutrophyls. C-reactive protein and serum procalcitonin were, respectively, 418 mg/L and 2,47 ng/ml. Blood chemistry found signs of important myonecrosis, with Creatinine kinase levels reaching 869 UI/L (normal range 30-170 UI/L).

The patient underwent a close reduction and traction therapy by a calcaneal pin. Few hours after initial evaluation, the patient developed fever (max Tc 39°), skin tenderness, and exacerbation of local pain. Importantly, the plain X-ray showed signs of gas formation at the wound level.

Prompt blood samples for microbiological cultures were obtained and intravenous antimicrobial therapy with piperacillin/tazobactam and clindamycin was started. Preliminary communication of *Cl. perfringens* positivity was obtained from the Microbiology laboratory and the Infectious Diseases specialist. As expected, phenotypic characterization revealed the pathogen to be susceptible to the prescribed antimicrobials. Locally a progressive swelling, crepitus, blisters and sequential discoloration of the tissue of the ankle were developed. An ultrasound was obtained and showed a diffuse melting of the

Keywords: ankle fracture; necrotizing fasciitis; clostridium perfringens

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subcutaneous tissue and the fascia on the medial and lateral side of the ankle.

An emergency surgery was performed: an accurate curettage showed a dark-brown tissue in front of the ankle; after incision odorous "dish-water-like" fluid exuded from the fascia and deep tissue and articulation, finger test was positive, all necrotic tissue were removed, pulsed washing and fasciotomy were performed in all muscular compartments (Fig. 2). A Negative pressure wound therapy was started on the fasciotomy. To stabilize the fracture an external fixation was put on.

Shortly after the initiation of antimicrobial therapy, the patient underwent a rapid improvement of both clinical and laboratory parameters and antibiotic therapy was de-escalated to penicillin G and clindamycin, for a total duration of 14 days. Creatinine kinase level returned to range of normality within one day from the beginning of antibiotic administration.

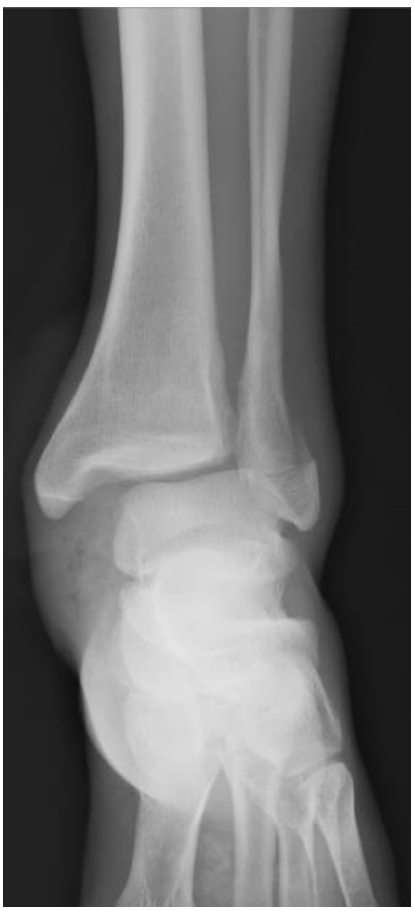

Fig. 1. *AP x-ray of the left ankle.*

Fig. 2. *Fasciotomy and external fixation.*

One week after the initiation of therapy a moderate increase of serum transaminases (peak ALT level 195 UI/L, peak AST 63 UI/L, normal range 7-45 UI/L). Of note, no signs of organ failure and haemolysis were noted. The conditions of the injured soft tissues gradually improved and after two months the patient underwent a dermal skin graft surgery with complete healing.

After six months the patient returned complaining of an unstable ankle, a lateral fistula and ankle osteomyelitis; biopsy, debridement and targeted antimicrobial therapy was started. After three months an ankle arthrodesis was performed. At one-year follow-up the patient is fine, he restored his routine life and work.

DISCUSSION

Necrotizing fasciitis (NF) was described in 1871 by the surgeon Joseph Jones (4). In 1952 Ben Wilson described the necrosis of the superficial fascia and subcutaneous tissues. NF follows an injury of the epidermidis that allows bacteria to invade the deep tissues (4). Despite this, in 45% of the cases is not possible to identify the site of initial infections (4). Commonly NF is polymicrobial, rarely caused by only one bacterium, like group A-Streptococcus (5).

The known risk factors are diabetes, renal impairment, immunocompromise, rheumatoid arthritis or similar rheumatoid conditions (6–9). In our case the patient had an open fracture. Initially the disease presents with fever, local edema and erythema. These symptoms simulate a cellulitis. Burning pain is a specific symptom, always present. Unfortunately, the use of nonsteroidal anti-inflammatory drugs for the management pain could cover the burning pain and make the diagnosis more difficult (10).

The mortality of NF ranges from 6% to 76%. During the first phase of the disease the diagnosis is mainly clinical. The average time between onset of symptoms and diagnosis is 2-4 days (4) but Shang et al demonstrated that a rapid diagnosis treatment, based on antimicrobial therapy and surgical debridement, guarantees good outcomes (10).

The late symptoms are severe pain, skin discoloration, blistering, bullae, crepitus and exudation like “dishwater” (11), followed by septic shock.

The “finger test” is a simple procedure: making a little incision in the fascia the surgeon pulls in the gloved finger: the presence of melted tissue and poor adherence of subcutaneous tissue defines a positive test and suggests the presence of NF

Standard radiological test seldom help for diagnosis since only in 20% of the cases a plain X-ray shows gas bubbles (11). Tomography and MRI have a better sensitivity and specificity and allow the study of muscle compartments and fascia layers.

Laboratory changes such as anemia, raised leucocyte count, creatinine, glucose concentration, decrease of sodium, coagulopathy and acidosis, are common in NF (11). C-reactive protein rises quickly in acute phase (12); while procalcitonin increases when sepsis arises.

Wong et al. (12) developed the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score. This score is based on modification of CRP, white cell count, hemoglobin, sodium, creatinine and glucose. LRINEC score <5 indicate a low risk of NF (<50%); score 6-7 indicates a medium risk (50%-75%); score >8 indicates high risk (>75%). LRINEC >6 has a predictive value of 92%. In our case the patient has a LRINEC score of 6, with a medium risk of developed NF. It must be considered that LRINEC score has a good specificity in high risk cases. Similarly, Cai et al. described a case of a 35-year-old man that developed a NF following a plate removal of distal radius with a LRINEC score of 5 (13). Murphy et al suggest that serum lactate of more than 2.0 mmml/L is strongly associated with NF (14).

The treatment of NF is based on prompt and deep surgical debridement of subcutaneous necrotic tissue and fascia and high dose antimicrobial treatment (15). The use of fasciotomy also helps in the management of edema and avoids the possibility of compartment syndrome. In some cases, a life-saving radical surgery, as major amputation or disarticulation is needed (5).

In the literature there are many case reports describing NF after orthopedic surgery. Jain et al described a lethal NF following a medial malleolus fracture treated by plaster. Santos et al described a NF after femur fracture, Shang et al faced a NF following a tibia fracture surgery while Weidle et al described a NF as a complication of a closed colles-fracture (4, 10,11). In all these cases the patients had risk factor. In our case, similarly to the case of Cai et al (13), the patients did not have any known risk factor and the infection was caused by only *Cl. perfringens*. Moreover, the patient eventually developed chronic osteomyelitis that can be treated with complex surgery, like Masquelet technique or arthrodesis (16,17); usually these surgeries were delayed in two-stage to reach better results, as demonstrated in other orthopedic surgeries (18). Arthrosis could be a common sequela of healing

in external fixator how happened also in vertebral stabilizations (19,20). Microbiological evaluation and bacterial identification were primarily to direct the clinical and surgical management likewise in other foot infection (21).

In conclusion, also "routine" fractures or "simple" fractures could hide a dreadful complication, such as NF. Prompt clinical awareness and microbiologic evaluation, early surgery and initiation of specific antibiotic therapy can prevent the evolution to septic shock and unfavorable outcomes. Laboratory parameters, such as creatinine kinase and C-reactive protein, are useful and rapid markers to monitor response to treatment. The close collaboration between the orthopedic surgeon infectious disease specialist and microbiology laboratory, in our case, was crucial in both diagnosis and management of a potentially rapidly fatal disease.

REFERENCES

1. Awad MM, Bryant AE, Stevens DL, Rood JI. Virulence studies on chromosomal alpha-toxin and theta-toxin mutants constructed by allelic exchange provide genetic evidence for the essential role of alpha-toxin in Clostridium perfringens-mediated gas gangrene. Mol Microbiol. 1995; 15(2):191-202.
2. Stevens DL, Tweten RK, Awad MM, Rood JI, Bryant AE. Clostridial gas gangrene: evidence that alpha and theta toxins differentially modulate the immune response and induce acute tissue necrosis. J Infect Dis. 1997; 176(1):189-95.
3. Yang C-C, Hsu P-C, Chang H-J, Cheng C-W, Lee M-H. Clinical significance and outcomes of Clostridium perfringens bacteremia--a 10-year experience at a tertiary care hospital. Int J Infect Dis. 2013; 17(11):e955-60.
4. Santos LEN, Pires RES, Figueiredo LB, Soares EAM. Necrotizing fasciitis after internal fixation of fracture of femoral trochanteric. Rev Bras Ortop. 2014; 49(1):78-81.
5. Monaghan SF, Anjaria D, Mohr A, Livingston DH. Necrotizing fasciitis and sepsis caused by Aeromonas hydrophila after crush injury of the lower extremity. Surg Infect (Larchmt). 2008; 9(4):459-67.
6. Jain MJ, Mavani K. Lethal Necrotizing Fasciitis Triggered by Plaster: Case Report and Review of Literature. J Orthop Case Rep. 2016; 6(5):73-5.
7. Galli M, Scavone G, Vitiello R, Flex A, Caputo S, Pitocco D. Surgical treatment for chronic Charcot neuroarthropathy. Foot (Edinb). 2018; 36:59-66.
8. Pitocco D, Spanu T, Di Leo M, Vitiello R, Rizzi A, Tartaglione L, et al. Diabetic foot infections: a comprehensive overview. Eur Rev Med Pharmacol Sci. 2019; 23(2 Suppl):26-37.
9. Pitocco D, Scavone G, Di Leo M, Vitiello R, Rizzi A, Tartaglione L, et al. Charcot Neuroarthropathy: From the Laboratory to the Bedside. Curr Diabetes Rev. 2019; 16(1):62-72.
10. Shang S, Zhang R, Hou Z. Necrotizing fasciitis-A catastrophic complication following routine tibia fracture surgery: A case report and literature review. Medicine (Baltimore). 2017; 96(23):e6908.
11. Weidle PA, Brankamp J, Dedy N, Haenisch C, Windolf J, Jonas M. Complication of a closed Colles-fracture: necrotising fasciitis with lethal outcome. A case report. Arch Orthop Trauma Surg. 2009; 129(1):75-8.
12. Wong C-H, Wang Y-S. The diagnosis of necrotizing fasciitis. Curr Opin Infect Dis. 2005; 18(2):101-6.
13. Cai Y, Gan Y, Yu C, Tang J, Sun Y. A successful treatment of necrotizing fasciitis following the surgery of distal radius plate removal: A case report and literature review. Medicine (Baltimore). 2018; 97(15):e0305.
14. Murphy G, Markeson D, Choa R, Armstrong A. Raised serum lactate: a marker of necrotizing fasciitis? J Plast Reconstr Aesthet Surg. 2013; 66(12):1712–6.
15. De Luna V, Mancini F, De Maio F, Bernardi G, Ippolito E, Caterini R. Intraoperative Disinfection by Pulse Irrigation with Povidone-Iodine Solution in Spine Surgery. Adv Orthop. 2017; 2017:7218918.
16. Careri S, Vitiello R, Oliva MS, Ziranu A, Maccauro G, Perisano C. Masquelet technique and osteomyelitis: innovations and literature review. Eur Rev Med Pharmacol Sci. 2019; 23(2 Suppl):210-6.
17. Simoni G, Maccauro G, Fenga D, De Santis V, Orani RA, Centofanti F, et al. Arthrodesis of the ankle joint in septic osteoarthritis: six years long term outcomes in authors' personal experience. Eur Rev Med Pharmacol Sci. 2019; 23(2 Suppl):139-44.

18. Ippolito E, Farsetti P, Valentini MB, Potenza V. Two-stage surgical treatment of complex femoral deformities with severe coxa vara in polyostotic fibrous dysplasia. J Bone Joint Surg Am. 2015; 97(2):119-25.
19. Proietti L, Scaramuzzo L, Schirò GR, Sessa S, Tamburrelli FC, Cerulli G. Degenerative facet joint changes in lumbar percutaneous pedicle screw fixation without fusion. Orthop Traumatol Surg Res. 2015; 101(3):375-9.
20. Proietti L, Schirò GR, Sessa S, Scaramuzzo L. The impact of sagittal balance on low back pain in patients treated with zygoapophysial facet joint injection. Eur Spine J. 2014; 23 Suppl 6:628-33.
21. Muratori F, Menghi A, Fantoni M, Visconti E, Pezzillo F, Nizegorodcew T, et al. Tubercular osteomyelitis of the second metatarsal bone: case report. J Orthop Traumatol. 2007; 8(4):182-

Predictable risk factors for infections in proximal femur fractures

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Proximal femur fractures are increasing, together with the aging of world population. One of the complications worsening this condition is infection. In this study, we try to identify risk factors that can lead to infection. We identified 122 patients with femoral neck fracture. The occurrence of infectious events was recorded (respiratory, urinary, superficial wound and periprostethic infection). There were 15 infections, mostly urinary and pulmonary, and all were treated using antibiotics. No statistical differences were found between infection and control group regarding waiting time for surgery, mean time of surgery, age, kind of fracture, type of surgery. Fever onset >38° within 72 hours from surgery was statistically correlated with early infections. Future studies must be led to identify risk factors for infection and to create a strategy to prevent this possibly lethal complication.

Femoral neck fracture incidence is increasing together with the aging of the world population, representing one of the main current health concerns. The outcome of the treatment of these fractures depends on several factors, related to surgery or to the patient. Of course, elderly patients with multiple comorbidities are associated with a poor outcome than younger patients (1).

One of the complications negatively influencing the patient's outcome after hip fracture is the presence of post-operative infection, which leads to increase mortality and duration of hospital stay.

The onset of systemic infection is a terrible post-operative complication, which increases the risk of perioperative mortality.Even peri-implant infections are a dangerous occurrence, especially in hip arthroplasty, involving a long and difficult treatment for the eradication of the responsible microorganisms with great economic expenditure for the health system (2).

The aim of our study is the identification of risk factors for infection after surgery in patient with hip fractures. It is primary to obtain an early diagnosis and not to underestimate alarm bells in postoperative elderly patients. We focused on demographic factors, blood tests, factors related to surgery and post-operative vital signs, first of all the fever. In a subpopulation of patients, the relationship between infection and Euthyroid Sick Syndrome (ESS) was evaluated.

METHODS AND MATERIALS

In our prospective study 122 patients were identified with proximal femoral fracture in Emergency Department of Fondazione Policlinico Universitario A. Gemelli (Roma – Italia) and enrolled from January to June 2019. All patients undergone to surgical treatment. All patients were followed for 1 month. Anthropometric and anamnestic data of the

Keywords: hip fracture; infection; risk factor.

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patients were collected in order to calculate the BMI and the Charlson Comorbidity Index (CCI).

All patients gave informed consent to participate to the study. Inclusion criteria were: 1) diagnosis of proximal femur fracture on arrival in our Emergency Department 2) surgery of hip arthroplasty or osteosynthesis using cancellous screws, nail or plate.

The diagnosis was performed by clinical evaluation and radiological findings such as x-rays; a CT-scan was necessary in particular cases to have better details in comminute fractures (3).

Several risks factors have been evaluated and related with outcomes, firstly the onset of local or systemic infection within one month from the surgery.

These factors depend on the patients: gender, age, comorbidity (DM, heart failure, COPD, liver cirrhosis, dementia, hemiplegia, rheumatological diseases, kidney failure, neoplasms, HIV) and pattern fracture; or depend on the surgery and the post-operative period, such as the type of intervention or the kind of anesthesia and home dismission or in rehabilitation clinic. Lastly, we evaluated the post-operative vital signs, firstly of all the post-operative temperature within 72 hours from surgery.

A subpopolation of patients (80 patients), which falls within the following inclusion criteria: i) no thyroid pathology, ii) no concomitant acute coronary syndrome and pneumonia iii) no concomitant active neoplastic disease and concomitant pharmacological therapy with any drug acting on thyroid function, was studied for the Euthyroid Sick Syndrome and its relationship with post-operative infections.

All patients were followed up for one month, and the occurrence of infectious events (respiratory, urinary, superficial wound, and periprosthetic infections) was recorded.

Table I. *Blood exams data of the patients.*

Parameter	**Infection**	**Non-infection**	**p**
Hb (g/dl)	12,1	12,3	0,7
WBC (x10^9/l)	9,9	9,0	0,5
Plt (x10^9/l)	244	246	0,1
Na (mmol/l)	140	139	0,5
K (mmol/l)	4,4	4,1	0,09
Ca (mg/dl)	9,4	10,5	0,7
Alb (g/dl)	8,7	8,5	0,8
Creatinine (mg/dl)	0,95	0,98	0,7
LDH (U/l)	289	279	0,4
INR	1,1	1,1	0,2
fT3 (pg/ml)	2,2	2,2	0,2
fT4 (pg/ml)	11,1	12,4	0,2
TSH (microIU/ml)	1,5	1,3	0,9
PTH (pg/ml)	82,1	85,8	0,8
Vit D (ng/ml)	23,5	20,4	0,5

Respiratory infection was defined as a positive chest X-ray (e.g. the appearance of pneumonia or pleural effusion) or a positive sputum culture.

Superficial wound infections (infections occur at the incision site or deeper underlying tissue within 30 days of a surgical procedure) or periprosthetic infections was recorded following the criteria of the National Center for Infectious Diseases (Centers for Disease Control and Prevention, USA) (4).

Urinal Tract Infection was defined observing alteration in leucocyte blood count or in urinary nitrite, or microorganism presence on urine culture. The relationship between every risk factor and the onset of local or systemic infection in post-operative infection has been investigated. For each factor we divided the population into two subgroups identifying infected and uninfected patients, and we conducted statistical analysis.

The database analysis was performed using Chi-Squared test, Yates's Chi-Squared test in the evaluation of patients with euthyroid syndrome and the Mann-Whitney U test for non-parametric variables. SPSS Version 25.0 was used for data analysis. A P value <0.05 was judged as statistically significant.

RESULTS

One hundred twenty-two patients met the inclusion criteria and were enrolled; there were 93 females and 29 males. There were 37% of intraarticular hip fracture (AO classification type B) treated by hip screw or hemiarthroplasty. The other fracture (AO classification type A) were treated by femoral nail. In 12 patients (hemiarthroplasty) a drain-wound was positioned; no statistical correlation with early infections (p=0,5).

There were 15 infections: 2 superficial wound infections, 9 urinary infections, 3 pneumonia and 1 panniculitis. No hardware infections were detected. All infections were treated by antibiotics and there was no need of surgical management. The early infection rate was 12%.

Mean age in the study population was 83, with a median of 84 years old; mean BMI was 23. There weren't' statistical differences between the two group for age and BMI.

In the infection group the mean time of surgery was 80 min (SD 23.5), in non-infection ones was 70 min (SD 37), no statistical difference (p=0,2). In the infection group the waiting time before the surgery was 28 hours (SD 24), in non-infection ones was 32 hours (SD 21); no statistical difference (p=0,5). The mean result of the routine blood exams was reported in Table I and showed no statistical difference between the two groups.

There were no difference in the two groups regarding age (p=0,1), type of fracture (p=0,7), type of surgery (p=0,8), type of anesthesia (p=0,9), CCI (p=0,9), diabetes (p=0,2), chronic obstructive pulmonary disease (p=0,9), dementia (p=0,5), chronic kidney disease (p=0,9).

Was analyzed also the type of discharge: home, rehabilitation and long- term care; there was no statistical difference (p=0,6).

Fever was monitored in the post-operative period. Temperature <38° within 72 hours of surgery was not correlated with early infections (p=0,3) instead temperature >38° within 72 hours of surgery that was statistically correlated with early infections (p=0,002).

Regarding the Euthyroid Sick Syndrome (ESS), only 80 patients met the inclusion criteria and were enrolled. The incidence of ESS was 56%. In the infection group there were 11 patients affected by ESS and only 4 without, but due to the weak number of series there was no statistical difference (p=0,2).

DISCUSSION

Hip fracture is a common accident in the elderly population; this condition is burdened by many complications due to the comorbidity, the aging and the acute event of fracture. The 1-year mortality is about 20% (1), stable in recent years, moreover there is an increased risk of infection and subsequent fractures (5). In this population of patients there are also a lack of muscle strength, sarcopenia (6) that could invalidate the post-surgery recovery.

The orthopedic surgery is burdened by an elevated incidence of infections, both in trauma patients than in elective ones (7–11). Among the infectious complications there can be superficial

wound infections (SSI), urinary infections (UI), pneumonia, panniculitis, osteomyelitis and hardware infections (12–14).

Many studies in literature focus on risk factors for infection in hip fractures, but there is discordance about many of these factors. Kastanis et al. carried out a study on 198 patients affected by hip fractures detecting a correlation between the ASA score and the incidence of complication; in their population there was a 12% of infectious complications (pneumonia, SSI, urinary infections) (13). This result is comparable with our population (12,2% of infection risk).

Simunovic et al. focused their research on the waiting time for surgery showing a positive reverse correlation between waiting time and pneumonia. Only two studies were eligible in the Simunovic metanalysis. In both studies the correlation between waiting time and pneumonia has no evidence, but thanks to the metanalysis this data raised a statistical correlation (14). Our data could not support the evidence of the metanalysis due to the reduced population study, moreover in our analysis we included all kind of infection and not only the pneumonia.

On this path, Cordero et al. associate waiting time for surgery before 24 hours with a reduction in SSI. Our data does not support this correlation, the mean time in infected group was 28 hours versus 32 hours in the non-infected group (p=0,5).

Urinary infections represent one of the most common bacterial infections in patients with hip fractures. The causes include postoperative urinary retention, neurogenic bladder dysfunction and use of urinary catheter. Bliemel et al. conducted a study among 402 patients with hip fractures; a total of 97 patients (24%) sustained an UI during in-hospital treatment (15). UI were associated with inferior functional outcomes and a longer hospital stay. There was no correlation with increased SSI in UI group (15). UI represent the 7% of total population in our study and the 60% of infection detected.

Hip arthroplasty is characterized by elevated risk of infection, that becomes even greater in trauma patients. Barbero et al demonstrated 3.3 times major hardware infection risk in hip arthroplasty in trauma patients respect to elective ones (16). In this study there are also a positive correlation with ASA score, already shown in Kastanis's paper. The authors also underline that in the trauma patients the hardware infections demonstrate a worse outcome (13,16).

In a study about the use of hemiarthroplasty in hip fractures the risk of infections is 5,5%. One of the major risk factors was the precedence admit in a long-term care. The authors suggest that in long-term care the patients experienced a change in the bacteria skin and this condition makes their much prone to developed gram-negative infections (17).

In our study we did not find difference between hip replacement and osteosynthesis, with a similar rate of infections. Regarding the blood exams we did not find correlation with risk of infections, although in the literature anemia and low albumin levels showed some connection. Yuwen et al demonstrated in their metanalysis that a concentration below 3,5 g/dl of albumin is associated with 2.5 times risk of infections in orthopedics surgery (18).

Fever is a common post-surgery event in orthopedics patients. Yoo et al analyzed 272 hip fractures, among this 49,6% developed postoperative fever. In the fever group routine exams were carried out, but only 26,7% were positive and developed an infection. The most common complication was pneumonia (12,6%), followed by UI (8.1%). The authors linked risk of infections with fever greater than 38.5° after 48 hours from surgery or the presence of multiple peaks (19).

Regarding ESS previous studies demonstrated a link between this condition in hip fracture with a worse outcome, in terms of anemization and calcium dysmetabolism (20).

Our data is not enough strong to demonstrate an association between ESS and infections (p=0,2), but must be underlined that in the ESS group there is a trend 3-times greater risk of infection. Probably, studies on larger samples could confirm this data. Ur study presents different limits: first of all a limited sample; we haven't collected drugs consumption of the patients; all patients are Caucasian; regarding ESS we do not have pre-fracture values at our disposal, thus not being possible to discriminate whether the ESS was a preexisting condition or

trauma-related. Future studies must focus on major risk factors for post-surgery infections to create a pre-surgery risk score and to create a strategy to prevent these complications in high-risk patients.

REFERENCES

1. Liu Y, Wang Z, Xiao W. Risk factors for mortality in elderly patients with hip fractures: a meta-analysis of 18 studies. Aging Clin Exp Res. 2018; 30(4):323-30.
2. Efremov K, Benedetti Valentini M, De Maio F, Potenza V, Caterini R, Farsetti P. Periprosthetic hip and knee infections: comparison of etiology, perioperative management and costs. Eur Rev Med Pharmacol Sci. 2019; 23(2 Suppl):217-23.
3. Arduini M, Mancini F, Farsetti P, Piperno A, Ippolito E. A new classification of peri-articular heterotopic ossification of the hip associated with neurological injury: 3D CT scan assessment and intra-operative findings. Bone Joint J. 2015; 97-B(7):899-904.
4. Borchardt RA, Tzizik D. Update on surgical site infections: The new CDC guidelines. JAAPA. 2018; 31(4):52-4.
5. Cazzato G, Masci G, Liuzza F, Capasso L, Florio M, Perisano C, et al. Secondary femur fracture following treatment with anterograde nailing: the state of the art. J Biol Regul Homeost Agents. 2018; 32(6 Suppl. 1):151-5.
6. Picca A, Calvani R, Lorenzi M, Menghi A, Galli M, Vitiello R, et al. Mitochondrial dynamics signaling is shifted toward fusion in muscles of very old hip-fractured patients: Results from the Sarcopenia in HIp FracTure (SHIFT) exploratory study. Experimental Gerontology. 2017; 96:63.
7. Farsetti P, De Maio F, Potenza V, Efremov K, Marsiolo M, Caterini A, et al. Lower limb lengthening over an intramedullary nail: a long-term follow-up study of 28 cases. Journal of Orthopaedics and Traumatology 2019; 20(1):30.
8. Pitocco D, Spanu T, Di Leo M, Vitiello R, Rizzi A, Tartaglione L, et al. Diabetic foot infections: a comprehensive overview. Eur Rev Med Pharmacol Sci. 2019; 23(2 Suppl):26-37.
9. Meluzio MC, Oliva MS, Minutillo F, Ziranu A, Saccomanno MF, Maccauro G. The use of knee mega-prosthesis for the management of distal femoral fractures: A systematic review. Injury. 2019;
10. Oliva MS, Masci G, Vitiello R, De Santis V, Liuzza F, et al. Hip megaprosthesis in oncological surgery: open questions. J Biol Regul Homeost Agents. 2019; 33(2 Suppl. 1):45-9.
11. Logroscino CA, Tamburrelli FC, Scaramuzzo L, Schirò GR, Sessa S, Proietti L. Transdiscal L5-S1 screws for the treatment of adult spondylolisthesis. Eur Spine J. 2012; 21(Suppl 1):128-33.
12. Careri S, Vitiello R, Oliva MS, Ziranu A, Maccauro G, Perisano C. Masquelet technique and osteomyelitis: innovations and literature review. Eur Rev Med Pharmacol Sci. 2019; 23(2 Suppl):210–6.
13. Kastanis G, Topalidou A, Alpantaki K, Rosiadis M, Balalis K. Is the ASA Score in Geriatric Hip Fractures a Predictive Factor for Complications and Readmission? Scientifica. 2016; 2016:1-6.
14. Simunovic N, Devereaux PJ, Sprague S, Guyatt GH, Schemitsch E, DeBeer J, et al. Effect of early surgery after hip fracture on mortality and complications: systematic review and meta-analysis. Canadian Medical Association Journal. 2010 Oct 19;182(15):1609-16.
15. Bliemel C, Buecking B, Hack J, Aigner R, Eschbach D-A, Ruchholtz S, et al. Urinary tract infection in patients with hip fracture: An underestimated event? Urinary tract infection in patients with hip fracture. Geriatrics & Gerontology International. 2017; 17(12):2369-75.
16. Barbero JM, Montero E, Vallés A, Plasencia MA, Romanyk J, Gómez J. [Prosthetic joint infection in patients with hip fracture. Differences from infection of elective prosthesis]. Rev Esp Quimioter. 2016; 29(5):273-7.
17. Gallardo-Calero I, Larrainzar-Coghen T, Rodriguez-Pardo D, Pigrau C, Sánchez-Raya J, Amat C, et al. Increased infection risk after hip hemiarthroplasty in institutionalized patients with proximal femur fracture. Injury. 2016; 47(4):872-6.
18. Yuwen P, Chen W, Lv H, Feng C, Li Y, Zhang T, et al. Albumin and surgical site infection risk in orthopaedics: a meta-analysis. BMC Surgery 2017; 17(1):7.
19. Yoo J-H, Kim K-T, Kim T-Y, Hwang J-H, Chang J-D. Postoperative fever after hemiarthroplasty in elderly patients over 70 years of age with displaced femoral neck fracture: Necessity of routine workup? Injury 2017; 48(2):441-6.

20. Raffaele V, Carlo P, Marcello C, Andrea P, Antonio B, Serena OM, et al. Euthyroid Sick Syndrome in Hip fractures: valuation of vitamin D and Parathyroid hormone axis. Injury 2020; S0020-1383(20)30013-9.

A rare case of post-traumatic infected pilomatricoma of the finger of the hand diagnosed after performing radioiodine therapy

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We present the clinical case of a young woman with pilomatricoma of the finger, a very rare location. The patient got infected after receiving radioiodine therapy to treat a thyroid carcinoma. Given the patient's high functional requirements we choose a minimal treatment which allowed her to maintain a sufficient functionality.

The calcifying epithelioma of Malherbe (CEoM), more recently known as pilomatricoma (PMT), is a common benign cutaneous tumor that originates from the hair follicle matrix cells (1-3). This neoplasm is more common in the first two decades of life (2-4) and the most frequent sites of localization are represented by the region of the neck, of the head and of the back (1, 4). Few cases have been reported in the upper extremities and rarely some authors described cases involving the fingers of the hand (5). In rare cases it can be ulcerated or infected (4-6). Although PMT is a frequent lesion, especially in children, it is often misdiagnosed and confused with other pathological conditions (2, 4, 7, 8). In this paper we present a rare case of an infected PMT located at the level of the fingertip of the second finger of a hand.

MATERIALS AND METHODS

A 24-year-old Caucasian woman, was admitted to the emergency room of our institution due to a fistous lesion, secreting purulent material localized to the distal phalanx of second finger of the right hand (Fig. 1a), in the absence of a recent trauma. The finger appeared painful and swollen with antalgic limitation of the bending and tendency to rigidity. In the clinical history there was a trauma of the second finger of the right hand in the pediatric age which resulted in deformity of the nail matrix, no history of trapezio-metacarpal osteoarthritis or other common causes of hand pain (9).

Papillary thyroid carcinoma recently treated with radioiodine was also present. Routine blood tests performed did not show neutrophil leukocytosis or alteration of ESR and CRP, rather a leukopenia (3.8*103 per cm3) probably caused by recent radioiodine therapy. Therefore, X-ray of the right hand was performed, which highlighted distal phalanx bone erosion and involvement of adjacent soft tissues in the second finger (Fig 1b). Furthermore, MRI was carried out which revealed cystic formation, about 6 mm in diameter and in close contact with the adjacent bone (Fig 1c). Suspecting the diagnosis of infected epidermoid cyst, fistulectomy, deep and soft tissue debridement with superficial bone curettage were performed

Keywords: pilomatricoma of the finger; pilomatricoma; hand infection; osteomyelitis; skin neoplasm; skin tumors

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with microbiological sampling of abundant material and excisional biopsy for histological examination. Moreover, antibiotic prophilaxis (cefazolin 2 g one-shot 30 minutes before surgery) was administered according to the centre's internal recommendations, dedicated to immuno-compromised patients (10).

RESULTS

Four days after the surgery the positive culture of the bioptic material for *Providencia rettgeri* sensitive to ciprofloxacin was communicated therefore it was confirmed already running antibiotic therapy. After 15 days, the presence of a chronic inflammatory process on a pilomatricomatous lesion and chronic osteomyelitis, on the analyzed bone fragments, was reported by the pathological anatomy department (*Fig. 2*). One month after surgery, the patient showed complete resolution of stiffness with recovery of finger articulation and reduction of edema and pain. The wound was dry and completely healed. No secretions were present. Therefore, antibiotic therapy was discontinued. Due to the high functional request of the patient (aspirant surgeon) it was decided in agreement with her for a "wait and watch" treatment evaluating the possibility of periodic cycles with antibiotic therapy. At the one-year follow-up visit, the patient is satisfied with the treatment received and the functional result. Furthermore, she did not present further episodes of fistulization and recurrence of symptoms.

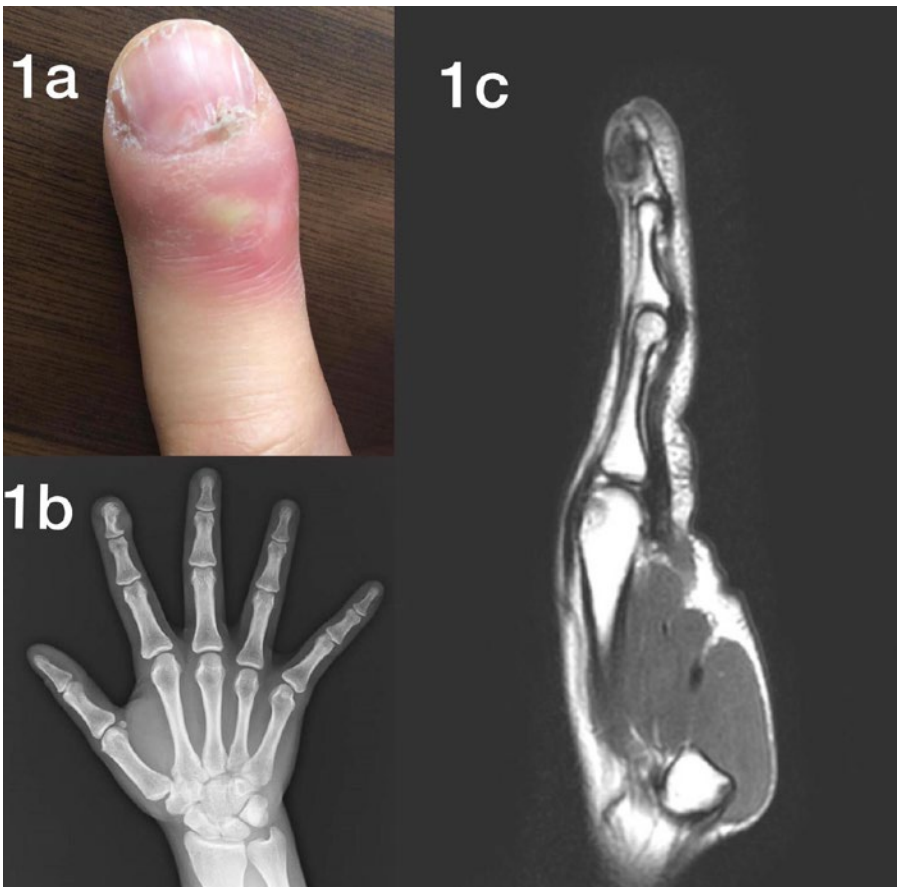

Fig. 1. ***A)*** *Preoperative clinical condition;* ***B)*** *Preoperative X ray;* ***C)*** *Preoperative MRI*

DISCUSSION

PMT is a skin tumor derived from the hair matrix cells with a tendency to calcification; it has benign characteristics and has slow growth (4, 2). PMT, generally presents as a small solitary subcutaneous nodule, covered by skin that may exhibit bluish discoloration, sometimes painful on palpation (2).

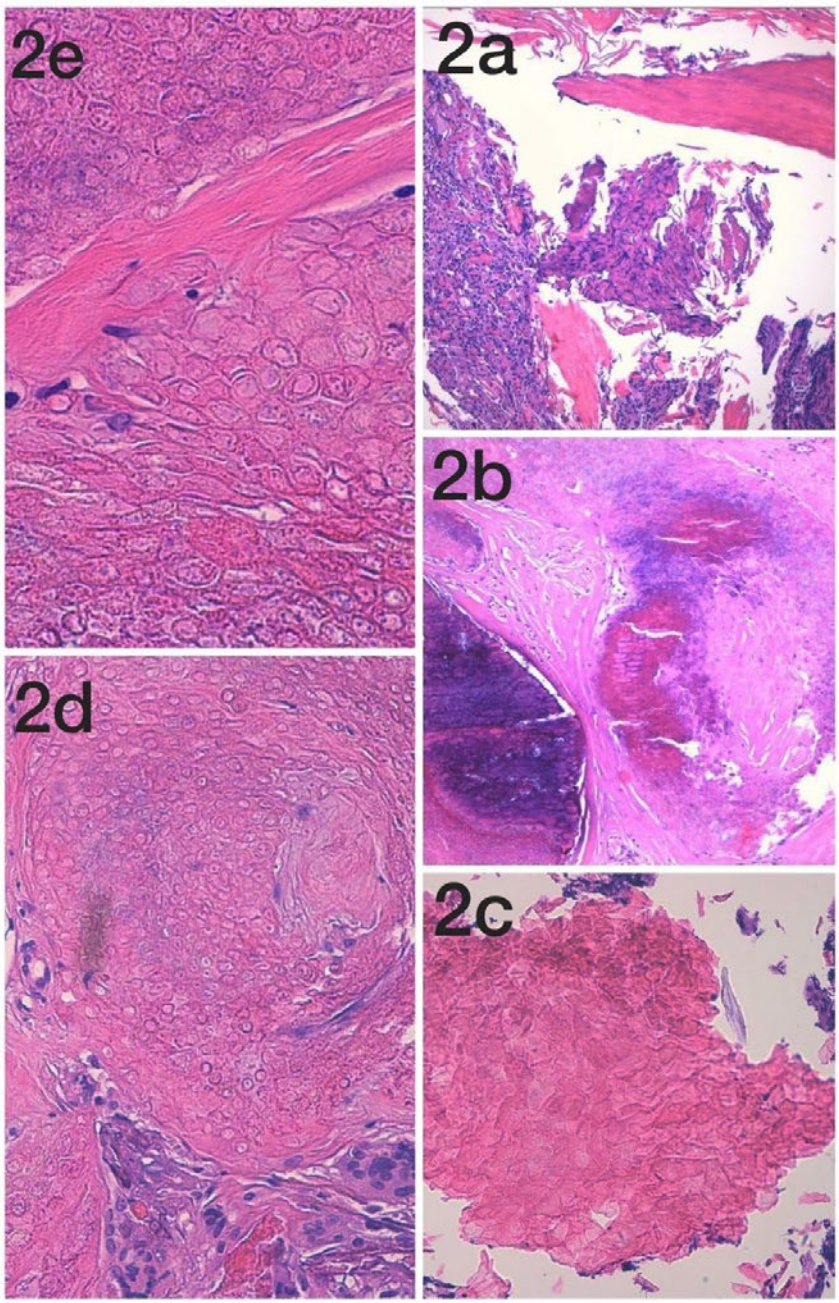

Fig. 2. ***A)*** (*EE 5x) In this picture you can see on the left side a fogistic process made of linphohistiocytic population, sometimes surrounding an eosinophilic material, more evident on the right upper corner;* ***B)*** *(EE 5x) The eosinophili material is made of appearently anuclear citoplasms, sometimes with microcalcifcations*; ***C)*** *(EE10x) In the majority of the pink material, some anucleated Keratopoietic cheratinocytes can be detected;* ***D/F)*** (*EE 20x and 40x) In a minority of pikk areas you can see some "ghost cells", that is cells with a pale nucleus, typical of Pylomatricoma*

In histological analysis, PMT generally appears as a well-demarcated tumor encapsulated by a membrane of fibro-connective tissue.

It is usually located in the superficial skin layers and very rarely in the deep dermis.

The tumor is composed of clusters of epithelial cells that degenerate at the center of the lesion giving rise to anucleate cells (ghost cells or shadow cells) typical but not pathognomonic of the lesion (2, 4). Although its etiopathogenesis is still not well understood, beta-catenin mutations seem to play a role; moreover, the incidence of PMT appears to be higher in patients presenting with other genetic disorders (4, 11). Pirouzmanesh et al (4) in a review of 346 cases found the presence of a previous trauma on the same site of localization of PMT in 10 patients (2.9%) and of infection in 7 patients (2%), suggesting the possible implication in the pathogenesis.

Although PMT is preferentially localized on the neck and face, some authors have described its location at the level of the upper extremities (1, 2, 4,), however the finger of a hand is a rather rare location described only by Nigam et al (5).

In the present case, the lesion probably originated from a fragment of skin tissue deepened to the bone level during childhood trauma. Because of its slow growth and benign characteristics, the lesion remained silent and undiagnosed until an infection occurred, most likely due to the transient immunosuppression caused by the radioiodine used to treat thyroid neoplasia. In fact, some authors sustained that radioiodine therapy may cause transient bone marrow suppression that may result in a decrease in white blood cell and platelet count for 6-10 weeks after therapy with increased susceptibility to infection (12).

In the present case, the infectious phenomena caused an erosion of the bone (Fig. 1b), determining the impairment of the supporting function and the establishment of an osteomilelitic process. The base area of the nail plate close to the matrix, already deformed because of the previous trauma, was also involved in the infectious process. Due to the complexity of the clinical case and the patient's need to maintain perfect finger function, the choice of treatment was not easy, in the absence of specific guidelines.

An aggressive and deep bone curettage or resection, accompanied by the removal of the nail plate and use of antibiotized cement and techniques such as Masquelet, with proven efficacy on diaphyseal portions (13) would have significantly reduced the risk of an infectious recurrence providing of an eradicating treatment, but this would have compromised the support structures of the distal phalanx, increasing the possibilities of intervening with an amputation thus invalidating the patient's functional request. Furthermore, the increased risk of poor functional outcome was considered, given the preoperative swelling conditions of the finger (14).

Therefore, in agreement with the patient, we decided to carry out a minimal surgical treatment together with a targeted and long-lasting antibiotic therapy, safeguarding the morphostructure of the finger with its functionality, and accepting the increased risk of chronic infection.

The diagnosis of pilomatricoma of the fingers is a rare occurrence that can often be confused with other pathological conditions, when it is associated with infection. The treatment proved to be satisfactory at all follow-up visits. It remains to evaluate its effectiveness over the long term.

REFERENCES

1. Birman MV, McHugh JB, Hayden RJ, Jebson PJL PILOMATRIXOMA OF THE FOREARM: A CASE REPORT. Iowa Orthop J 2009; 29:121-3.
2. Requena L, Sangüeza O Pilomatricoma. In: Requena L, Sangüeza O (eds) Cutaneous Adnexal Neoplasms. Springer International Publishing, Cham, 2017; 645-69.
3. Song E-H, Lee S-Y, Park H-J, et al Cystic pilomatrixoma of the wrist mimicking a ganglion cyst in a child. J Clin Ultrasound 2013; 41:313-5.
4. Pirouzmanesh A, reinisch Jf, Gonzalez-Gomez I, smith em, meara JG. Pilomatrixoma: A review of 346 cases. Plast Reconstr Surg 2003; 112:1784-1789.
5. Nigam JS, Singh S. Fine-needle aspiration cytology of pilomatrixoma: A short series of three cases. Cytojournal 2018; 46(5):452-5
6. Ieni A, Todaro P, Bonanno AM, Catalano F, Catalano A, Tuccari G. Limits of fine-needle aspiration cytology in diagnosing pilomatrixoma: A series of

25 cases with clinico-pathologic correlations. Indian J Dermatol 2012; 57:152- 5.

7. Agarwal RP, Handler S, Mattews MR, Carpentieri D. Pilomatrixoma of head and neck in children. Otolaryngol. Head Neck Surg 2001; 125:510.
8. Stomeo D, Tulli A, Ziranu A, Perisano C, De Santis V, Maccauro G. Acrometastasis: A literature review. Eur Rev Med Pharmacol Sci. 2015; 19(15):2906-15. Review. Pub Med PMID: 26241547.
9. De Maio et al. J Orthop Traumatol. 2019; 20:25. https://doi.org/10.1186/s10195-019-0532-4.
10. Ziranu A., Lillo M, Fantoni M, Maffulli N, Maccauro G. Single dose cefazolin is safe and effective for pre-operative prophilaxis in orthopaedic oncology. J Biol Regul Homeost Agents. 2018; 32(6 Suppl. 1): 45-49. PubMed PMID: 30644281.
11. Kajino, Y., Yamaguchi, A., Hashimoto, N., Matsuura, A., Sato, N., and Kikuchi, K. -Catenin gene mutation in human hair follicle-related tumors. Pathol Int 2001; 51:543.
12. Fard-Esfahani A, Emami-Ardekani A, Fallahi B, et al. Adverse effects of radioactive iodine-131 treatment for differentiated thyroid carcinoma. Nucl Med Commun. 2014; 35(8):808-17.
13. Careri S, Vitiello R, Oliva MS, Ziranu A, Maccauro G, Perisano C. Masquelet technique and osteomyelitis: innovation and literature review. Eur Rev Med Pharmacol Sci. 2019; 23(2 Suppl):210-216.
14. V. Potenza et al. Injury Int. J. Care Injured 43. 2012; 242-5.

Posterior approaches in malleolar fracture: when, why and how

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The treatment of posterior malleolus fractures has radically changed over the last few years, therefore this study aims to summarize the current evidence on the usefulness of posterior approaches in the management of malleolar fractures. The main elements that suggest the use of a posterior approach to the ankle are: the posterior malleolus fragment shape and size; the presence of loose bodies at the fracture site; the possibility to obtain an anatomic fixation of the fracture; the presence of a posterior ankle subluxation; the eventually osteochondral impaction of the tibial plafond and the mechanical stability of the joint (9). The postero-lateral approach has been widely used to treat these fractures, but the posteromedial approach should be considered in specific cases. The anatomic reduction of these fractures leads to joint stability, with a consequent lesser occurrence of post-traumatic arthritis and better functional outcomes.

Ankle fractures or fracture-dislocations account for about 4-5% of all body fractures, with approximately 120-180/100.000 affected persons/ year. The presence of the fracture of the third malleolus, that occurs in about one-third of ankle fractures, correlates with a poorer prognosis and a worse clinical outcome (2). Therefore, it is reported that trimalleolar fractures have a higher risk of post-traumatic osteoarthritis compared with bimalleolar fractures (2).

In recent years, the orthopaedic community is paying increasing attention to the correct analysis and classification of posterior malleolus fractures, but there is still a lack of consensus about the best surgical management of this kind of injuries (1, 2).

Several authors have recently depicted that different fracture features, including fracture pattern, comminution, fragment impaction and orientation, should be assessed to perform a successful surgery (2-5). Moreover, the relationship between posterior malleolus and syndesmosis should be evaluated, since the posterior inferior tibiofibular ligament, which provides about 40% of the stability of the syndesmosis, extends from the posterior malleolus to the posterior tubercle of the fibula. Consequently, a fracture of the posterior malleolus can impair the stability of the posterior syndesmosis, thus leading, if not correctly managed, to a chronic tibiofibular instability (2, 4-7). All these findings have caused a significant evolution of the surgical management of posterior malleolus injuries (2, 3). This study aims to summarize the current evidence on the usefulness of posterior approaches in the management of malleolar fractures.

From percutaneous anteroposterior fixation to open posterior approaches

In the past, percutaneous anteroposterior fixation

Keywords: ankle fractures; posterior approach; bimalleolar fracture; trimalleolar fracture; ankle fracture and dislocation.

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was generally used in the management posterior malleolus fractures (8). Therefore, after the fixation of lateral and medial malleoli, with the patient in the supine position, the posterior malleolus was addressed by a 3.5/4.0 cannulated screw (1, 9). This minimally invasive technique aimed to reduce the malleolar fracture through ligamentotaxis.

However, this percutaneous technique was endowed with several disadvantages, including the limited effectiveness of ligamentotaxis, the impossibility to remove loose fragments eventually observed at the fracture site, and the potential tibialis anterior nerve or artery damage. Furthermore, the anteroposterior partially threated screw may not provide enough interfragmentary compression when the thread of the lag screw partially crosses the fracture line (2, 10).

In the last two decades, the increasing use of the preoperative CT has led to a better knowledge of the posterior malleolus anatomy and a more accurate study of the posterior malleolus fracture, therefore the percutaneous fixation of the posterior malleolus fracture has been progressively reconsidered (10-11).

Based on CT images, Haraguchi et al. (5) and Bartonicek et al. (6) have realized two different classification system, to better describe the posterior malleolus fracture pattern. It has also been strongly suggested that three-dimensional morphology of the posterior malleolar fragment might be more important than the fracture size in decision making (1, 11).

These recent acquisitions have raised two main questions concerning both the surgical indication for the fixation of the posterior malleolus fracture and how the choice of the correct surgical approach.

It could be argued, however, that percutaneous anteroposterior fixation could be useful in presence of a big posterior fragment (i.e. Haraguchi type I or Bartonicek type IV). The posterior approach, on the other hand, can effectively expose the posterior aspect of the tibia, thus allowing an accurate fracture reduction and fixation.

WHEN AND WHY TO USE THE POSTERIOR APPROACH(ES)

The posterior approach is the preferred choice when the percutaneous antero-posterior fixation is not indicated (9). The main elements that should be assessed in the decision-making process are: the posterior malleolus fragment shape and size; the presence of loose bodies at the fracture site; the possibility to obtain an anatomic fixation of the fracture; the presence of a posterior ankle subluxation; the eventually osteochondral impaction of the tibial plafond and the mechanical stability of the joint (9).

Size and shape of the posterior malleolus and orientation of the fracture line

As we mentioned above, a percutaneous antero-posterior fixation can effectively stabilize the third malleolus in case of a single, bulky, fragment (Haraguchi I / Bartonicek IV). The fragment should be big enough to contain the whole screw thread, otherwise there the lag screw may distract – rather than compress – the fracture (1, 3) (Fig. 1a).

Furthermore, as it could be noticed on a CT scan, the fracture line is usually oblique; in such a case, it is extremely difficult to evaluate the effective percutaneous fixation of the fracture under fluoroscopic control. Since fracture compression has a crucial role in posterior malleolus fractures healing (8), it should be noted that when it is not possible to perform a complete fracture compression with a percutaneous antero-posterior screw, an open reduction and internal fixation through the posterior approach should be considered (4,5).

Therefore, when fixing the fracture from the posterior approach, the screws, either inside or outside the plate, have a postero-anterior direction. With these screws, the fracture compression could be achieved regardless of the dimension of the posterior malleolus (4, 5).

Interposed fragments/loose bodies

It is quite common, especially in ankle fracture-dislocations, that a bone fragment (i.e. cortical bone, cancellous bone, or osteochondral fragment) can be found at the fracture site (Fig. 1b). A preoperative CT scan is mandatory, to lower the risk missing these loose bodies, that could prevent the fracture percutaneous reduction. The posterior approach is very useful to remove these interposed fragments before reducing and fixing the fracture (4, 6).

Anatomic reduction of the fracture

Occasionally, the reduction of the posterior malleolus is obtained with the anatomic reduction of the lateral malleolus, since these two anatomic structures are connected by the posteroinferior tibiofibular ligament. However, when it is not possible to achieve the posterior malleolus fracture reduction through ligamentotaxis, the lesion should be performed by forcing the foot in talus (5). When this manual manipulation does not lead to the fracture reduction, this could be achieved by performing the posterior approach. Failure to restore the joint congruence, with a step of more than 2 mm, is associated with a bad functional outcome at one-year follow-up (1-3, 5-6). Additionally, a significant incidence of postoperative osteoarthritis is reported in presence of a residual articular step greater than 1 mm, regardless of the fragment size.

Posterior joint subluxation

Even when the posterior malleolus fracture consists of small-size fragments (less than 10-25% of articular surface of the distal tibia), it is possible that the fracture could cause a posterior subluxation of the ankle joint (Fig. 1c), because of the presence of the tibiofibular ligament, whose posteroinferior part create a connection between the posterior malleolus and the posterior tubercle of the lateral malleolus (3). This ligament is responsible for the posterior stability of the syndesmosis. If posterior talar translation persists on lateral fluoroscopic view, the posterior malleolar fragment should be addressed. In these cases, a fixation of the posterior malleolus fracture with plate and screws could firmly fix the fragments (including the small ones) with their ligamentous connections.

Osteochondral impaction of the posterior plafond

Especially in cases of posterior fracture with medial extension (Haraguchi II / Bartonicek III), there is an impaction of the posterior part of the plafond (12) (Fig. 1d). Through the posterior approach, this impaction can be disengaged and properly reduced. In case of severe fragmentation of the articular surface, with a risk of residual loose bodies, the fragments can be removed before reducing the malleolus.

Mechanical stability

The plate obviously provides higher stability, compared with a percutaneous antero-posterior screw, since it acts as an anti-glide device, by contrasting the tendency of the posterior malleolus to displace superiorly (1,4). A strong fixation can consequently allow an early weight-bearing (1, 4- 5).

HOW TO PERFORM THE POSTERIOR APPROACHES

Postero-lateral approach

The postero-lateral approach is indicated when there is an involvement of posterior malleolus, regardless of the dimension of the fragments (7, 10). However, through this approach the most medial

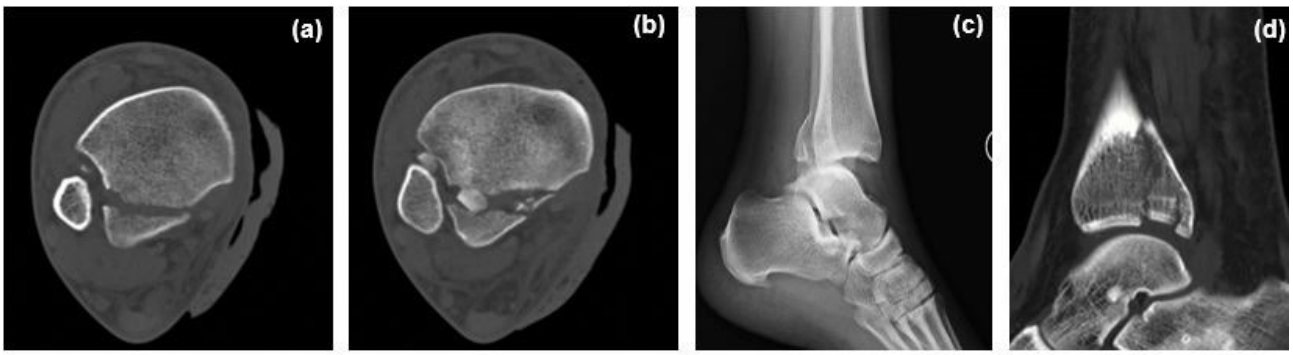

Fig. 1. *Posterior approach to the ankle: main indications.* ***1a****): Small posterior fragment, not large enough to contain the whole screw thread;* ***1b****): Interposed fragment at the fracture site;* ***1c****): Posterior talar subluxation, with a concomitant fracture of the posterior malleolus;* ***1d****): Osteochondral impaction of the tibial plafond.*

part of the distal tibia could not be reached, therefore when the fracture involves the medial tibia, the postero-medial approach should be preferred.

The patient lies in prone position or in a sloppy lateral decubitus. A tourniquet is applied at the ipsilateral thigh and inflated just before starting the procedure. The skin incision is placed between the medial border of the posterior fibula and the lateral edge of the Achilles tendon. It could be a little more medial rather than lateral, depending on the presence of a fibular fracture to be fixed. The sural nerve lies in the subcutaneous tissue and runs from medial to lateral at about 7-10 cm from the Achilles tendon calcaneal insertion.

The peroneal tendons are retracted laterally, the flexor hallucis longus is lifted off the interosseous membrane and the posterior aspect of the tibia. The flexor hallucis longus is the medial limit of the deep extension of the approach because the neurovascular bundle lies just medial to it (Fig. 2).

During the deep dissection, care must be taken to isolate and ligate the collateral rami of the fibular artery and vein, that cross the tibia from lateral to medial side.

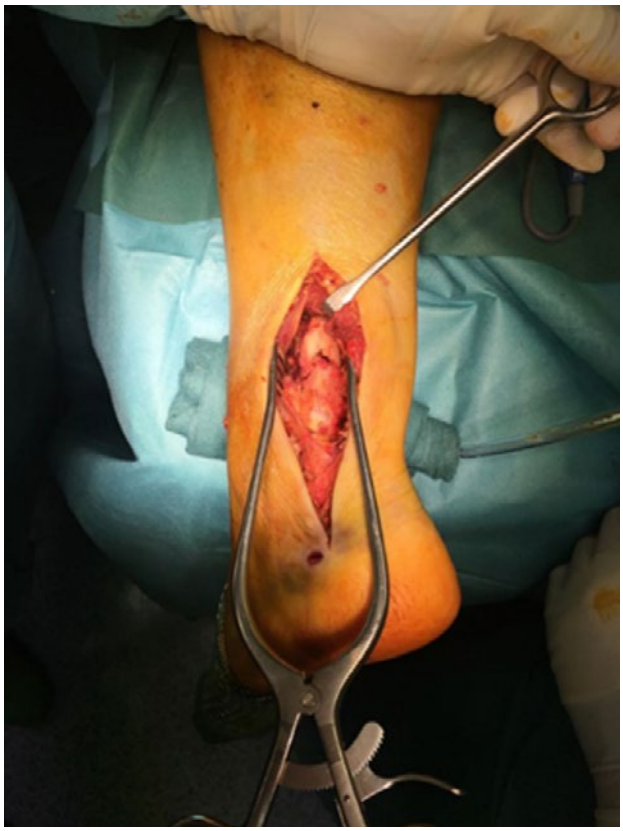

Fig. 2. *Posterolateral approach to posterior malleolus.*

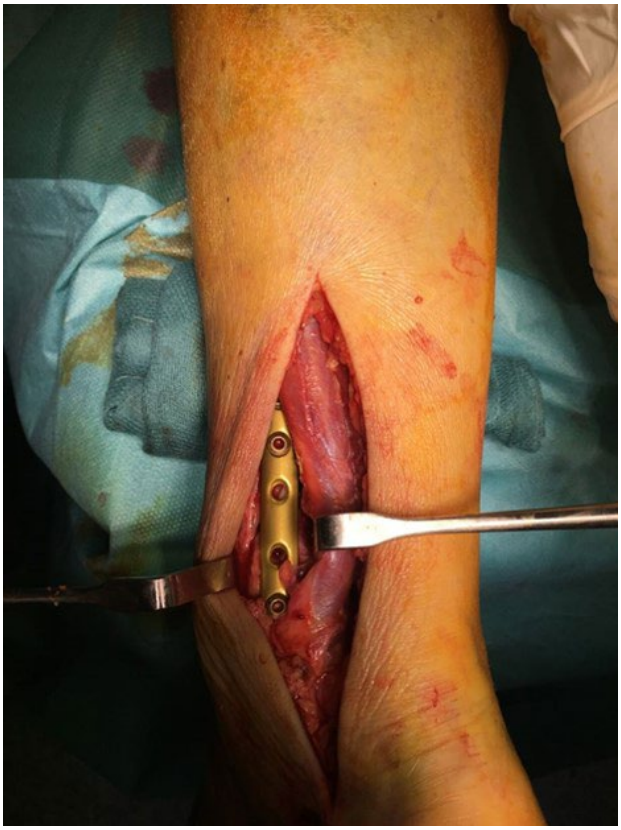

Fig. 3. *Fixation of the fibula through the posterolateral approach.*

The posterior malleolus is usually attached to the fibula by the posterior sindesmosis (postero-inferior tibio-fibular ligament, typically intact in these fractures): care must be taken to avoid any surgical damage to this structure (14). If the posterior malleolus needs to be opened (for inspection of the joint surface), this should be done from its medial edge, leaving the lateral ligament attachment.

After an accurate fracture debridement, the reduction is achieved through a gentle traction and anterior push on the foot (rather than with simple dorsiflexion of the ankle). Spike pusher can help to gain the adequate reduction. The reduction is confirmed by the cortical congruence of the fracture fragments and by lateral image on fluoroscopy. Temporary fixation of the fracture is obtained with small K-wires.

After obtaining a satisfactory reduction, the fixation can be performed with screws or an anti-glide plate; it depends on the morphology and on the dimension of the posterior fragment. In presence of a large fragment, a 3.5 mm plate can be used, while in case of a more complex fracture pattern, a T plate, a distal radius volar plate or a dedicated plate can be used. Regardless of the plate used, it is fundamental to obtain compression at the fracture site. Compression can be achieved with a lag screw (in or outside the plate); anti-glide plate increases this effect.

The main complications related with the postero-lateral approach (5-40% in the different studies) are skin problems (especially if a fibular fracture is treated with the same approach), wound infection, sural nerve numbness and complex regional pain. This complication rate is comparable with other approaches to the ankle.

In presence of a concomitant lateral malleolar fracture, its fixation can be achieved through this approach. The peroneal tendons are elevated and mobilized medially, thus exposing the posterior aspect of the distal fibula (Fig. 3).

Postero-medial approach

In 2004, Weber described a trimalleolar fracture with involvement of the posterior malleolar margin, the entire posterior tibial surface and the posterior colliculus of the medial malleolus (12). Many of these fractures had impacted osteochondral fragments at the posteromedial corner of the tibial plafond.

Later, some authors described this particular lesion as “posterior pilon variant”. This injury was caused by combined forces, i.e. low energy torsion and high energy compression. The radiological sign of “double contour” on AP view indicates the presence of posterior pilon variant (13).

Haraguchi et al. classified this pattern as type II, considering this lesion intrinsically unstable because of the fracture of the posterior colliculus of the medial malleolus, where the deep deltoid is attached. Failure to identify and properly treat this lesion can lead to persistent talar subluxation.

The patient is positioned prone with the tourniquet applied at the thigh. The incision is carried out along the tibialis posterior tendon and it can curve anteriorly in case of involvement of the anterior portion of the medial malleolus. The approach is deepened through the subcutaneous fat and fascia, in line with the postero-medial crest of the tibia. The flexor tendons and the neurovascular bundle are retracted laterally (Fig. 4). The distal limit of exposure of the posterior portion of the medial malleolus is the presence of the flexor retinaculum; in such cases, the flexor tendons can be mobilized medially and the dissection carried out between them

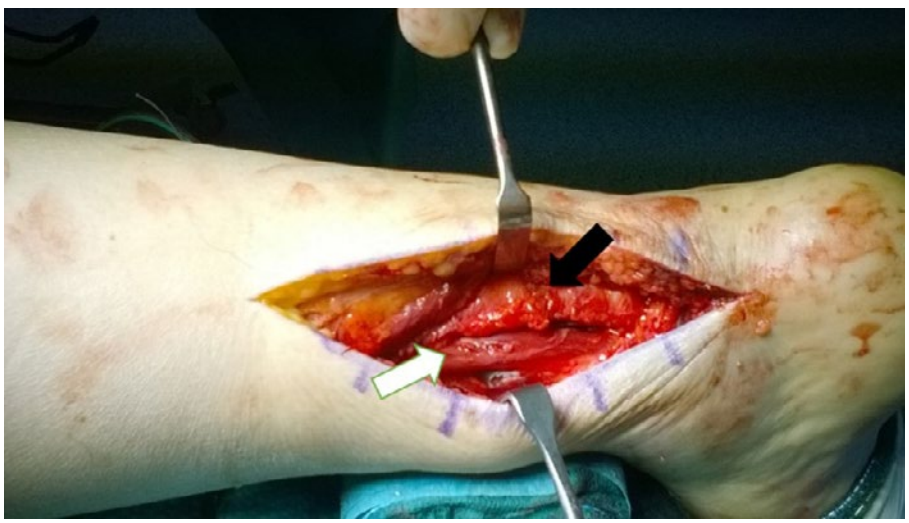

Fig. 4. *Posteromedial approach: posterior tibialis muscle (white arrow) and neurovascular bundle (black arrow).*

and the neurovascular bundle. If this is not enough for the exposure, the retinaculum can be cut and the flexor tendons mobilized anteriorly; at the end of the procedure the retinaculum should be repaired.

This approach can be extended anteriorly to address the anterior part of the medial malleolus, paying attention to protect the saphenous vein. It is difficult, through this approach, to reach the central and lateral third of the posterior malleolus; excessive retraction applied to the neurovascular bundle can cause neurapraxia of the posterior tibialis nerve or vascular lesions.

An alternative postero-medial approach can be adopted via a more lateral incision, carried out between the Achilles tendon and the postero-medial border of the tibia (13). In this case, the neurovascular bundle is isolated, protected and retracted medially to gain access to the posterior malleolus, or laterally to have access to the postero-medial malleolus. After exposure, the fracture should be debrided, reduced and fixed, as described for the postero-lateral approach.

Choice of the posterior approach and fixation timing

The postero-lateral approach is the most popular and the most employed approach in the fixation of the posterior malleolus fractures. Caution is required in identifying and protecting the sural nerve. This approach can be used to treat both posterior and lateral malleolar fractures.

The postero-medial approach should be performed in case of involvement of the postero-medial border of the tibia. Care should be taken to identify and protect the posterior neuro-vascular bundle, especially in the variant of the postero-medial approach.

In some cases, because of the morphology of the fracture of the lateral malleolus (i.e. plurifragmentary, distal fibular involvement), a formal lateral approach is necessary for the proper fixation of the fibular fracture. In all these cases, the lateral and postero-lateral approaches could be too close to one another, resulting in a short skin bridge between the two incisions. In such cases, as described above, a modified postero-medial approach is extremely useful to address the posterior malleolus; this allows to obtain a safe skin bridge between the two surgical incisions.

The order of fixation of the fractures of the malleoli is a matter of debate (2, 4). The fixation of the fibula restores length and facilitates the posterior malleolar reduction, but the fibular plate can hinder the fluoroscopic visualization of the joint line in the lateral view.

In case of posterior malleolus fractures with interposed small osteochondral fragments, these fragments can interfere with the anatomic reduction of the lateral malleolus, because of the strong ligamentous connections between the posterior fibula and the lateral portion of the posterior malleolus (posterior syndesmosis). Therefore, it is advisable to first reduce and fix the posterior malleolus and, subsequently, the medial or lateral malleolar fractures.

The treatment of posterior malleolar fractures has radically changed over the last few years. Anatomic studies together with a better understanding of the fundamental functional role of the posterior malleolus in ankle stability have led to a more aggressive surgical treatment of these lesions. Currently, the posterior approaches to the ankle have gained a central role in the correct management of posterior malleolar injuries.

REFERENCES

1. Odak S, Ahluwalia R, Unnikrishnan P et al. Management of Posterior Malleolar Fractures: A Systematic Review. J Foot Ankle Surg. 2016; 55(1):140-5.
2. Duan X1, Kadakia AR. Operative Treatment of Posterior Malleolar Fractures. Open Orthop J. 2017; 11:732-42.
3. Evers J, Barz L, Wähnert D et al. Size matters: The influence of the posterior fragment on patient outcomes in trimalleolar ankle fractures. Injury. 2015; 46 Suppl4:S109-13.
4. Tenenbaum S, Shazar N, Bruck N et al. Posterior Malleolus Fractures. Orthop Clin North Am. 2017; 48(1):81-9
5. Haraguchi N, Haruyama H, Toga H et al. Pathoanatomy of posterior malleolar fractures of the ankle. J Bone Joint Surg Am. 2006; 88(5):1085-92.

6. Bartoníček J1, Rammelt S, Kostlivý K et al. Anatomy and classification of the posterior tibial fragment in ankle fractures. Arch Orthop Trauma Surg. 2015; 135(4):505-16
7. Hoogendoorn JM. Posterior Malleolar Open Reduction and Internal Fixation Through a Posterolateral Approach for Trimalleolar Fractures. JBJS Essent Surg Tech. 2017; 7(4)e31.
8. Irwin TA, Lien J, Kadakia AR. Posterior malleolus fracture. J Am Acad Orthop Surg. 2013; 21(1):32-40.
9. Verhage SM, Hoogendoorn JM, Krijnen P et al. When and how to operate the posterior malleolus fragment in trimalleolar fractures: a systematic literature review. Arch Orthop Trauma Surg. 2018; 138(9):1213-22.
10. Zhong S1, Shen L2, Zhao JG et al. Comparison of Posteromedial Versus Posterolateral Approach for Posterior Malleolus Fixation in Trimalleolar Ankle Fractures. Orthop Surg. 2017; 9(1):69-76.
11. Mangnus L, Meijer DT, Stufkens SA et al.Posterior Malleolar Fracture Patterns. J Orthop Trauma. 2015; 29(9):428-35.
12. Weber M. Trimalleolar fractures with impaction of the posteromedial tibial plafond: implications for talar stability. Foot Ankle Int. 2004; 25(10):716-27
13. Wang Y, Wang J, Luo CF. Modified posteromedial approach for treatment of posterior pilon variant fracture. BMC Musculoskelet Disord. 2016; 17:328.
14. Carrozzo M, Vicenti G, Pesce V et al. Beyond the pillars of the ankle: A prospective randomized CT analysis of syndesmosis' injuries in Weber B and C type fractures. Injury. 2018; 49Suppl3S54-S60.

Humeral shaft butterfly fractures managed with intramedullary nail: could the third fragment features predict the fracture healing time?

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To assess the impact of the radiological features of the third fragment on the outcome of humeral shaft fractures type 12-B managed with endomedullary nails. We retrospectively evaluated a series of 80 patients, divided into 3 groups, according to the fracture healing time: within 6 months (group-A), between 6 and 12 months (group-B) or fracture non-union after 12 months (group-C). In 26 patients out of 80 the fracture healing was observed at 6 months follow-up; in 47 out of 80 at 12 months after trauma and in 7 out of 80 no fracture healing was observed at 12 months follow-up. Regression analysis showed that the third fragment displacement and angulation are the most important features that affect the fracture healing. The mean third fragment dislocation (cut-off: 12 mm) is the main parameter to influence the fracture healing within or in more than six months.

Humeral shaft fractures are a quite common injury, accounting for about 3%-5% of all fractures in the adults (1-2). Non-union is a frequent complication occurring in 10% of humeral shaft fractures conservatively managed (2-4) and in 30% of fractures surgically treated (5). A higher incidence of non-union has been reported in humeral shaft fractures with butterfly or wedge fragment, i.e. type 12-B fractures according to the AO/OTA classification (4), which account for about 26.2%-29.6% of humeral shaft fractures (6–8).

Closed reduction and fixation with intramedullary nail is one of the most accepted treatment for humeral shaft fractures with butterfly fragment, since it avoids the exposure of the fracture and preserves the integrity of the hematoma, thus promoting the fracture healing (9-15). Nonetheless, a non-union rate of about 5.5%-6% is reported in such a kind of fractures (9-14).

The predicting factors of delayed-union or non-union for AO/OTA 12-B fractures are unfortunately still unclear. Castellá et al. have recently depicted a great lateral butterfly fragment is a predictive factor for humeral shaft fractures non-union, because of the abduction moment produced by the third fragment, which is not counterbalanced by the deltoid muscle; furthermore, in women with pendulous or large breasts a varus angulation of the fracture may be observed, thus increasing the facture displacement and distraction (2). An et al. have recently argued that displacement and angulation of the fracture could delay the bone healing, in humeral and femoral shaft fractures with butterfly fragment managed with closed reduction (16).

None of the previous studies however, to the Authors' knowledge, has investigated how the radiological aspect of humeral shaft fractures with butterfly fragment could affect the bone healing time.

Keywords: Humeral shaft fractures; third fragment; butterfly fragment; intramedullary nailing.

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This retrospective study aims to evaluate the impact of the radiological features of the third fragment, observed on post-operative X-Rays, on the outcome of AO/OTA type 12-B fractures managed with closed reduction and fixation with elastic systems, in order to obtain an algorithm which could predict the fracture healing time.

MATERIALS AND METHODS

We retrospectively reviewed a series of 88 patients with humeral shaft fractures referring to our Department between January 2010 and December 2015. Clinical and radiological data were obtained from our trauma database.

Inclusion criteria were type 12-B fracture according to AO/OTA classification system; minimum clinical and radiological 12-months follow-up and surgical management with close reduction and fixation with endomedullary nail.

Exclusion criteria were: type 12-A or 12-C fractures according to AO/OTA classification system; surgical management with open reduction and internal fixation; periprosthetic fractures; exposed fractures; history of infections or malignant neoplasms; osteoporosis, defined as lumbar or hip T-score<2.5; diabetes mellitus; BMI>35 kg/m^2.

By applying the inclusion and exclusion criteria, eighty patients (29 male and 51 female, mean age 63.4, range 48-72) were recruited for the current study. All the patients had undergone a clinical and radiographic follow-up at 1, 2, 3, 6, 9 and 12 months postoperatively.

The patients were then divided into three groups according to the time needed to reach the bone healing: group A: fracture healing occurred within 6 months; group B: fracture healing occurred between 6 and 12 months; group C**:** fracture non-union after 12 months.

Surgical management and postoperative care

The mean time from trauma to surgery was about 54 hours (range 27-81 hours); the affected arm was immobilized with an upper arm sling preoperatively. All the patients underwent anterograde endomedullary nailing (MultiLoc Humeral Nailing System, Synthes GmbH, Oberdorf, Switzerland). The mean length of postoperative hospital stay was 5 days (range 3-9 days). After surgery, a compression bandage was performed and the limb was protected with a sling for 4 weeks. Two weeks post-operatively, the patient was asked to execute pendulum exercises of the shoulder and passive flexion and extension of the elbow; four weeks post-operatively, the sling was removed and the patients were encouraged, under the supervision of a physiotherapist, to actively mobilize the shoulder and the elbow progressively.

Radiographic study

Post-operative anteroposterior (AP) and lateral (LL) shoulder X-rays were analysed by two orthopaedic surgeons with more than five years of experience in shoulder surgery. On each X-ray, the following parameters (figure 1a-d) were measured in AP view:

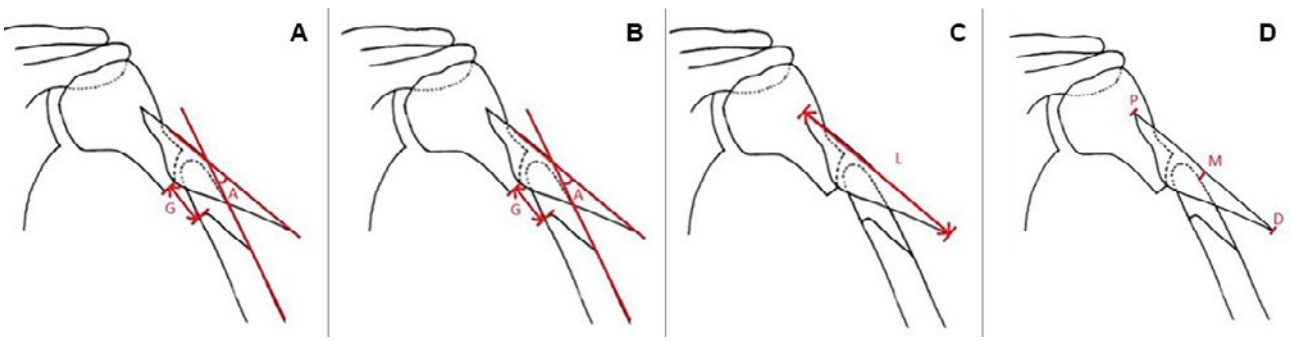

Fig. 1. *Description of the radiographic parameters:*
***a**): third fragment angle (A): defined as the angle between a line parallel to the humeral diaphyseal cortex and a line parallel to the third fragment cortex; **b**): fracture gap (G): defined as the distance between the proximal diaphyseal fragment and the distal one; **c**): third fragment size (L): defined as the length of the major axis of the fragment; **d**): mean third fragment displacement (M): defined as the perpendicular distance between the midpoint of the fragment and the nearest humeral shaft cortex.*

- third fragment angle (A): defined as the angle between a line parallel to the humeral diaphyseal cortex and a line parallel to the third fragment cortex;
- fracture gap (G): defined as the distance between the proximal diaphyseal fragment and the distal one;
- third fragment size (L): defined as the length of the major axis of the fragment;
- mean third fragment displacement (M): defined as the perpendicular distance between the midpoint of the fragment and the nearest humeral shaft cortex.

Other two orthopaedists evaluated the follow-up X-rays, performed at 1, 2, 3, 6, 9 and 12 months postoperatively, to assess the bone healing. The fracture was considered healed when a bone callus could be depicted in at least three bone cortices out of four in AP and LL views.

Statistical Analysis:

Statistical analysis was performed using STATA/MP 14 for Windows (Stata Corp LP, College Station, USA). The Shapiro-Wilk test was conducted to verify the normal distribution of the data. One-way ANOVA (Analysis of Variance) was used to assess the differences between the three groups. Bonferroni multiple-comparison test was then executed to evaluate the differences between each group.

Pearson correlation test was performed in group-A and group-B, to assess the association between union time and the fracture gap, third fragment size, angle and mean displacement. Logistic regression analysis was conducted to investigate the effects of the fracture gap and the third fragment size, angle and mean displacement on the fracture union. The tests were two-tailed with a confidence level of 5%.

RESULTS

Eighty patients (29 male and 51 female, mean age 63.4, range 48-72) were recruited for the current study. In 26 patients out of 80 (32.5%) the fracture healing was observed at 6 months follow-up (group-A), in 47 out of 80 (58.75%) the fracture healed within 12 months after trauma (group-B) and in 7 out of 80 (8.75%) no fracture healing was observed at 12 months follow-up (group C). The

Table I. *General data of the study.*

	Group-A	Group-B	Group-C
# of patients	26	47	7
Age			
Mean ±SD	59.2±12.6	64.5±10.4	57.5±10.3
Gender			
Male. n (%)	8 (30.77%)	19 (40.425%)	2 (28.57%)
Female. n (%)	18 (69.23%)	28 (59.575%)	5 (71.43%)
BMI (Kg/m^2)			
Mean ±SD	27.2±5.1	28.4±5.8	26.3±4.9
Side			
Left. n (%)	10 (38.46%)	21 (44.68%)	2 (28.57%)
Right. n (%)	16 (61.54%)	26 (55.32%)	5 (71.43%)
Smoking status			
# of smokers. n (%)	4 (15.38%)	6 (12.765%)	1 (14.28%)
AO Classification			
12-B1. n (%)	11 (42.3%)	10 (21.28%)	-
12-B2. n (%)	9 (34.63%)	16 (34.04.%)	1 (14.25%)
12-B3. n (%)	6 (23.07%)	21 (44.68%)	6 (85.75%)
Union time (months)			
Mean ±SD	4.43±0.975	8.33±1.862	N/D
Range	3-6	7-11	N/D

main data of the study are summarized in Table I.

Shapiro-Wilk test results are reported in Table II: the radiological features of the third fragment showed a normal distribution.

Table III shows the One-way ANOVA results and Table IV summarizes the Bonferroni multiple-comparison test results: mean third fragment displacement was significantly different in each group ($p<0.05$), while the third fragment angle was significantly higher in group-C, compared with other groups (Table IV).

Pearson Correlation Test is shown in Table V, in group-A, a positive correlation was found between union time, mean third fragment displacement ($R=0.698$; $p=0.0018$) and third fragment angulation ($R=0.645$; $p=0.0052$); in group-B, the fracture union time was positively related to third fragment size ($R=0.616$; $p=0.008$), mean third fragment displacement ($R=0.683$; $p=0.0025$) and third fragment angulation ($R=0.724$; $p=0.00613$) (Table V).

The linear regression analysis results are summarized in Table VI: the impact of the mean third fragment displacement (x) on the fracture healing (y) is summarized by the following equation: $y=3.268 + 0.208x$.

It could be noted that a humeral shaft fracture with a third fragment reduced needs about 3 months and 9 days to heal; every millimetre of third fragment displacement increases the fracture healing time of about 0.7 days. The influence of the third fragment angulation (y) on bone healing (x) is described by the following equation: $y=2.93 + 0.214x$.

It could be argued that a humeral shaft fracture with a third fragment with a null angulation needs about three months to heal; every degree of third fragment angulation increases the fracture healing time of about 0.8 days. Multiple regression analysis was finally conducted to evaluate the concomitant effect of mean third fragment displacement (x) and mean third fragment angulation (y) on the fracture healing; thus, the following equation was obtained: $y=3.15 + 0.215x + 0.209y$

Based on this data, we have proposed a prognostic algorithm which is shown in Fig. 2.

DISCUSSION

Humeral shaft fractures with butterfly or wedge

Table II. *Normality investigation.*

	Shapiro-Wilk	
	W	*p*
Third Fragment Size	0.948	0.308
Mean Third Fragment Displacement	0.956	0.355
Third Fragment Angle	0.884	0.107
Fracture Gap	0.925	0.294

Table III. *Radiological Study: comparison between the three groups (One-way ANOVA).*

	Group-A	Group-B	Group-C	*p*-value
Third Fragment Size (mm)	67±31.64	98.68±33.36	83.75±56.43	0.256
Mean Third Fragment Displacement (mm)	5.58±3.27	10.28±3.23	14.64±5.53	**0.013***
Third Fragment Angle (°)	6±2.64	8.5±3.26	15.5±4.8	**0.0017***
Fracture Gap (mm)	3.64±2.79	3.9±2.4	5.75±2.63	0.2811

***Significant *p*-value**

Table IV. *Bonferroni multiple-comparison test.*

Mean Third Fragment Displacement (mm)	
Comparison between Group A and B	
Comparison between Group A and C	
Comparison between Group B and C	
Third Fragment Angle (°)	
Comparison between Group A and B	
Comparison between Group A and C	
Comparison between Group B and C	

***Significant *p*-value**

fragment are a quite common injury; they result from the combined action of compression and bending or torsional forces (17-18). This kind of injuries constitutes a specific subset of humeral shaft fractures since the presence of a butterfly fragment could influence the fracture healing process. The third fragment size is considered a critical feature to predict its fate: while smaller fragments could be disregarded, larger pieces may contribute to the stability and the healing of the fracture, thus it should be carefully considered in the surgical planning (19).

According to AO principles, open reduction and internal fixation (ORIF) with plate and screws is the

Table V. *Pearson Correlation Test.*

	Union Time			
	Group-A		**Group-B**	
	R	***p***	**R**	***p***
Third Fragment Size (mm)	0.0215	0.933	0.616	**0.008***
Mean Third Fragment Displacement (mm)	0.698	**0.0018***	0.683	**0.0025***
Third Fragment Angle (°)	0.645	**0.0052***	0.724	**0.00613***
Fracture Gap (mm)	0.401	0.11	0.46	0.0632

Table VI. *Linear Regression Analysis.*

Union time	**Mean Third Fragment Displacement**	**Third Fragment Angle**
R^2	0.6276	0.7875
p	**0.018***	**0.0077***
Intercept		
Coefficient	3.268	2.9286
Std. Error	0.6	0.3951
95% CI	1.7-4.82	1.92-3.944
p	**0.003***	**0.0007***
Slope		
Coefficient	0.2	0.2143
Std. Error	0.095	0.04978
95% CI	-0.037-0.453	0.086-0.3423
p	**0.008***	**0.0077***

***Significant *p*-value**

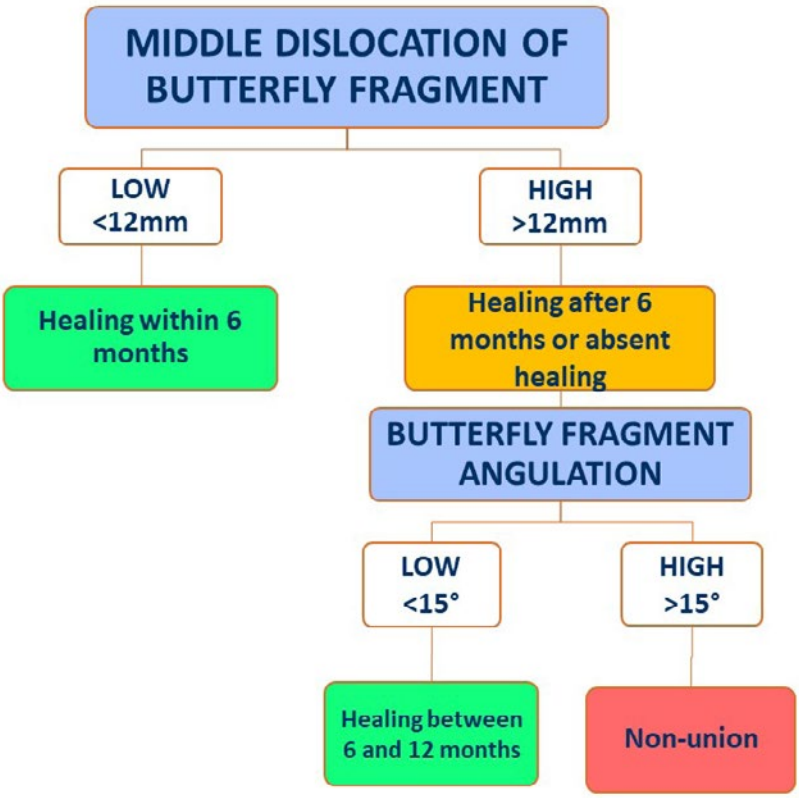

Fig. 2 *The prognostic algorithm.*

most effective treatment for this fracture pattern. This surgical procedure, however, shows some critical aspects that cannot be overcome. Firstly, the evacuation of the fracture haematoma performed in ORIF procedure could obstruct the bone healing, especially in fractures with a large and butterfly fragment, due to the precarious local blood supply. Secondly, while a unicortical fracture configuration is stable after fixation, a bicortical butterfly segment represents an unstable configuration which could require a supplemental stabilization with cerclage wires or bone grafts. Finally, ORIF often needs an extensive and invasive approach, exposing a great part of the humeral diaphysis; wider is the approach, higher is the infection risk, consequently the non-union rate.

To avoid these problems, closed reduction and internal fixation with elastic systems is widely used in last years to treat this fracture pattern. Despite the minimal access, the respect of soft tissue, the fracture locus and the local haematoma, the non-union rate for this fracture pattern is about 5.5%-6% (9-11). The predicting factors of non-union, however, are still not clarified. The third fragment size, displacement and angulation have been found to influence the healing of both humeral shaft (2, 13-16) and femoral shaft fractures (16, 20-23). Nonetheless, it is unclear how the third fragment features could affect the fracture healing time.

In the current study, we retrospectively reviewed a series of 80 patients with 12-B fracture type according to AO/OTA classification, to assess the impact of the third fragment features on the healing time. Our data show that the third fragment dislocation and angulation, evaluated on post-operative X-rays of humeral shaft fracture treated with intramedullary nail, are the two key features which could affect the fracture healing time.

Consequently, the aim of the closed reduction of 12-B fractures is to minimize the wedge fragment

dislocation and angulation, to shorten the fracture healing time.

Indeed, we found that a third fragment dislocation shorter than 12mm. is a predictive factor of fracture union within six months, whereas a dislocation greater than 12mm. may suggest a healing time longer than six months. In presence of a high wedge fragment dislocation (>12mm), the fragment angulation should be taken into account: if the third fragment angulation is less than 15°, the fracture healing could be seen within 12 months, whereas a third fragment angulation greater than 15°, combined with a high dislocation, may predict a fracture non-union, thus a surgical revision of the fracture may be needed in this case.

We remark that our data agree with the ones reported in other studies (2, 12, 16, 20-21), but we also propose a prognostic algorithm which could help the physician in decision making, in the closed treatment of humeral shaft fractures.

This study has some limitations, that could not be overcome. Even if all the data were collected in blind manner, the sample size is quite small, thus future studies with a greater sample size are needed to confirm our data with a higher statistical power. Moreover, future prospective randomized trials will be necessary to finally validate our algorithm.

Humeral shaft fractures with butterfly fragment are an insidious fracture pattern. In this study, we have proposed a prognostic algorithm to predict the healing time of humeral shaft fractures treated with closed reduction with intramedullary nail. Our data shows that the mean third fragment dislocation (cut-off: 12 mm.) is the main parameter which influences the fracture healing within or in more than six months. The third fragment angulation (cut-off: 15°), on the other hand, impacts on the fracture delayed rather than absent healing.

REFERENCES:

1. Bergdahl C, Ekholm C, Wennergren D, Nilsson F, Möller M. Epidemiology and patho-anatomical pattern of 2011 humeral fractures: data from the Swedish Fracture Register. BMC Musculoskelet. Disord. 2016; 17:159.
2. Castellá FB, Garcia FB, Berry EM, Perelló EB, Sánchez-Alepuz E, Gabarda R. Nonunion of the humeral shaft: long lateral butterfly fracture--a nonunion predictive pattern? Clin. Orthop. Relat. Res. 2014; 227-30.
3. Rutgers M, Ring D. Treatment of diaphyseal fractures of the humerus using a functional brace. J. Orthop. Trauma. 2006; 20, 597-601.
4. Ring D, Chin K, Taghinia AH, Jupiter JB. Nonunion after functional brace treatment of diaphyseal humerus fractures. 2007; J. Trauma 62, 1157–8.
5. Volgas DA, Stannard JP, Alonso J E. Nonunions of the humerus. Clin. Orthop. Relat. Res. 2004; 46-50.
6. Tytherleigh-Strong G, Walls N, McQueen MM. The epidemiology of humeral shaft fractures. J. Bone Joint Surg. 1998; Br. 80, 249-53.
7. Tsai C-H, Fong Y-C, Chen Y-H, Hsu C-J, Chang C-H, Hsu H-C. The epidemiology of traumatic humeral shaft fractures in Taiwan. Int. Orthop. 2009; 33, 463-7.
8. Ekholm, R. et al. Fractures of the shaft of the humerus: an epidemiological study of 401 fractures. J. Bone Jt. Surg. 2006; Br. Vol. 88-B, 1469-73.
9. Hall RF. Closed intramedullary fixation of humeral shaft fractures. Instr. Course Lect. 1987; 36, 349-58.
10. 10.Brumback RJ, Bosse MJ, Poka A, Burgess AR. Intramedullary stabilization of humeral shaft fractures in patients with multiple trauma. J. Bone Joint Surg. Am. 1986; 68, 960-70.
11. Ingman AM, Waters DA. Locked intramedullary nailing of humeral shaft fractures. Implant design, surgical technique, and clinical results. J. Bone Joint Surg. Br. 1994; 76:23-9.
12. Cadet ER, Yin B, Schulz B, Ahmad CS, Rosenwasser MP. Proximal humerus and humeral shaft nonunions. J. Am. Acad. Orthop. Surg. 2013; 21:538-47.
13. Yum JK, Lim DJ, Jung EY, Sohn SE. Clinical and Radiographical Follow-up for Residual Displacement of Fracture Fragments after Interlocking Intramedullary Nailing in Humeral Shaft Fractures. J. Korean Shoulder Elb. Soc. 2013; 107-14.
14. Sahu RL, Ranjan R, Lal A. Fracture union in closed interlocking nail in humeral shaft fractures. Chin. Med. J. (Engl). 2015; 128:1428-32.
15. Scaglione M, Fabbri L, Dell' Omo D, Goffi A, Guido G. The role of external fixation in the treatment of

humeral shaft fractures: A retrospective case study review on 85 humeral fractures. Injury. 2015; 46, 265-9.
16. An KC, Kim YJ, Choi JS, Seo SS, Gwak HC, Jung DW, Jeong DW. The Fate of Butterfly Fragments in Extremity Shaft Comminuted Fractures Treated with Closed Interlocking Intramedullary Nailing. J. Korean Fract. Soc. 2012; 25:46.
17. Muller M, Koch P, Schatzker, J. The Comprehensive Classification of Fractures of Long Bones. Springer Verlag, 1990.
18. Ramachandran M. Basic orthopaedic sciences: the Stanmore guide. Hodder Arnold, 2007.
19. D' Sousa P, Umer M, Lakdawala RH. The ring butterfly fragment. J Pak Med Assoc. 1993; 43(4):80-2
20. Lin SJ, Chen CL, Peng KT, Hsu WH. Effect of fragmentary displacement and morphology in the treatment of comminuted femoral shaft fractures with an intramedullary nail. Injury 2014; 45, 752-6.
21. Lee JR, Kim HJ, Lee KB. Effects of third fragment size and displacement on non-union of femoral shaft fractures after locking for intramedullary nailing. Orthop. Traumatol. Surg. Res. 2016; 102, 175-81.
22. Vicenti G, Carrozzo M, Caiaffa V et al. The impact of the third fragment features on the healing of femoral shaft fractures managed with intramedullary nailing: a radiological study. International Orthopaedics. 2019; 43:193-200
23. Vicenti G, Bizzoca D, Carrozzo M et al. The ideal timing for nail dynamization in femoral shaft delayed union and non-union. International Orthopaedics. 2019; 43:217-22

A comparative study of combined intravenous and topical administration of tranexamic acid with topical tranexamic acid alone for blood loss reduction after primary uncemented total hip arthroplasty

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The aim of the present study was to evaluate the efficacy of topical versus combined (intravenous + topical) tranexamic acid (TXA) to reduce perioperative blood loss after uncemented primary total hip arthroplasty (THA). Seventy-five patients were randomized in three comparable experimental groups: 1) topical TXA (3 g in 50 ml of saline solution); 2) intravenous + topical TXA (3 g topical + 2 g in 100 ml of saline solution intravenously); 3) controls. Pre- and post-operative hemoglobin (Hb) levels and hematocrit (Hct) values along with the rate of blood transfusion in the 3 groups were compared. The intravenous + topical TXA group demonstrated higher Hb levels and Hct values at postoperative day one (Hb = p <0.05, Hct = p <0.001), postoperative day three (Hb = p <0.05, Hct = p <0.001), and discharge (Hct = p <0.01) compared to the control group. The intravenous + topical group had a lower transfusion rate compared to the control group (0% vs 20%, p = 0.014). With the numbers available, no difference in postoperative Hb level and transfusion rate emerged between topical TXA and control group.

Total hip arthroplasty is an effective procedure to manage end-stage osteoarthritis of the hip. However, it may cause significant perioperative blood loss and 16% to 37% of patients need allogeneic blood transfusion (1). Blood transfusion is associated with serious complications including infection, blood transfusion accidents, acute pulmonary embolism, cardiovascular events, and death (2). Furthermore, postoperative bleeding can lead to prolonged hospital stay with increase of costs and to delay in mobilization and rehabilitation of patients. Different techniques can be used to reduce bleeding and the need for allogeneic transfusions in THA, including controlled hypotension, regional anesthesia, and autologous blood predonation.

Among strategies for blood management in THA, the synthetic antifibrinolytic tranexamic acid (TXA) may play a pivotal role. TXA inhibits fibrinolysis by acting competitively by reversibly blocking the lysine binding in the plasminogen, plasmin and tissue plasminogen activator sites, delaying fibrinolysis and degradation of blood clots (3-4). TXA has been proven to reduce total blood loss by nearly 50% and to markedly decrease the need for allogenic blood transfusion after THA (5). However, the optimal dose and methods to deliver TXA in total hip arthroplasty is still controversial. One previous study showed that intravenous (IV) TXA is effective and safe in reducing the total blood loss in THA (6). Topical administered TXA also may represent an

Key words: total hip arthroplasty, tranexamic acid, blood loss, transfusion

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effective option because of the easy administration, high concentration in the bleeding site, and minimal systemic absorption (7). Several studies (8-10) found that topical TXA reduces postoperative bleeding and decreases blood transfusion rates in THA. Combining IV and topical TXA has been shown to give satisfactory results in THA (11).

However, the efficacy and safety of combined topical and IV TXA versus topical TXA alone in THA has not been yet identified. Thus, we performed a prospective study to compare combined topical and IV TXA versus topical TXA alone for reducing total blood loss in THA.

MATERIALS AND METHODS

Seventy-five patients who underwent cementless THA from January 2017 to December 2018 at the Orthopedic Department of "Federico II" University of Naples (Italy) were included in this study. All patients had primary hip osteoarthritis, were operated through a postero-lateral approach under spinal anasthesia and received uncemented prosthetic components including a short femoral stem.

Postoperative antithrombotic prophylaxis involved the administration of low molecular weight heparin (LMWH) 6 hours after surgery and then once a day. Patients who had severe cardiovascular disease, chronic venous insufficiency, hemodynamically relevant arterial pathology, severe nephropathies, and congenital or acquired clotting defect conditions were excluded. Patients who required prophylaxis or treatment with anticoagulant or anti-platelet drugs were also excluded. Once all patients enrolled in the study gave their informed consent, they were randomized to receive topical TXA, both topical and IV TXA, or nothing. On this basis, three groups were created.

The first group included 25 patients who received topical TXA alone at the time of the surgical procedure. Three grams of TXA diluted in 50 mL of 0.9% sodium chloride solution (total volume = 80 ml) were injected into the acetabulum and medullary channel prepared for the implantation of prosthesis and after the reconstruction of joint capsule.

The second group also consisting of 25 patients was given both IV and topical TXA. The topical administration followed the same protocol as the first group. The IV solution was administered in two 50 ml doses, one started 10 minutes prior to incision, and the second during the fascial closure.

The third group did not receive TXA. Patients in the

Table I. *Preoperative data of experimental groups. Data shown as mean ± standard deviation.*

Group	Age	Sex (F/M)	BMI (Kg/m^2)	Hb (g/dL)	Hct
Topical TXA	60.1 ± 10.1	8/17	28.2 ± 3.7	14.1 ± 1.6	42.3 ± 4.4
IV + topical TXA	57.4 ± 13.6	8/17	28.7 ± 3.6	14.4 ± 1.1	43.7 ± 3.5
NO TXA	55.7 ± 12.3	8/17	27.8 ± 4.0	13.9 ± 1.5	41.1 ± 4.4
p value	0.439	1.000	0.715	0.522	0.091

TXA = tranexamic acid; IV = intravenous; BMI = body mass index; Hb = hemoglobin; Hct = hematocrit

Table II. *Hemoglobin level (g/dL) in the three experimental groups. Data shown as mean ± standard deviation.*

	Topical TXA group	IV + topical group	Control group
Preoperative	14.1 ± 1.6	14.4 ± 1.1	13.9 ± 1.5
1st postoperative day	11.3 ± 1.2	11.8 ± 0.9†	10.8 ± 1.3
3rd postoperative day	10.4 ± 1.2	11.1 ± 1.2†	9.9 ± 1.2
Discharge	10.4 ± 1.3	11.0 ± 1.2	10.2 ± 1.3
Lowest postoperative	10.0 ± 1.3	10.5 ± 1.2	9.7 ± 1.2

TXA = tranexamic acid; IV = intravenous

† = $p < 0.05$ compared to the control group

three groups had similar characteristics of age, gender, body mass index (BMI), and preoperative hemoglobin (Hb) and hematocrit (Hct) (Table I). Hemoglobin levels and Hct values were obtained preoperatively and daily thereafter until discharge. Postoperative changes in Hb levels and Hct values between the three groups were analyzed comparing pre-operative with post-operative findings at three time points: first post-operative day, 3rd post-operative day, and discharge. Moreover, the lowest postoperative Hb and Hct was recorded.

Perioperative blood transfusions in the 3 groups were also noted. Finally, the operating time in minutes and length of hospital stay in days were recorded. There was no routine screening for thromboembolic events, but Doppler ultrasonography was obtained in case of clinical suspicion.

Statistical analysis

A T-test for paired data was used to evaluate changes in each group in Hb levels and Hct value. An ANOVA test with Bonferroni post hoc test was used to check cross-sectional differences in continuous variables between the three groups. The chi-square test and Fisher's exact tests was used to assess possible differences in number of blood transfusions in the three groups.

RESULTS

Pre-operative and post-operative Hb levels until discharge in the three groups are reported in Table II. The IV + topical group demonstrated higher post-operative Hb level at postoperative days one and three compared to the control group. There were no significant differences at discharge.

Postoperative changes in Hb level in the three groups are reported in Table III. Significant post-operative drop in Hb level was detected in all groups at the two first time intervals (pre-operative - 1st postoperative day and 1st - 3rd postoperative day), without significant difference in Hb decrease between groups.

Table IV shows pre- and postoperative Hct values in the three groups. Higher Hct value in IV + topical group compared to the control group was detected throughout the postoperative period until discharge, whereas a difference between topical

Table III. *Post-operative changes in hemoglobin level in the three experimental groups. Data shown as mean ± standard deviation.*

	Topical TXA group	p value	IV + topical TXA group	p value	Control group	p value
Pre-operative – Post-operative day 1	2.8 ± 1.0	< 0.001	2.6 ± 0.8	< 0.001	3.2 ± 1.5	< 0.001
Post-operative day 1 – Post-operative day 3	0.9 ± 0.8	< 0.001	0.7 ± 0.8	0.001	1.1 ± 0.9	< 0.001
Post-operative day 3 – Discharge	0.1 ± 0.8	0.648	0	1.000	-0.3 ± 0.6	0.068

TXA = tranexamic acid; IV = intravenous

Table IV. *Hematocrit value in the three experimental groups. Data shown as mean ± standard deviation.*

	Topical TXA group	IV + topical TXA group	Control group
Preoperative	42.3 ± 4.4	43.7 ± 3.5	41.1 ± 4.4
1st postoperative day	33.8 ± 3.1*	35.5 ± 2.2††	31.2 ± 4.2
3rd postoperative	30.8 ± 3.6	33.1 ± 3.9††	28.4 ± 3.4
Discharge	31.1 ± 3.9	32.9 ± 4.0†	29.4 ± 3.8
Lowest postoperative	29.8 ± 3.5	31.3 ± 3.6†	28.1 ± 3.5

TXA = tranexamic acid; IV = intravenous

*= $p < 0.05$ compared to control group

† = $p < 0.01$ compared to control group

††= $p \leq 0.001$ compared to control group

group and control group was appreciable only on postoperative day 1.

Significant postoperative ($p < 0.05$) drop in Hct value compared to the preoperative value was detected in all groups at the two first considered time intervals (Table V), with no significant differences between groups.

The transfusion rate was 8 % (n=6) for all patients, with 5 of 6 transfusions occurring in the control group. The IV + topical group had a lower transfusion rate compared to the control group (0% vs 20%, p=0.014). With the numbers available, no difference in transfusion rate emerged between topical and control group. The total operative time was 85.0 ± 25.2 minutes in the topical group, 84.8 ± 20.8 minutes in the IV + topical group, and 79.8 ± 25.2 minutes in the control group, with no significant difference between groups. Likewise, the difference in length of hospital stay between groups was not significant (topical group = 5.8 ± 3.5 days; IV + topical group = 5.5 ± 1.8 days; control group = 7.2 ± 4.6 days). No thromboembolic complications were observed in any groups.

DISCUSSION

The use of TXA is one of the strategies to reduce the rate of allogenic perioperative transfusion in THA (12). According to previous studies (13), blood transfusions may lead to prolonged hospital stay and delayed postoperative rehabilitation which lead to low patient satisfaction with surgery. Pre-operative autologous blood predonation also demonstrates some drawbacks. Indeed, it is a time-consuming procedure and some patients tolerate acute blood withdrawal poorly. Moreover, this procedure carries its own risks such as ischaemia if the target Hct is very low, bacterial contamination, fever, phlebitis, and technical errors (5, 14). Lastly, the most suitable patients for pre-operative autologous blood predonation are those who are actually less likely to require transfusions (15).

In the current study postoperative changes in Hb level and Hct value were used to assess the efficacy of TXA admnistration. These parameters represent an effective estimate of perioperative blood loss. Indeed, measuring the volume of blood lost intraoperatively has been shown to be very inaccurate (16). A reliable estimate should include the assessment of postoperative bleeding in drainage and hematoma that can be accurately quantified only by using ultrasonography (17). According to previous authors (12, 18), the current study showed that the simultaneous administration of IV and topical TXA was effective in reducing postoperative blood loss after primary uncemented THA, thus decreasing the need for allogenic blood transfusion. Indeed, this combined regimen of TXA administration resulted in higher postoperative Hb levels and Hct values as well as lower transfusion rates compared to controls.

These results were obtained without additional thromboembolic complications. In the present study, the combined use of topical and IV TXA was more effective than the topical TXA alone. Indeed, with the numbers available, the positive results of simultaneous administration of IV and topical TXA on the postoperative drop in Hb levels and Hct values cannot be achieved using topical TXA alone. Moreover, significant reduction in transfusion requirements with respect to the control group occurred only using the combined IV + topical regimen.

These results aren't in keeping with some previous studies (1, 8-10). A possible explanation for this discrepancy is that the sample size in the current study was not large enough to make the efficacy

Table V. *Post-operative changes in in hematocrit value in the three experimental groups. Data shown as mean ± standard deviation.*

	Topical TXA group	p value	IV + Topical TXA group	p value	Control group	p value
Pre-operative – Post-operative day 1	8.5 ± 3.2	< 0.001	8.2 ± 2.6	< 0.001	10.3 ± 4.9	< 0.001
Post-operative day 1 – Post-operative day 3	2.9 ± 2.6	< 0.001	2.4 ± 2.9	0.002	3.0 ± 3.0	0.001
Post-operative day 3 – Discharge	0.1 ± 2.5	0.898	-0.3 ± 3.4	0.655	-0.8 ± 2.1	0.129

TXA = tranexamic acid; IV = Intravenous

of topical TXA clear in reducing blood loss. The simultaneous use of both local and systemic TXA did not result in longer operative time in the current study. There is a lack of published data on this aspect, likely because many different factors may influence the operative time. Even though reduced length of hospital stay was recorded in patients who received TXA in the current study compared to controls with the numbers available this difference was not significant. The optimal dosing of IV TXA to reduce blood loss in THA is still unclear.

In the current study we adopted the same protocol as North et al. (12) consisting of 2 grams of IV TXA divided in two doses. Zhou et al (10) administered a lower dose of systemic TXA and failed to find superiority of IV on topical TXA. This data indicates that a sufficient dose should be used to maximize the effect of IV TXA. Like the previous study (8) our topical way of administration consisted of 3 g of TXA in saline solution divided in three aliquots. Chang et al, (9) used 0.5 g of topical TXA, also reported significant reduction in blood loss and transfusions after primary THA.

We acknowledge that some characteristics of the present study are not ideal. The most important limitation of the current study is the small sample size that limited the statistical power of tests and might have clouded significant differences between therapeutic groups and controls (particularly those regarding the efficacy of topical TXA alone). However, significant differences indicating the superiority of the combined regimen of TXA adminstration compared to the control group were detected despite the small study group.

nother limitation of the current study is that some parameters to evaluate the total blood loss such as drain output volume and postoperative hematoma were not analyzed. Conversely, the strengths of our study are its prospective randomized design with thorough matching of the experimental groups. Moreover, to the best of our knowledge this is the first analysis comparing the efficacy and safety of combined IV and topical TXA versus topical TXA alone for reduction of blood loss after primary uncemented THA.

The combined administration of IV and topical TXA is effective in decreasing blood loss and transfusion rate without increasing the risk of thromboembolic accidents in patients undergoing uncemented primary THA. With the numbers available in the current study, the efficacy of topical TXA alone is not demonstrated. Taken the limitations into consideration, larger samples and well-designed clinical trials are warranted to assess the superiority of combined TXA over topical TXA alone in reducing bleeding and the transfusion need after uncemented primary THA.

REFERENCES

1. Li J, Zhang Z, Chen J. Comparison of efficacy and safety of topical versus intravenous tranexamic acid in total hip arthroplasty: A meta-analysis. Medicine 2016; 95:e4689.
2. Madjdpour C, Spahn DR. Allogeneic red blood cell transfusions: efficacy, risks, alternatives and indications. Br J Anaesth 2005; 95:33-42.
3. Cardone D, Klein AA. Perioperative blood conservation. Eur J Anaesthesiol 2009; 26:715-21.
4. Nagashima M, Yin ZF, Zhao L, et al. Thrombin-activatable fibrinolysis inhibitor (TAFI) deficiency is compatible with murinelife. J Clin Invest 2002; 109:101-10.
5. Lamaire R. Strategies for blood management in orthopaedic and trauma surgery. J Bone Joint Surg 2008; 90B:1128-36.
6. Moskal JT, Capps SG. Meta-analysis of intravenous tranexamic acid in primary total hip arthroplasty. Orthopedics 2016; 39: e883-9.
7. Wong J, Abrishami A, El Beheiry H, et al. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. J Bone Joint Surg 2010; 92A:2503-13.
8. Konig G, Hamlin BR, Waters JH. Topical tranexamic acid reduces blood loss and transfusion rates in total hip and total knee arthroplasty. J Arthroplasty 2013; 28:1473-6.
9. Chang CH, Chang Y, Chen DW, Ueng SW, Lee MS. Topical tranexamic acid reduces blood loss and transfusion rates associated with primary total hip arthroplasty. Clin Orthop Relat Res 2014; 472:1552-7.
10. Zhou KD, Wang HY, Wang Y, Liu ZH, He C,

Feng JM. Is topical or intravenous tranexamic acid preferred in total hip arthroplasty? A randomized, controlled, noninferiority clinical trial. PLoS One. 2018; 13. doi: 10.1371/journal.pone.0204551.

11. Yi Z, Bin S, Jing Y, Zongke Z, Pengde K, Fuxing P. Tranexamic acid administration in primary total hip arthroplasty: a randomized controlled trial of intravenous combined with topical versus single-dose intravenous administration. J Bone Joint Surg 2016; 98A:983-91.
12. North WT, Mehran N, Davis JJ, Silverton CD, Weir RM, Laker MW. Topical vs intravenous tranexamic acid in primary total hip arthroplasty: a double-blind, randomized controlled trial. J Arthroplasty 2016 ;31:1022-6.
13. Carson JL, Duff A, Berlin JA, et al. Perioperative blood transfusion and postoperative mortality. JAMA. 1998; 279:199-205.
14. Bierbaum BE, Callaghan JJ, Galante JO, Rubash HE, Tooms RE, Welch RB. An analysis of blood management in patients having a total hip or knee arthroplasty. J Bone Joint Surg 1999; 81A:2-10.
15. Mercuriali F, Inghilleri G. Transfusion risks and limitations. Minerva Anestesiol 1999; 65:286-92.
16. Johansson T, Lisander B, Ivarsson I. Mild hypothermia does not increase blood loss during total hip arthroplasty. Acta Anaesthesiol Scand 1999; 43 :1005-10.
17. Thorsson O, Leander O, Lilja B, et al. Comparing ultrasonography, magnetic resonance imaging and scintigraphy in evaluating experimentally- inducted hematoma. Scand J Med Sci Sports 1993; 3:110-6.
18. Liu X, Liu J, Sun G. A comparison of combined intravenous and topical administration of tranexamic acid with intravenous tranexamic acid alone for blood loss reduction after total hip arthroplasty: a meta-analysis. Int J Surg 2017; 41:34-43.

New plates with polyaxial locking system and PSI technique in medial open-wedge high tibial osteotomy: preliminary results

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Medial open-wedge (MOW) high tibial osteotomy (HTO) is proven treatment option, indicated in medial unicompartimental knee osteoarthritis (OA) and in varus OA. New devices and techniques were developed in last years, such as Activemotion plates with polyaxial locking system (Dualtec System®, NewClip-Technics) and PSI technique. We describe outcomes and rate of complications in patients treated with Activemotion plates and PSI technique. From January 2019 to August 2019 a sample of 77 cases (72 NCT plates, 5 PSI technique) was observed, evaluating the rate of complications and the return to activity. The rate of complications is 2.6% and the mean time to return to activity is 10 weeks. MOW HTO with Activemotion plate has showed good results with a low rate of complications. About PSI technique, the preliminary results are excellent, but we need to increase the sample.

Medial open-wedge (MOW) high tibial osteotomy (HTO) is proven treatment options, especially in patients with medial unicompartmental knee osteoarthritis (OA) and in varus-OA knee, also associated to lesion of anterior cruciate ligament (ACL) (1, 2). In last year, there was a technological evolution of devices used to perform MOW HTO (3, 4). We went from staples or external fixation to modern plates with polyaxial locking system (i.e. Activemotion plates) and PSI (patient specific instrument) technique. The new devices showed better outcomes than the historical plates, such as Puddu plate (5). The aim of our study is to described outcomes, return to activity and rate of complications, in patients undergone to MOW HOT with Activemotion plates and PSI technique, for medial unicompartmental and varus OA.

MATERIAL AND METHODS

From January 2019 to August 2019 a sample of 75 patients (46 males and 29 females, mean age 45.7) was evaluated. In two patients a bilateral MOW HTO was performed for a total of 77 MOW HTO. In 72 cases Active motion plate was used, while in 5 cases the surgery was performed with a PSI technique. Inclusion criteria were medial un-compartmental knee OA, Varus knee <10°, ROM >90°, age <60 years, no rheumatic diseases. All the procedures were performed in "IRCCS Ospedale Sacro Cuore – Don Calabria" in Negrar di Valpolicella (VR).

In post-operative we used the rehabilitation protocol of the institute, that consists of partial weightbearing for first 10 days, then gradual full weightbearing for the next 2 weeks. If necessary, application of hinged brace at 0°-90° for first 15 days, then 0-120° for next 2

Key words: high tibial osteotomy, nct plate, psi technique, return to activity

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weeks. Immediate isometric and isokinetic contractions of the quadriceps; at first week CPM to full tolerance. We evaluated the consolidation of HTO through post-operative x-rays at 1 month and 3 months. The outcomes evaluated are the return to activity and the rate of complications.

In our study the rate of complications is 2.6% (2:77). After 1 month, one complication was observed: a superficial surgical site infection, treated successfully with oral antibiotic therapy. After 3 months, the consolidation of HTO was not observed only in one case: a device insufficiency (rupture of one screw) was observed; the chosen treatment was the revision of MOW HTO, with removal of the insufficient device and implant of a different plate (Tomofix plate), that is more invasive than the Activemotion plate. No complication was observed in patients treated with PSI technique. The patients followed the rehabilitation protocol of the institute, except the case of the rupture of the screw. Therefore, early mobilization was performed, and within first month full weightbearing was allowed in all patients. No difference was applied in bilateral MOW HTO and in patients treated with PSI technique and ACL reconstructions. The mean time to return to activity was 10 weeks.

MOW HTO is an effective surgical procedure, with a low rate of complications and good results to long follow-up: however, it is important to respect the restricted indications of HTO (6). The evolution of devices to perform HTO has a relevant role in improving the results of MOW HTO: this is possible thanks to the improvement of the plates itself, the surgical technique (3, 4) and the rehabilitation in post-operative period with early weightbearing (7). Hoorntje et al. (8) in 2017 systematically reviewed the rate of return to activity in HTO according different devices: it was observed a better outcome with the new devices than the older ones. In our study we observed a return to activity even lower than Hoorntje et al. (weeks 10 vs 16 weeks).

Ekhtiari et al. (9) analysed the complications after HTO and they observed a rate of 5.8%; this is an improvement compared to the experience with Puddu plate, described in literature (10): it points out the importance of devices evolution. In our study we observed a rate of complications even lower than Ekhtiari et a. (2.6% vs 5.8%).

The improvement of the observed outcomes is due to the evolution of fixation devices; unlike the historical plates, such as Puddu plate, the Activemotion plates allows to choose a different angulation of one screw (±12.5) with a polyaxial locking system, performing a more stable and resistant fixation with a minor exposure (11, 12). Activemotion plates also allows to have a less stiff construct in the knee: it means a minor rate of malunion, because of the stiffness can cause malunion (13).

PSI technique have been introduced to enhance surgical accuracy and ease of implantation in patients underwent total knee replacement (14). In HTO allows to improve even more the advantages of Activemotion plates: excellent fixation, good resistance, respect for anatomy; the preliminary results showed good results in terms of return to activity (9 weeks) and rate of complications (0%); however the sample observed was small (5 patients), therefore it will be fundamental to increase the sample in further studies (15).

In literature there are study about the possibility to perform HTO and ACL reconstruction in the same time, with good outcomes (16, 17): in this study the concomitant ACL reconstructions were performed with a different plate (Activemotion Ligamento, Dual System®, NewClip-Technics), but the sample is too small to obtain an acceptable analysis.

In recent decades, HTO is compared to unicompartmental knee arthroplasty (UKA) in medial unicompartmental OA in terms of surgical options: although the two technique have similar indications, the results of HTO are better than UKA, in particular in the young patients (<50 years) (17, 18). A point of weakness of our study is the short follow-up and the lack of objective and subjective scores: in future we are going to increase follow-up and to submitted scores to patients at set times (pre-operative, 6 months, 12 months).

A point of strength of our study is the sample of Activemotion plates and the standardization of the procedure (surgery performed, protocol rehabilitation, x-rays at first and third month). In conclusion the MOW HTO with Activemotion plate has showed good results with a low rate of complications. About PSI technique, we absolutely need to increase the sample, although the preliminary results are excellent.

REFERENCES

1. Van Outeren MV, Waarsing JH, Brouwer RW, Verhaar JAN, Reijman M, Bierma-Zeinstra SMA. Is a high tibial osteotomy (HTO) superior to non-

surgical treatment in patients with varus malaligned medial knee osteoarthritis (OA)? A propensity matched study using 2 randomized controlled trial (RCT) datasets. Osteoarthritis Cartilage. 2017; 25(12):1988-1993.
2. McNamara I, Birmingham TB, Fowler PJ, Giffin JR. High tibial osteotomy: evolution of research and clinical applications: a Canadian experience. Knee Surg Sports Traumatol Arthrosc. 2013; 21(1):23-31.
3. Gao L, Madry H, Chugaev DV, et al. Advances in modern osteotomies around the knee: Report on the Association of Sports Traumatology, Arthroscopy, Orthopaedic surgery, Rehabilitation (ASTAOR) Moscow International Osteotomy Congress 2017. J Exp Orthop. 2019; 6(1):9.
4. Golovakha ML, Orljanski W, Benedetto KP, et al. Comparison of theoretical fixation stability of three devices employed in medial opening wedge high tibial osteotomy: a finite element analysis. BMC Musculoskelet Disord. 2014 Jul 10; 15:230
5. Polat G, Balcı Hİ, Çakmak MF, Demirel M, Şen C, Aşık M. Long-term results and comparison of the three different high tibial osteotomy and fixation techniques in medial compartment arthrosis. J Orthop Surg Res. 2017 Mar 16; 12(1):44.
6. Smith JO, Wilson AJ, Thomas NP. Osteotomy around the knee: evolution, principles and results. Knee Surg Sports Traumatol Arthrosc. 2013; 21(1):3-22.
7. Lee OS, Ahn S, Lee YS. Effect and safety of early weight-bearing on the outcome after open-wedge high tibial osteotomy: a systematic review and meta-analysis. Arch Orthop Trauma Surg. 2017; 137(7):903-911.
8. Hoorntje A, Witjes S, Kuijer PPFM, Koenraadt KLM, van Geenen RCI, Daams JG, Getgood A, Kerkhoffs GMMJ. High Rates of Return to Sports Activities and Work After Osteotomies Around the Knee: A Systematic Review and Meta-Analysis. Sports Med. 2017; 47(11):2219-2244.
9. Ekhtiari S, Haldane CE, de Sa D, Simunovic N, Musahl V, Ayeni OR. Return to Work and Sport Following High Tibial Osteotomy: A Systematic Review. J Bone Joint Surg Am. 2016; 98(18):1568-77.
10. Asik M, Sen C, Kilic B et al. High tibial osteotomy with Puddu plate for treatment of varus gonarthrosis. Knee Surg Sports Traumatol Arthrosc. 2006; 14:948.
11. Liu X, Chen Z, Gao Y, Zhang J, Jin Z. High Tibial Osteotomy: Review of Techniques and Biomechanics. J Healthc Eng. 2019; 2019:8363128.
12. Schröter S, Hoffmann T, Döbele S et al. Biomechanical properties following open wedge high tibial osteotomy: Plate fixator combined with dynamic locking screws versus standard locking screws. Clin Biomech (Bristol, Avon). 2018; 60:108-114.
13. Röderer G, Gebhard F, Duerselen L, Ignatius A, Claes L. Delayed bone healing following high tibial osteotomy related to increased implant stiffness in locked plating. Injury. 2014; 45(10):1648-52.
14. De Santis V, Burrofato A, D'Apolito R, et al. Evaluation of accuracy of bone cuts and implant positioning in total knee arthroplasty using patient specific instrumentation. J Biol Regul Homeost Agents. 2017; 31(4 suppl 1):51-60.
15. Yang JC, Chen CF, Luo CA et al. Clinical Experience Using a 3D-Printed Patient-Specific Instrument for Medial Opening Wedge High Tibial Osteotomy. Biomed Res Int. 2018; 2018:9246529.
16. Gupta A, Tejpal T, Shanmugaraj A, et al. Surgical Techniques, Outcomes, Indications, and Complications of Simultaneous High Tibial Osteotomy and Anterior Cruciate Ligament Revision Surgery: A Systematic Review. HSS J. 2019; 15(2):176-184.
17. Mancuso F, Hamilton TW, Kumar V, Murray DW, Pandit H. Clinical outcome after UKA and HTO in ACL deficiency: a systematic review. Knee Surg Sports Traumatol Arthrosc. 2016; 24(1):112-22.
18. Santoso MB, Wu L. Unicompartmental knee arthroplasty, is it superior to high tibial osteotomy in treating unicompartmental osteoarthritis? A meta-analysis and systemic review. J Orthop Surg Res. 2017; 12(1):50.

Volar distal radius vascularized bone graft vs non-vascularized bone graft: a prospective comparative study

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The pseudoarthrosis (PSA) of scaphoid leads to alteration in load transfer in the wrist joint. Its treatment aims to achieve consolidation to improve clinical complaints and prevent post-traumatic arthritis. The indication for using vascularized bone grafts is still controversial. This prospective comparative study aimed to compare consolidation rate and time to healing of scaphoid PSA treated by volar distal radius vascularized bone graft vs non-vascularized iliac bone graft. Nine patients underwent vascularized grafting of scaphoid PSA. These patients were compared to a control group consisting of twelve patients treated with iliac crest-free bone graft. PSA consolidation was obtained in 8 of 9 patients (88%) and 9 of 12 patients (75%) in the study and control group, respectively. The difference in consolidation rate was not significant. Two of three patients with AVN of the proximal pole in the study group (66%) went to consolidation. In the control group no patient with AVN obtained bone consolidation. This difference almost reached statistical significance ($p = 0.083$). The mean time to consolidation was 8.6 weeks (range 8-11) and 11.7 weeks (range 10-16), respectively, in the study and control group. This difference was significant ($p < 0.05$). In conclusion, the distal radius vascularized graft led to satisfactory consolidation rate of PSA in the current study, even in cases of AVN of the proximal pole. Moreover, the vascularized bone graft resulted in shorter healing time compared to the non-vascularized graft.

Scaphoid fracture is the most common lesion of carpal bones, accounting for 50-80 % of carpal injuries (1). The terminal blood supply of the scaphoid exposes these fractures to a particularly high risk of non-consolidation (2). Fracture localization plays a decisive role in the healing process, as fractures of the distal third have a higher possibility of consolidation than those of the proximal pole. The pseudoartrhosis of scaphoid (PSA) leads to alteration in load transfer, because of an increase in the flexion and pronation of the bone.

Due to lack of stability from the distorted scaphoid, a dorsal intercalated segment instability (DISI) can be developed. This leads to increased risk of arthritic degeneration, with a 5-year prevalence ranging from 75 to 97% and a 10-year prevalence of 100% (3).

The primary goal of the treatment of scaphoid PSA is to achieve the consolidation to improve clinical complaints and prevent post-traumatic arthritis of the wrist. Several surgical options have been proposed for the management of PSA. The techniques mainly differ for site of harvesting of the graft site, the method of fixation, and use of vascularized or non-vascularized bone grafts. There is still controversy on the most successful surgical option for PSA and

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especially fair indications for using vascularized bone grafts are lacking in the literature.

The pedicled vascularized bone graft of distal radius was first described by Kuhlmann et al (1987) (4). It is harvested from the medial part of the radial epiphysis and its blood supply is provided by the palmar carpal artery, running between the volar periosteum and the distal aponeurosis of the quadratus pronator muscle. The purpose of this paper was to analyze results of the pedicled distal radius vascularized graft in the treatment of scaphoid PSA, assessing the rate of consolidation and time to healing of PSA in a group of patients treated with this technique. Clinical results in these patients were also evaluated.

MATERIALS AND METHODS

From April 2016 to May 2018 nine patients underwent vascularized scaphoid graft according to Kuhlmann for scaphoid PSA. All operations were performed by a single surgeon. The patients were all males with mean age 25.4 years (range 19 - 34).

The inclusion criteria in the study were 1) no previous conservative or surgical treatment for the scaphoid fracture, 2) age over 18 years. These patients were compared to a control group consisting of twelve patients, treated from April 2016 to September 2016 with iliac crest-free bone graft. Surgery in the control group was performed by three different hand surgeons. The patients were all male with similar age as the study group (mean age = 28.2 years; range 19 - 42; p = ns). The inclusion criteria in the control group were the same as in the study group. All data were collected prospectively.

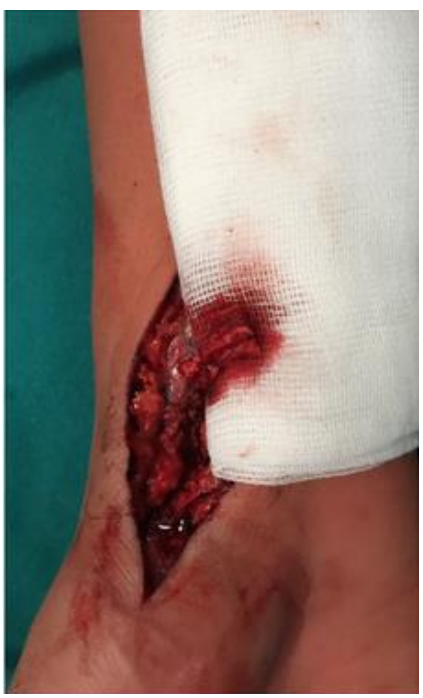


Fig. 1. *Vascularization evaluation of the graft after pneumatic tourniquet release.*

Before being enrolled in the study, all patients gave their informed consent. Before surgery, X-rays (antero-posterior, lateral, and ulnar deviation views) and magnetic resonance imaging (MRI) were obtained to evaluate the structure and vascularization of the proximal pole of scaphoid. Three of nine patients in the study group (33 %) had avascular necrosis (AVN) of the proximal pole, while in the remaining patients (6/9) the PSA concerned the scaphoid body. In the control group three of twelve patients (25 %) presented an AVN, whereas in the remaining patients (9/12) the PSA involved the body of scaphoid. The following parameters were used for the subjective and functional preoperative assessment in all patients: visual analogue pain (VAS) scale (0 = absence of pain; 10 = maximum pain), Disability of the Arm, Shoulder and Hands (DASH) scale (5) (0 = complete function; 100 = maximum disability), flexion and extension of the wrist (in degrees; goniometric evaluation), and hand grip strength (JAMAR dynamometer evaluation).

The same parameters were evaluated by one single observer 6 months post-surgery. All patients underwent monthly radiographic examination until consolidation of the fracture or at 6 months postoperatively. Computed tomography (CT scan) was obtained 8- and 12-weeks post-surgery to assess PSA bony consolidation. A PSA was healed when there was presence of a trabecular bone bridge.

Vascularized graft surgical technique

Surgery was performed in day surgery. Brachial plexus anesthesia and a high arm tourniquet was utilized in all cases. The anterior Henry approach was distally extended to the tubercle of the scaphoid. The volar carpal artery was subperiosteally isolated using a chisel and carefully freed until its emergence from the lateral aspect of radial artery. The graft was then harvested using a chisel. Once the graft

had been taken, the pneumatic tourniquet was released to evaluate the blood supply (Fig. 1). The PSA site was therefore treated with gentle removal of non-viable bone.

The two main fragments of the scaphoid were fixed with a Kirschner wire, while the bone graft with a second wire. The correct reduction was then evaluated by C-arm. Finally, the capsule suture was carried out paying attention to not compress the arterial pedicle of graft. After surgery, the wrist was immobilized in a dorsal spica cast for 15 days. Subsequently, a long arm plaster cast with thumb included was worn for a further 6 weeks. Kirschner wires were removed 8 weeks after surgery. Upon plaster cast removal, the patients started physiotherapy.

Non-vascularized graft surgical technique

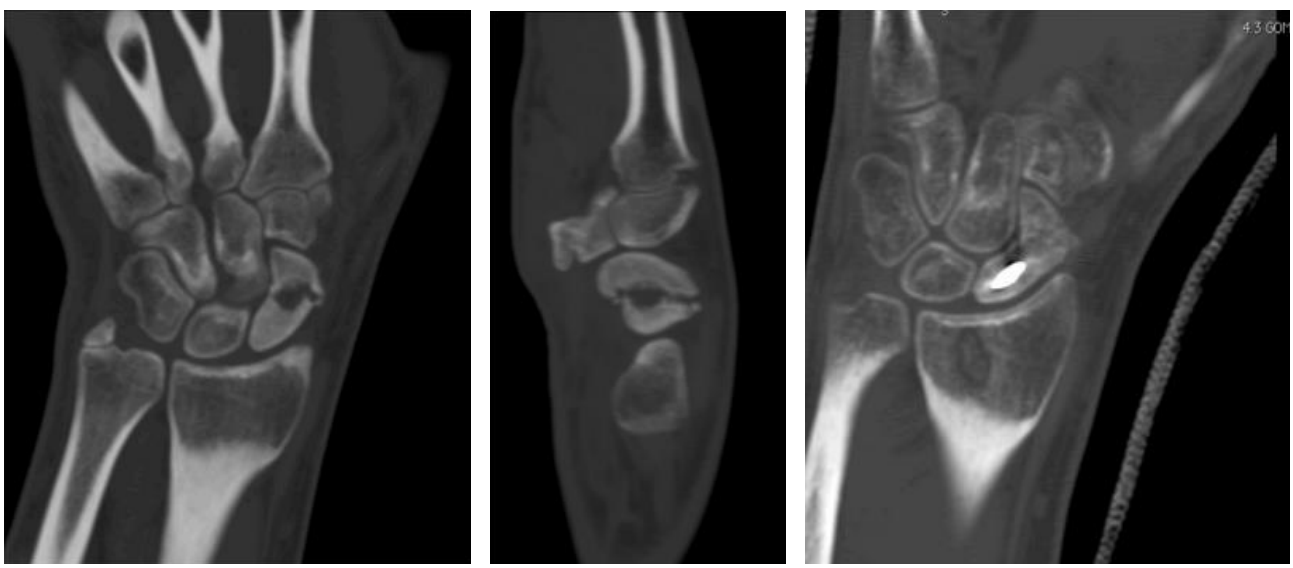
The surgery is carried out under ordinary hospitalization. General anesthesia and a high arm tourniquet utilized were used in all cases. A standard approach for the scaphoid was performed and the PSA site was revitalized. Subsequently an iliac crest bone graft was harvested through a small anterior approach. Graft synthesis was performed with a headless compression screw. The wrist is then immobilized with a dorsal spica cast for 15 days until sutures are removed. A long arm plaster cast with thumb included was worn for an additional 6 weeks. Upon plaster cast removal, the patients started physiotherapy.

Statistical analysis

A Fisher exact test was performed to evaluate possible differences in dichotomous variables between the two groups (i.e. consolidation rate). A T- test for unpaired data was performed to evaluate differences in continuous variables (time to consolidation, range of movement, VAS, and DASH score). $P \leq 0.05$ was considered significant. Data were analyzed using SPSS software version 23.0 (SPSS, Chicago, IL, USA).

RESULTS

None of the patients was lost to follow-up. PSA consolidation was obtained in 8 of 9 patients (88%) and 9 of 12 patients (75%) in the study and control group, respectively. With the numbers available, the difference in consolidation rate was not significant. Two of 3 patients with AVN of the proximal pole in the study group (66 %) went to consolidation. In the control group no patient with AVN obtained bone consolidation. The difference between groups



A B C

Fig. 2. *Patient of 19 years with pseudoarthrosis of the scaphoid body.* ***A, B****: CT scan of pseudoarthosis of the scaphoid body with humpback deformity;* ***C****: eight-week CT scan shows the healing of pseudoarthosis.*

almost reached statistical significance ($p = 0.083$). The mean time to consolidation was 8.6 weeks (range 8-11) and 11.7 weeks (range 10-16), respectively, in the study and control group (Fig. 2).

This difference was significant ($p < 0.05$). In the study group, the patient who did not obtain the consolidation underwent proximal row carpectomy one year after the index surgery. In the control group (non-vascularized graft) two of the patients who did not achieve consolidation underwent four corner fusion and one patient refused any further surgery.

Patients who did not achieve PSA consolidation were excluded from the postoperative clinical assessment 6 months after surgery. In the study group, surgery led to an increase in wrist flexion of 6.8 degrees compared to the preoperative value, from 53.8 degrees (range 35-65) preoperatively to 60.6 degrees (range 40-75) postoperatively. Mean increase in extension was 5.5 degrees, ranging from 60.5 degrees (range 45-75) preoperatively to 66 degrees (range 55 -80 postoperatively. In the control group there was a postoperative increase in wrist flexion of 14 degrees, from the pre-operative value of 52 degrees (range 40-65) to the post-operative of 66.6 degrees (range 55-75). The increase in extension was 3.3 degrees, passing from 63.7 degrees (range 55-75) preoperatively to 67 degrees (range 50°-75°) postoperatively.

Patients in the study group had a postoperative improvement in grip strength of 18.3 kg, passing from 24.2 kg (range 18-30) preoperatively to 42.5 Kg (28-58) postoperatively. Also, in the controls the grip strength increase of 15.3 kg after surgery, and passed from 26.7 kg (range 20-34) preoperatively to 42 kg (32-52) postoperatively.

The VAS scale for pain in the study group improved from 5.1 (range 2-8) preoperatively to 1 (range 0-3) postoperatively. Even in the controls, there was improvement in pain with the VAS scale that decreased from 5.6 (range 2-9) before operation to 0.7 (range 0-2) post-surgery. Finally, the functional assessment with DASH scale showed improvement in both groups. In the study group, it passed from 43 (range 18-70) preoperatively to 19 (range 5-32) postoperatively. In the control group, the DASH scale decreased from 51 (range 31-73) before operation to 18 (range 7-31) 6 months later. With the numbers available, no difference in any subjective or functional outcomes between the study and control group was detected.

DISCUSSION

The consolidation rate of scaphoid PSA treated with non-vascularized bone grafts is variable from 70 to 90% in the literature (6, 7, 8, 9). In the meta-analysis by Merrell et al (10) the consolidation rate was reported to be 47% in cases of AVN of the proximal pole. In the current study the consolidation rate of PSA managed with vascularized bone graft was 88%, and a 100% consolidation rate was obtained in patients with PSA of the scaphoid body. This rate decreased to 66% in cases of AVN of the proximal pole. Although not significantly, these results compared positively with the findings in the control group treated with non-vascolarized bone grafts.

Our results are slightly inferior than previous data by Lim et al, (11) who reported a consolidation rate of 86% in patients with AVN using the same vascularized bone graft. Merrell's meta-analysis (10) also reported a higher consolidation rate in AVN (88%) with the use of a different type of vascularized bone graft. These discrepancies can be explained by the small number of AVNs in the current study; hence, one single failure in our study group dramatically affected the total numbers. One recent large systematic review (9) reported a 92% and 88 % consolidation rate, respectively, using vascularized and non-vascularized bone graft, but this study did not differentiate among various types of PSA.

Bone healing in our study group always took place in 8-11 weeks and was faster compared to the control group. This data concurs with those of previous published PSA series treated with vascularized bone grafts (4, 12, 13, 14). In one recent meta-analysis (15), the volar radius bone graft was shown to be the fastest in achieving consolidation.

In our study group the grip strength improved by 18.3 Kg with surgery, with a 44% increase with respect to the pre-operative value. This improvement is lower compared to the findings of the meta-analysis

by Ditsios (15), who reported a mean improvement in strength of 66.69% in patients treated with the Khulmann's graft.

The improvement of the gripping force obtained in our series is higher than the findings reported by the same author with other types of vascularized grafts. The most used vascularized bone graft for PSA is the dorsal graft described by Zaidenberg et al (16). However, the dorsal access used to harvest this graft prevents proper correction of the humpback scaphoid deformity, where instead the volar access guarantees a perfect view of the whole scaphoid body. Furthermore, the consolidation rate of the dorsal graft is lower and much more variable compared to the Khulmann graft (15). The vascularized bone grafts from medial femoral condyle has been showed to result in a 100% success rate regardless of the PSA site and the state of blood supply of the proximal pole of scaphoid (15). This technique is much more demanding than the radial graft, mainly because of the need for microsurgical vascular anastomoses. As far as the 6-month subjective outcomes are concerned, no difference was observed between the two therapeutic groups in the current study.

The present study has several shortcomings. The first limitation is the presence in both groups of patients with PSA of different localization and nature (i.e. scaphoid body and AVN of proximal pole). Another limitation is the small sample size that lowered the statistical power of our tests and might have clouded significant differences between the two therapeutic groups.

The short follow up did not allow us to evaluate the possible long-term progression of arthritic changes, but this analysis was beyond the objectives of the study. In patients with necrosis of the proximal pole it would have been useful to evaluate the vascular status of the proximal pole using MRI, but the routine adoption of this examination would have markedly increased the costs of this study. Lastly, different types of synthesis were used in the two therapeutic groups (Kirschner wire vs cannulated screw) and the different stability of the synthesis could be a confounding variable. However, the present study presents strengths such as its perspective design and the presence of a control group. These characteristics are not common in the literature on this topic (17, 18).

In summary, distal radius vascularized graft led to satisfactory consolidation rate of PSA in the current study, even in difficult cases such as the AVN of proximal pole. In these latter cases the non-vascularized bone graft does not represent a valuable therapeutic option. Moreover, the vascularized bone graft resulted in shorter time to consolidation compared to the non-vascularized graft in the current study. The lack of a significant difference in clinical and radiographic outcomes between the two groups is likely to be due to small number of patients in the present comparison.

REFERENCES

1. Alshryda S, Shah A, Odak S, Al-Shryda J, Ilango B, Murali SR. Acute fractures of the scaphoid bone: Systematic review and meta-analysis. The surgeon: journal of the Royal Colleges of Surgeons of Edinburgh and Ireland 2012; 10:218–29.
2. Gelberman RH, Panagis JS, Taleisnik J, Baumgaertner M. The arterial anatomy of the human carpus. Part I: The extraosseous vascularity, J Hand Surg Am 1983; 8:367-375.
3. Inoue g, Sakuma M. The natural history of scaphoid non-union. Radiographical and clinical analysis in 102 cases. Arch Orthop Trauma Surg 1996; 115:1–4
4. Kuhlmann JN, Mimoun M, Boabighi A, Baux S. Vascularized bone graft pedilced on the volar carpal artery for non-union of the scaphoid. J Hand Surg Br 1987; 12:203–210.
5. Hudak PL, Amadio PC, Bombardier C. Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand). The Upper Extremity Collaborative Group (UECG). Am J Ind Med 1996; 29:602- 8.
6. Green DP. The effect of avascular necrosis on Russe bone grafting for scaphoid nonunion. J Hand Surg Am 1985 ;10:597-605.
7. Cooney WP, Linscheid RL, Dobyns JH. Scaphoid fractures: problems associated with nonunion and avascular necrosis. Orthop Clin North Am 1984;15:381-391.
8. Andrews J, Miller G, Haddad R. Treatment of scaphoid nonunion by volar inlay distal radius bone

graft. J Hand Surg Br 1985; 10:214-16.
9. Pinder RM, Brkljac M, Rix L, Muir L, Brewster M. Treatment of Scaphoid Nonunion: A Systematic Review of the Existing Evidence. J Hand Surg Am 2015; 40:1797-805.
10. Merrell GA, Wolfe SW, Slade JF, 3rd. Treatment of scaphoid nonunions: quantitative meta- analysis of the literature. J Hand Surg Am 2002; 27:685-91.
11. Lim TK, Kim HK, Koh KH, Lee HI, Woo SJ, Park MJ. Treatment of avascular proximal pole scaphoid nonunions with vascularized distal radius bone grafting. J Hand Surg Am 2013; 38:1906-12.
12. Mathoulin C, Haerle M. Vascularized bone graft from the palmar carpal artery for treatment scaphoid nonunion. J Hand Surg Br 1998; 23:318-23.
13. Malizos KN, Dailiana ZH, Kirou M, Vragalas V, Xenakis TA, Soucacos PN. Longstanding nonunions of scaphoid fractures with bone loss: successful reconstruction with vas- cularized bone grafts. J Hand Surg Br 2001;26:330-4.
14. Dailiana ZH, Malizos KN, Zachos V, Varitimidis SE, Hantes M, Karantanas A. Vascularized bone grafts from the palmar radius for the treatment of waist nonunions of the scaphoid. J Hand Surg Am 2006; 31:397-404.
15. Ditsios K, Konstantinidis I, Agas K, Christodoulou A. Comparative meta-analysis on the various vascularized bone flaps used for the treatment of scaphoid nonunion. J Orthop Res 2017; 35:1076-1085.
16. Zaidemberg C, Siebert JW, Angrigiani C. A new vascularized bone graft for scaphoid nonunion. J Hand Surg Am.199; 16:474-8.
17. Caporrino FA, Dos Santos JB, Penteado FT, de Moraes VY, Belloti JC, Faloppa F. Dorsal vascularized grafting for scaphoid nonunion: a comparison of two surgical techniques. J Orthop Trauma 2014; 28:e44-8.
18. Ribak S, Medina CE, Mattar R Jr., Ulson HJ, Ulson HJ, Etchebehere M. Treatment of scaphoid non-union with vascularised and nonvascularised dorsal bone grafting from the distal radius. International orthopaedics 2010; 34:683-8.