Article

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Sevoflurane Represses the Malignancy of Colorectal Cancer by Regulating the p38/MAPK Pathway

Xu Zhang[1], Saisai Mu[2], Xin Song[3], Yan Zhou[1,*]

[1]Anesthesia Operating Room, Qingdao Hiser Hospital Affiliated of Qingdao University (Qingdao Traditional Chinese Medicine Hospital), 266033 Qingdao, Shandong, China
[2]Department of General Surgery (II), Qingdao Hiser Hospital Affiliated of Qingdao University (Qingdao Traditional Chinese Medicine Hospital), 266033 Qingdao, Shandong, China
[3]Customer Service Department, Qingdao Hiser Hospital Affiliated of Qingdao University (Qingdao Traditional Chinese Medicine Hospital), 266033 Qingdao, Shandong, China
*Correspondence: jntm_25@126.com (Yan Zhou)
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Objective: Sevoflurane is an inhalation anesthetic that exhibits a crucial role in cell growth, invasion, and apoptosis across various tumor types. Nevertheless, the underlying molecular mechanism remains largely unknown. Therefore, this study aimed to investigate sevoflurane's effects on colorectal cancer (CRC) progression and its underlying mechanisms.

Materials and Methods: The SW480 and LOVO cells were divided into two groups: a control group (cells without treatment) and a sevoflurane group (cells treated with 4% sevoflurane for 6 hours). Cell viability, proliferation, and clone formation ability were determined through 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), 5-Ethynyl-2′-deoxyuridine (EdU), and clone formation assays, respectively. Moreover, metastasis in these cells was determined using transwell and wound healing assays. Furthermore, flow cytometry was utilized to assess cell apoptosis rate. Additionally, Western blot assay was employed to determine the p38/mitogen-activated protein kinases (MAPK) pathway.

Results: Sevoflurane hindered CRC cell proliferation, clone formation, and metastasis while promoting apoptosis. Mechanically, sevoflurane restrained the p38/MAPK pathway in CRC cells. However, p38/MAPK agonist dehydrocorydaline (DHC) restored the inhibitory effect of sevoflurane on the cell function.

Conclusion: These results uncover an antitumor activity of sevoflurane on the invasion and migration of CRC through the p38/MAPK pathway, offering a novel mechanism for studying surgery-mediated CRC treatment.

Keywords: sevoflurane; colorectal cancer; proliferation; metastasis; p38/MAPK

Introduction

Colorectal cancer (CRC) is one of the leading causes of morbidity and mortality, posing severe threats to human health and safety [1]. Although significant progress has been made in the immunotherapy and targeted treatment of CRC, the post-diagnosis five-year or above survival rate is just 63%, primarily due to drug resistance and extremely poor prognosis at advanced disease stages [2]. Therefore, there is an urgent need to identify new strategies to combat the progression of this disease.

Previous studies have demonstrated that anesthetics used during surgical procedures affect the metastatic ability and growth of tumor cells [3–5]. Consequently, the effect of surgical intervention measures on the prognosis of tumor patients has been widely concerned and is an important area of current research. Sevoflurane is an inhalation anesthetic that affects cell growth, invasion, and apoptosis in multifarious tumors [6–8]. For example, a principal finding revealed that sevoflurane repressed the growth and invasion of lung adenocarcinoma cells, with its mechanism being related to the decreased expression of matrix metalloproteinase-(MMP)-2 and MMP-9 [9]. Another study indicated that sevoflurane hindered the multiplication and metastatic capacity of ovarian cancer cells by modulating p38/mitogen-activated protein kinases (MAPK) and c-Jun N-terminal kinase (JNK) pathway [10]. Besides this, a study reported that sevoflurane blocked cell proliferation, invasion, and migration in breast cancer [11]. However, a study demonstrated that sevoflurane promoted the cell viability, chemical resistance, and migration of renal cell carcinoma, suggesting varying impacts of sevoflurane on metastasis and chemical sensitivity across various tumor types [12]. Notably, Sun *et al.* [13] illustrated that sevoflurane repressed CRC cell metastasis through the microRNA-34a/ADAM10 axis. Similarly, Hu *et al.* [14] observed that sevoflurane restrained CRC cell invasion and migration while promoting apoptosis through the miR-637/WNT1 axis. Nevertheless, the mechanisms of sevoflurane on CRC development need to be further elucidated.

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Furthermore, it has been recognized that sevoflurane mediates multiple signaling pathways, including the p38/MAPK pathway, regulating the balance between cell proliferation and apoptosis [10,15]. Most importantly, the role of p38/MAPK in the malignant progression of CRC has been established, presenting it as a novel target for cancer therapy [16,17]. Thus, it is hypothesized that sevoflurane hinders the progression of CRC through the p38/MAPK pathway.

This research was intended to advance our understanding of the mechanisms of sevoflurane in CRC. Additionally, exploring the role and correlation of sevoflurane and p38/MAPK in CRC cells will offer new insights into investigating the regulatory mechanism of sevoflurane in CRC.

Materials and Methods

Cell Culture and Sevoflurane Treatment

Human CRC cell lines (SW480 and LOVO) were purchased from the National Infrastructure of Cell Line Resource (NICR, Beijing, China). These cells were cultured in Dulbecco's modification of Eagle's medium Dulbecco (DMEM) containing 10% fetal bovine serum (FBS) and double antibodies followed by incubation at 37 °C in the presence of 5% CO_2. The cells with stable growth in the 3rd–5th generations were selected for subsequent analysis. All cells were identified by STR and tested negative for mycoplasma.

The cells (5×10^5 cells/well) were inoculated into 6-well plates and incubated for 24 hours. Subsequently, the cells were randomly divided into two groups: the sevoflurane-treated group and the control group. The cell culture plates were placed within an airtight container and incubated at 37 °C in a water bath. The air inlet of the container was connected to the anesthesia machine to facilitate gas flow. The concentration of sevoflurane was measured using the gas detector. The cells in the sevoflurane group were exposed to a mixture of 4% sevoflurane with 5% CO_2 balanced with air, while the control group was treated with 5% CO_2 balanced with air alone [18,19]. The gas was administered at a flow rate of 1 µL/min for 6 hours. After 24 hours of incubation at 37 °C and 5% CO_2, the cells underwent functional analysis.

3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide (MTT) Assay

The treated cells were seeded into 96-well plates at a density of 5×10^3 cells/well, followed by incubation for 24 hours. Afterward, the culture medium was abandoned, and 10 µL of MTT solution (5 g/L) was added and incubated for another 4 hours. Finally, the optical density (OD) values were assessed at 490 nm using a microplate reader (JC-1086A, Juchuang Group Co., Ltd., Qingdao, China).

5-Ethynyl-2′-Deoxyuridine (EdU) Assay

CRC cells, harvested in the logarithmic growth stage, were inoculated into 96-well plates at a density of 4×10^3 cells per well, followed by incubation with 100 µL of EdU solution (10 µM) for 2 hours. After this, the cells were fixed with 50 µL of 4% paraformaldehyde for 30 minutes and washed with 50 µL of 2 mg/mL glycine for 5 minutes in a shaker. In the next step, 100 µL of 1× Apollo® staining solution was added and incubated for 30 minutes. Afterward, the cells were washed with 100 µL of penetrant and 100 µL of methanol in a shaker. The cells then underwent incubation with 100 µL of Hoechst 33342 staining solution for 30 minutes. Finally, the cells were observed using a fluorescence microscope (V5800, VIYEE, Tianjin, China) to capture their images for further analysis.

Clone Formation Assay

The cells were seeded in 6-well plates at a density of 1×10^3 cells per well followed by incubation until visible clones appeared. Subsequently, the cells were fixed with 40 g/L paraformaldehyde solution and stained with crystal violet dye. The clone formation was observed using an optical microscope (V2900, VIYEE, Tianjin, China), and more than 15 cells were identified as valid clones.

Cell Apoptosis Assay

The apoptosis rate of CRC cells was assessed through flow cytometry using the Annexin VFITC/PI double staining kit (40302ES50, YEASEN, Shanghai, China). For this purpose, 1.0×10^6 cells were initially seeded in 24-well plates. Subsequently, the cells underwent 10 minutes of incubation with 10 µL Annexin V-FITC, followed by adding 5 µL PI for 10 minutes. The cell apoptosis rate (%) was determined using the formula: (number of early apoptotic cells + number of late apoptotic cells)/total cell count × 100%.

Transwell Assay

For the invasion assay, the transwell inserts were precoated with Matrigel glue, while the migration assay was performed without Matrigel glue. Initially, 200 µL of CRC cells (2×10^5 cells/mL) were resuspended in a medium containing 20% FBS and subsequently added to both the upper and lower chamber of the transwell inserts, followed by incubation at 37 °C for 24 hours. In the next step, the cells were fixed with 4% paraformaldehyde and stained with 0.1% crystal violet dye. Finally, the cells were counted within 10 randomly selected fields using an optical microscope.

Wound Healing Assay

The treated cells were resuspended in a culture medium and subsequently seeded in 60 mm culture dishes at a density of 1×10^6 cells/dish. A sterile 200 µL gun tip was utilized to develop a scratch perpendicular to the direction

of cell growth. Following incubation, the cells were washed with pre-chilled PBS, incubated at 37 °C for 24 hours. Finally, the cells were observed using an inverted microscope (V2900, VIYEE, Tianjin, China), and photographs were recorded for further analysis.

Western Blot (WB) Assay

Total protein was extracted from the cells using radioimmunoprecipitation assay (RIPA) lysate and quantified through a bicinchoninic acid (BCA) kit (P0012S, Beyotime, Beijing, China). After this, 20 μg of the protein was resolved through sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and subsequently transferred onto polyvinylidene fluoride (PVDF) membranes. The membranes were sealed with 5% FBS for 45 minutes, followed by overnight incubation with primary antibodies, including anti-p38 (1:1000, #8690, Cell Signaling Technology (CST), Boston, MA, USA), anti-p38 (1:1000, #4511, CST, Boston, MA, USA), anti-MKK3 (1:1000, #8535, CST, Boston, MA, USA), anti-p-MKK3 (1:1000, #12280, CST, Boston, MA, USA), and anti-Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (1:1000, #2118, CST, Boston, MA, USA) at 4 °C. The following day, the membranes were incubated with secondary antibody goat anti-rabbit IgG H&L (HRP) (1:2000; ab205718, Abcam, Cambridge, UK) for 1 hour. The immunoblot was developed using an Enhanced chemiluminescence (ECL) system, and the bands were statistically analyzed through a gel imaging system and Image J software v5.2.1 (National Institutes of Health, Bethesda, MD, USA). The expression levels of the target proteins were expressed as the ratio of gray values of the target band to the GAPDH band.

Statistical Analysis

Statistical analysis was conducted using SPSS 21.0 statistical software (IBM, Chicago, IL, USA), and the data were expressed as the mean ± standard deviation (SD). Moreover, a one-way analysis of variance (ANOVA) followed by Tukey's test was employed for multiple group comparisons, and the comparison between the two groups was performed using the Student's *t*-test. A p-value < 0.05 was deemed statistically significant.

Results

Sevoflurane Restrained CRC Cell Multiplication and Enhanced Apoptosis

We elucidated sevoflurane's effects on CRC cell proliferation, colony formation, and apoptosis. CRC cells were cultured without or with 4% sevoflurane. MTT results revealed that the viability was significantly inhibited following sevoflurane treatment compared to the untreated group ($p < 0.01$, Fig. 1A). Moreover, the number of EdU-positive cells was substantially reduced in the sevoflurane group versus the untreated group ($p < 0.05$, Fig. 1B). Similarly, colony formation results demonstrated a significantly reduced colony formation capability in CRC cells following sevoflurane treatment ($p < 0.01$, Fig. 1C). Furthermore, the flow cytometry assay illustrated that compared to the untreated group, the apoptotic rate was substantially elevated in CRC cells exposed to sevoflurane ($p < 0.01$, Fig. 1D). The findings manifest that sevoflurane restrains CRC cell *multiplication* and enhances apoptosis.

Sevoflurane Hindered the Ability of CRC Cells to Invade and Migrate

We investigated sevoflurane's effects on the metastasis of CRC cells. CRC cells were cultured with 4% sevoflurane, and their metastatic ability was assessed utilizing transwell and scratch assays. Transwell assay revealed that the invading capability was significantly decreased in sevoflurane-treated CRC cells compared to the untreated group ($p < 0.01$, Fig. 2A). Similarly, the migration assay displayed that compared to the untreated group, sevoflurane significantly reduced the migration of CRC cells ($p < 0.01$, Fig. 2B). Furthermore, the scratch assay showed that the sevoflurane-treated CRC cells exhibited a significantly alleviated healing rate compared to the untreated group ($p < 0.05$, Fig. 2C). These findings suggest that sevoflurane hinders metastasis in CRC cells.

Sevoflurane Inhibited the p38/MAPK Signaling Pathway in CRC

The p38/MAPK pathway has been indicated as a potential target for treating CRC [17]. In this study, we analyzed the levels of these signaling-related proteins in CRC cells using WB. We observed that p-p38 and p-MKK3 levels were significantly reduced in both SW480 and LOVO cells following sevoflurane treatment ($p < 0.01$, Fig. 3A,B). However, applying p38/MAPK agonist dehydrocorydaline (DHC) restored the inhibitory effect of sevoflurane on the p38/MAPK pathway in CRC cells ($p < 0.05$, Fig. 3C,D). These findings illustrate that sevoflurane inhibits the p38/MAPK signaling pathway in CRC.

DHC Restored Sevoflurane's Inhibitory Effects on the Malignancy of CRC

To probe into the mechanisms of sevoflurane in CRC, the p38/MAPK pathway was activated by the p38/MAPK agonist, DHC. SW480 cells were treated with sevoflurane alone or combined with DHC. The MTT assay revealed that DHC treatment significantly restored the inhibitory effect of sevoflurane on the viability of the cells ($p < 0.05$, Fig. 4A). However, the proliferation was significantly increased in the sevoflurane+DHC group when compared to the sevoflurane group ($p < 0.05$, Fig. 4B). Additionally, the cell apoptosis was significantly elevated in the sevoflurane group, while DHC treatment substantially attenuated this induction in CRC cells ($p < 0.01$, Fig. 4C). Furthermore, the transwell assay demonstrated that DHC partly restored

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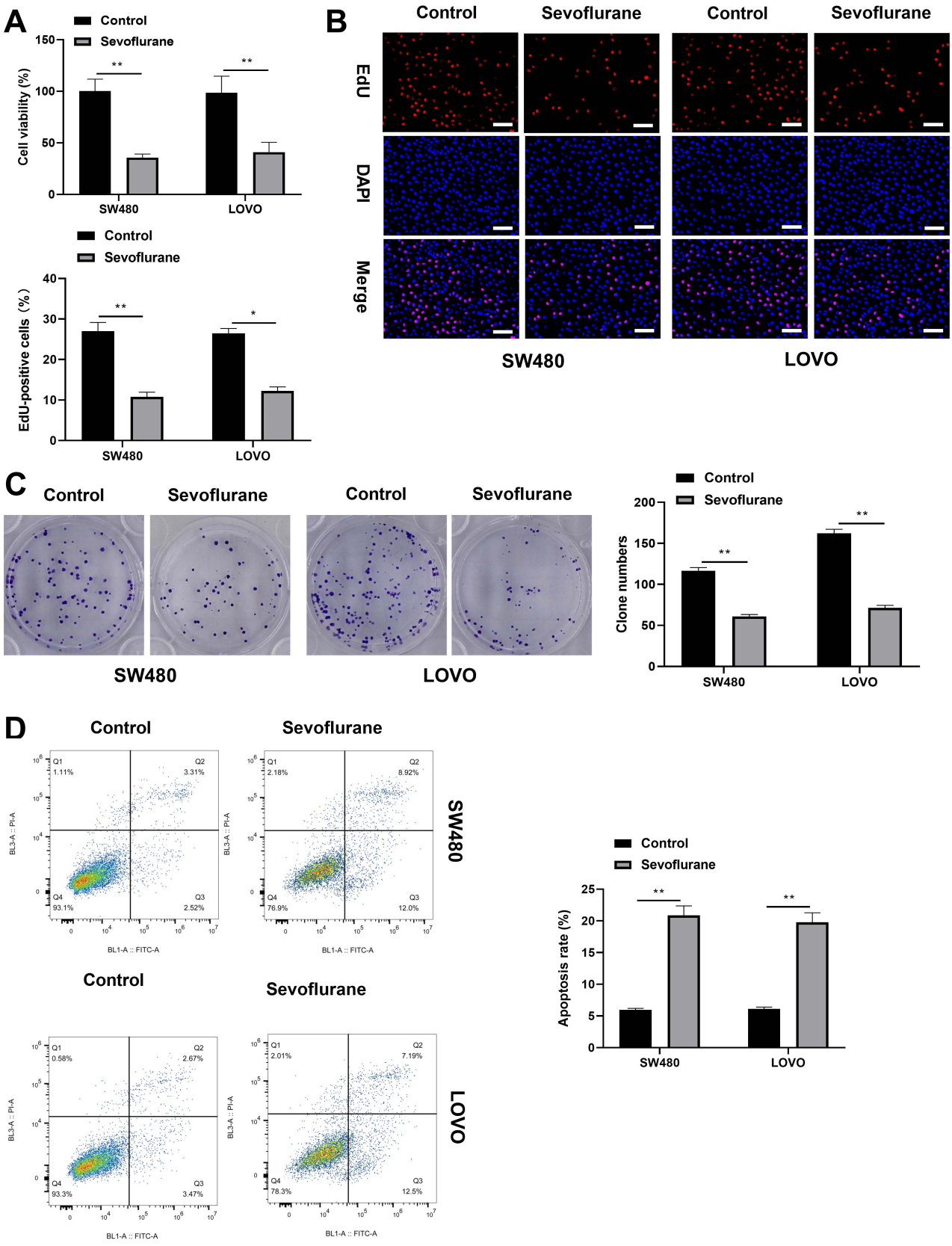

Fig. 1. Sevoflurane reduced cell multiplication and induced apoptosis in colorectal cancer (CRC). (A) Cell viability assessment through 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT). (B) Cell proliferation measurement through 5-Ethynyl-2′-deoxyuridine (EdU) (Scale bar = 50 μm). (C) Cell clone formation rate assessment using colony formation assay. (D) Cell apoptosis evaluation through flow cytometry. N = 5; *$p < 0.05$, **$p < 0.01$.

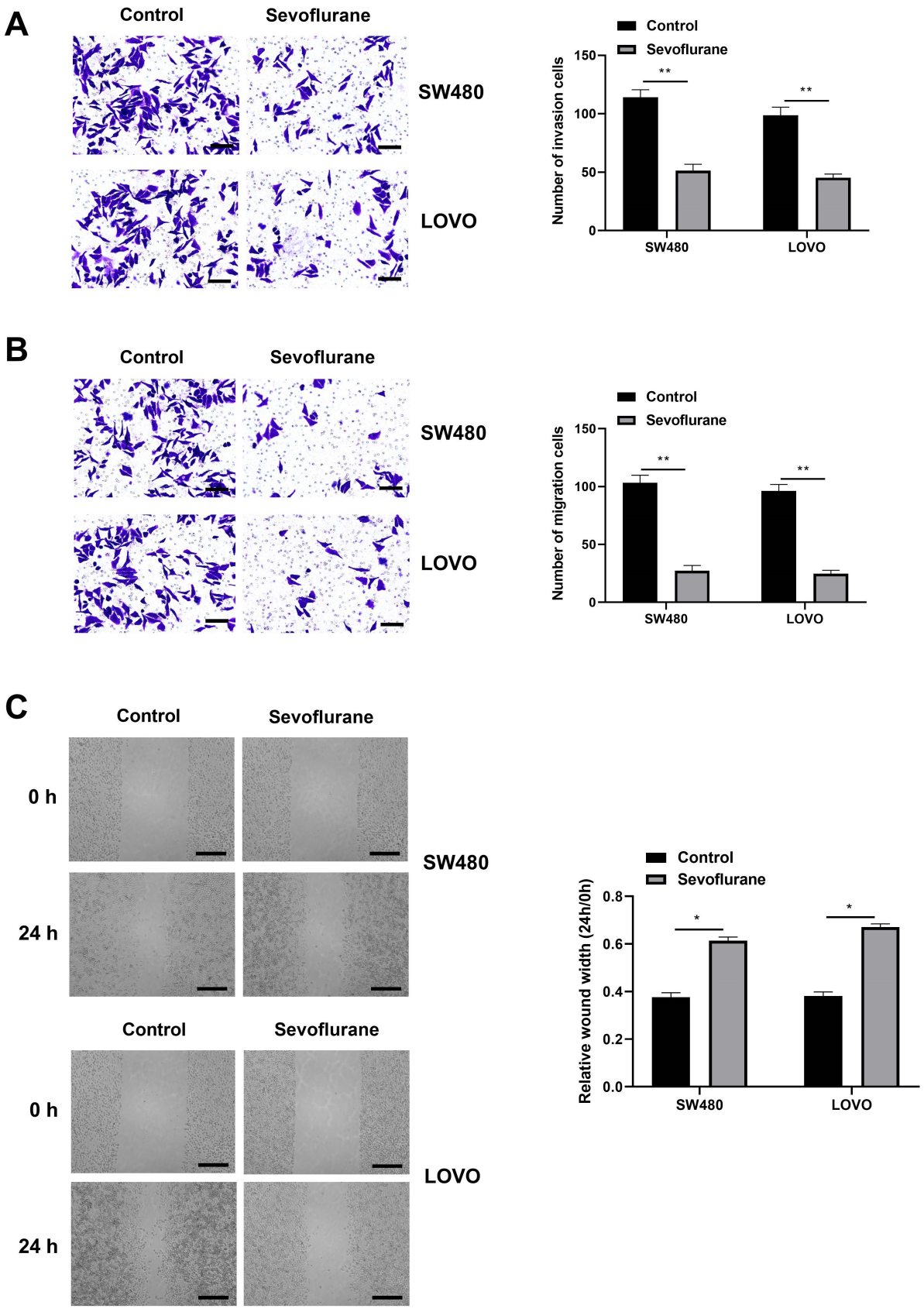

Fig. 2. Sevoflurane repressed CRC cell invasion and migration. (A) The invasiveness and (B) migratory capacity assessment through transwell assay (Scale bar = 50 μm). (C) The healing rate was observed using the scratch assay (Scale bar = 100 μm). N = 5; *$p < 0.05$, **$p < 0.01$.

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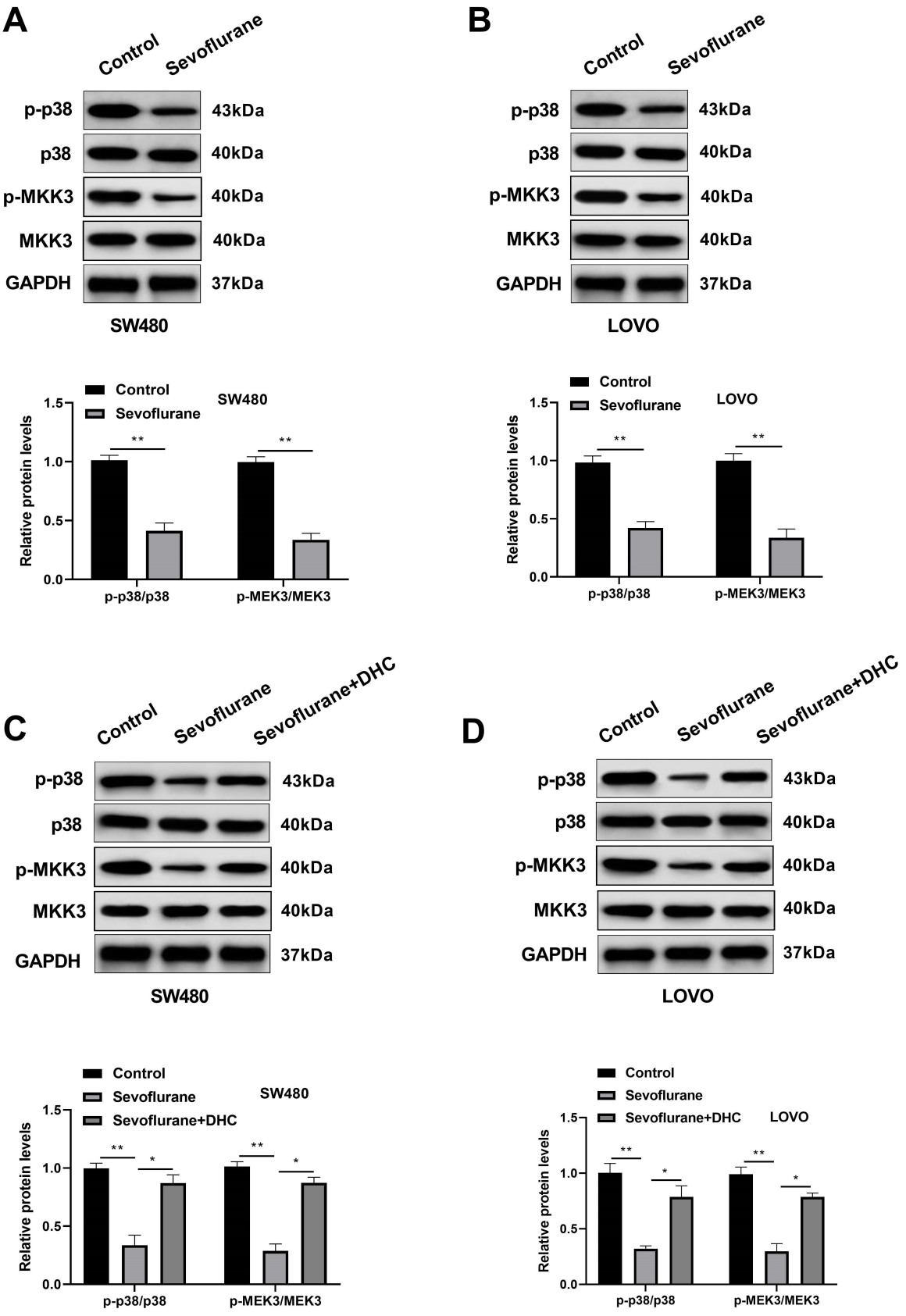

Fig. 3. Sevoflurane inhibited p38/mitogen-activated protein kinases (MAPK) pathway in CRC. (A,B) WB was used to assess p-p38 and p-MKK3 levels in sevoflurane-treated CRC cells. (C,D) The impact of dehydrocorydaline (DHC) on the p38 and p-MKK3 levels in sevoflurane-treated CRC cells. N = 5; *$p < 0.05$, **$p < 0.01$. GAPDH, Glyceraldehyde-3-phosphate dehydrogenase.

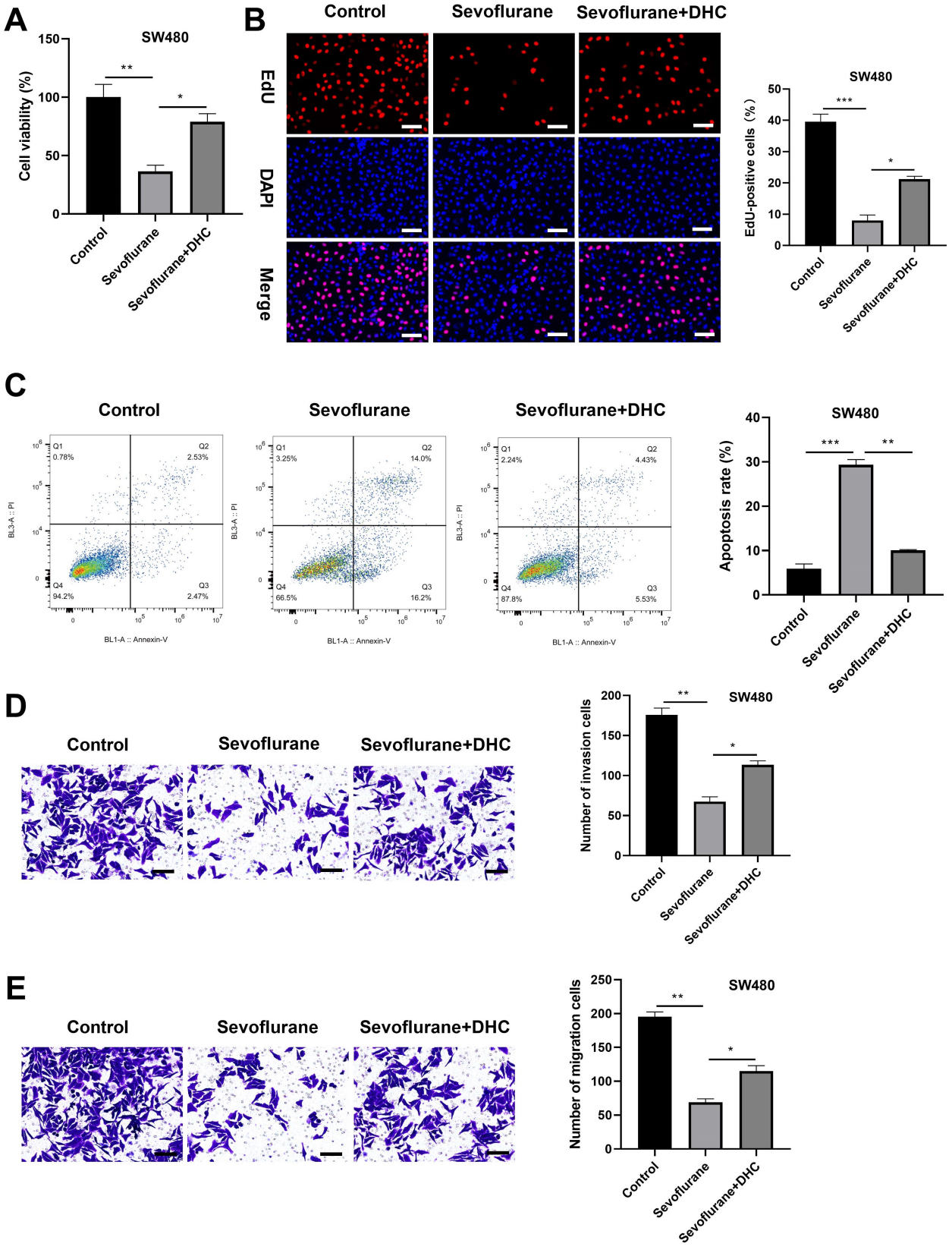

Fig. 4. DHC partly abolished the inhibitory effect of sevoflurane on the malignancy of CRC. SW480 cells were treated with sevoflurane alone, or combined with DHC. (A) Cell viability assessment using MTT assay. (B) The evaluation of cell multiplication utilizing EdU assay (Scale bar = 50 μm). (C) Cell apoptosis assessment through flow cytometry. (D) Cell invasion and (E) migration measurement employing transwell assays (Scale bar = 50 μm). N = 5; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

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sevoflurane's inhibitory effects on the invading and migratory capabilities of CRC cells ($p < 0.05$, Fig. 4D,E). These results confirm that sevoflurane hinders the progression of CRC through the p38/MAPK pathway.

Discussion

CRC is one of the most common malignancies worldwide, with the second-highest mortality rate among malignant tumors [20,21]. Currently, studies have shown that narcotic drugs can reduce the probability of tumor recurrence and metastasis after surgery [22,23]. For instance, Li *et al*. [24] uncovered that propofol repressed CRC cell migration and proliferation through the miR-124-3p.1/AKT3 axis. Furthermore, Wu *et al*. [25] indicated that propofol inhibited the growth, metastasis, and glycolysis of CRC by suppressing LDH activity. This study demonstrates that sevoflurane hinders CRC cell malignancy. Moreover, DHC, a p38/MAPK agonist, reversed the inhibitory effect of sevoflurane on CRC cell malignancy, suggesting that sevoflurane affects the progression of CRC via the p38/MAPK pathway.

Sevoflurane is a commonly used anesthetic in clinical settings [26,27]. A current study has revealed its anti-metastasis potential in breast cancer [6]. Another research illustrated sevoflurane's ability to restrain invasion and proliferation of head and neck squamous cell cancer cells while promoting cell apoptosis by activating the HIF-1α pathway [28]. Furthermore, another research displayed that sevoflurane reduced the aggressiveness of lung cancer cells by inhibiting MMP-9 [29]. However, Nishiwada *et al*. [30] revealed a significant increase in the proliferation of human hepatocellular carcinoma cells exposed to sevoflurane under high glucose and insulin. Moreover, Shi *et al*. [31] illustrated that sevoflurane can promote the growth of glioma stem cells by up-regulating the level of the hypoxia-inducing factor. Thus, sevoflurane exhibits varying effects on the carcinogenic properties of tumor cells. Regarding CRC, it has been reported that sevoflurane hindered CRC cell migration and invasion through the microRNA-34a/ADAM10 axis [13]. Another study identified the inhibitory impacts of sevoflurane on CRC progression by sponging miR-622 [32]. In our current research, we observed that sevoflurane repressed the proliferative, invasive, and migratory capabilities of CRC cells, aligning with previous research.

The p38/MAPK, a stress-activated protein kinase, plays an extensive regulatory role in cell proliferation, migration, apoptosis, and other biological processes and is closely linked to apoptosis initiation and cell cycle stasis [33,34]. Studies have reported that p38/MAPK promotes the expression of p53 by mediating the degradation of MDM2 protein, thereby activating the p53-mediated apoptosis pathway [35,36]. The activation of p38/MAPK has been found to negatively regulate cancer cell proliferation, which has been linked to tumor suppression [37,38]. Numerous studies have shown that the increased activity of p38/MAPK significantly facilitated cell proliferation, thereby promoting the prognosis of liver cancer and thyroid cancer [39,40]. Notably, recent research underscores the implication of p38/MAPK in the progression of CRC [16]. Interestingly, our study suggested that the level of p-p38 protein significantly declined following sevoflurane treatment. However, adding p38/MAPK agonist DHC partly abolished the suppressive effect of sevoflurane on p-p38 expression in CRC cells. Based on previous research and our findings, we speculate that sevoflurane might impede the malignancy of CRC by mediating the p38/MAPK pathway.

Though our research has yielded specific results, this study also has some limitations. Firstly, more clinical evidence is needed to confirm this hypothesis. Moreover, further studies are required to explore the antitumor activity of sevoflurane in animals and comprehensively elucidate its molecular mechanism.

Conclusion

Our findings revealed that sevoflurane effectively inhibited cell viability, proliferation, and cloning formation capabilities. Moreover, sevoflurane repressed cell invasion and migration. Our findings further validated the inhibition of the p38/MAPK pathway by sevoflurane in CRC cells. These observations suggest a new direction for studying the use of sevoflurane in surgeries for CRC patients.

Availability of Data and Materials

The data used to support these findings of this study are available from the corresponding author upon request.

Author Contributions

YZ conceptualized and designed the research study. XZ performed the manuscript draft. XZ and SM performed the research. XS made significant contributions to data acquisition and analysis. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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