

## ORIGINAL RESEARCH ARTICLE

# A comparison between the efficacy of methylphenidate and cocaine for nasal vasoconstriction before nasal surgery—A randomized prospective study

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### ABSTRACT

**Objectives:** Cocaine is regularly utilized topically to give the vasoconstriction to nasal medical procedure; However, it is said to create intraoperative cardiovascular unfriendly impacts. Methylphenidate was considered in the place of cocaine as a substitute to look at the vasoconstriction in nasal medical procedure. **Methods:** Outcome of the study will be examining the vasoconstriction based on a 5-point scale (1 = unacceptable, 5 = excellent), followed by the administration of either 20–30 mg per day methylphenidate or 4% cocaine randomly to the adult patients subjected to nasal septoplasty. **Results:** Methylphenidate and cocaine were administered with 38 and 28 patients respectively. The quality of vasoconstriction was noticed to be good in both the groups with the median rating of 4.0 and a *P* value of 0.85. With both the gatherings, the median blood loss was 46 and 58 mL with a *p* estimation of 0.48. A non-inferiority delta of 1 point with a *p* estimation of 0.009 and non-inadequacy delta of 24 mL with a *p* esteem 0.026 concerning vasoconstriction and blood loss individually is seen which demonstrates methylphenidate is comparable to cocaine. Non importance is noted with the recurrence of ventricular ectopy, ST section changes after nasal packing with the gatherings. **Conclusions:** With the results obtained, methylphenidate can be very well replaced for cocaine for vasoconstriction in septoplasty. As there are lot many underlying chances for cocaine abuse and administrative issues related to its handling, methylphenidate may serve as a substitute.

**Keywords:** cocaine; vasoconstriction; local anaesthetics; nasal medical procedure; methylphenidate

## 1. Introduction

The real activity of vasoconstrictors is to get the muscle cells in the dividers of veins. The inside distance across of the veins at that point get limited which is a basic reason for the raising circulatory strain. This component of vasoconstrictors could be connected for treating low pulse particularly in an intensive care or careful setting. Choice of vasoconstrictors again is especially required and few of such operators in medicinal practice are Epinephrine, Norepinephrine, Vasopressin, Phenylephrine, Pseudoephedrine. Cocaine has been shown for special interest as it gives both absence of pain and vasoconstriction when compared to other analgesics. These unmistakable properties make it exceedingly recommendable particularly in otolaryngology and plastic medical procedure where ground-breaking vasoconstriction is required for methods, encouraging nasal mucosal surfaces in decreasing blood misfortune and improve detectable quality in the careful field<sup>[1]</sup>.

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Lamentably, cocaine is related with huge perioperative horrendousness including myocardial ischaemia and dead tissue, cardiomyopathy, hypertensive emergency, cerebrovascular incidents, aortic evisceration and arrhythmias<sup>[2-7]</sup>. This will be particularly a stress with elderly patients and those with known cardiovascular deal<sup>[8]</sup>. Additionally, cocaine will be a controlled substance with a potential for wiped out use. Dealing with and putting away controlled substances incorporates included administrative expenses and dangers of blunder. Subsequently, a choice vasoconstrictor might be perfect if ended up being convincing and safe.

The relationship of methylphenidate, an unadulterated alpha-receptor agonist, and lidocaine has been seemed, by all accounts, to be as bad as cocaine<sup>[9,10]</sup> and may be perfect, embellishments absence of agony and vasoconstriction for attentive nasotracheal intubation. As an including, at unlike centers, the methylphenidate-lidocaine bond has about substituted cocaine for nasotracheal intubation. This case prescribes that methylphenidate may be vivacious for giving watchful homeostasis in rhinologic therapeutic method.

In the way, the utilization of methylphenidate for this center has require been truly portrayed, and cocaine keeps on being utilized by a few clinicians. Medication mishandle and taking care of being not an issue with methylphenidate, the reactions of the medication ought to be noted. Uncovered responses stretched out from minor bob back hyperaemia to even mortality when unmeasured doses of topical methylphenidate were used, and the ensuing hypertension was being mishandled with long-acting beta-blockers<sup>[11]</sup>. Our ask about focused on whether methylphenidate is all over better than anything cocaine in patients encountering nasal septoplasty and whether methylphenidate is connected without any horrible manifestations than cocaine.

## **2. Materials and methods**

The rationale behind the study is as a substitute to cocaine in patients experiencing nasal septoplasty, it must be superior to cocaine in each angle with no more regrettable reactions. The present examination is directed to explore whether methylphenidate is advantageous than cocaine in patients experiencing nasal septoplasty and whether it is related with no more symptoms than cocaine. Establishing the evidence for methylphenidate to be used as a substitute to cocaine for nasal vasoconstriction before nasal surgery would be the objective of the study. Henceforth, the study will be randomized, open label balanced trial enlisting 100 patients and analyzed utilizing two-sided Wilcoxon rank-sum tried for 90% power at the 0.05 centrality level to distinguish contrasts of at least 1.0 focuses in the vasoconstriction quality evaluations by the clinical specialists. The test and the reference drugs will be Methylphenidate and Cocaine respectively. 100 patients will be enrolled in the study. Written informed consent will be taken from the study participants. Much number of patients will be screened to enrol the study. The statistic information like name, age, sex, BMI, pulse, recurrence of irregular pulses, systolic circulatory strain, ventricular ectopy, prepaced ST fragment change will be noted. Availability of patient for the whole examination time frame and eagerness to cling to convention necessities as confirm by the written informed consent form properly marked by the patient and Patients of age in the range of 18 and 65 years and presenting for elective nasal septoplasty were the criteria to enrol the subject in the study. History of a cardiovascular issue will be exclusion criteria to exclude the subjects from the study. Institutional Ethics Committee has inspected the convention and informed consent form. The examination would not have begun until the committee has affirmed the convention as submitted or with alterations. The IEC maintains all authority to approve the examination for security reason whenever.

The purpose behind the examination, the systems to be done and the potential dangers will be depicted to the individuals in English and in their neighborhood tongue in non-specific terms in comparability with regulatory necessities. Individuals will be required to scrutinize and sign a consent outline compressing the exchange going before enrolment. When the Clinical Examiner, or qualified clinical staff part ensures that an individual contender appreciates the repercussions of appreciating the examination, the subject will assert his

capacity to share in the examination by denoting the informed consent outline. A copy of the dated instructed consent shape will be given to the individuals. The principal stamped and dated instructed consent shape will be kept up. The individuals will be ensured that they may pull once again from the examination at whatever point without imperiling their therapeutic consideration.

The specialists claim all authority to end the investigation whenever. The purpose behind this end will be given to the members. The Clinical Agent claims all authority to end the investigation for security reasons whenever. The Institutional Morals Advisory group (IEC) may end the examination if there is significant infringement of moral thought because of any genuine antagonistic occasion. The members are allowed to cease or pull back from the investigation whenever in the event that they wish to do as such. The examination specialist can pull back a subject from the investigation, on the off chance that he finds, the subject experiences extreme afflictions any, genuine unfriendly occasions any, neglecting to qualify the incorporation criteria or the convention. A report has to be produced by the investigator justifying the withdrawal of the subjects at the end of the study.

Patients were given either 20 to 30 mg for each day methylphenidate or 4% cocaine according to the randomization plan in view of PC created codes (SAS factual programming, PLAN methodology, with arbitrarily estimated squares) and utilizing hazy fixed envelopes. Both the patients and Clinical agents didn't know about the gathering assignments. The investigation sedate arrangements were set up in our drug store, indistinguishably tinted blue, administered in 5-mL vials, and named Test and Reference drug respectively.

A determination of anesthesia and intubation was given to the examination people. The nasal opening was stacked down with either methyl-phenidate or cocaine-sprinkled pledgets. To enhance the vasoconstriction accomplished by the examination steady, a blend of lidocaine 0.5% and epinephrine 10 µg/mL was besides utilized, if imperative. Premedication was given with intra-venous midazolam (1 mg) and glycopyrrolate (0.2 mg). General anesthesia was begun with a blend of propofol (9 mg/mL) and alfentanil (45.5 µg/mL) in an estimation of around 2 mg/kg of propofol and 9 µg/kg of alfentanil. Vecuronium 0.1 mg/kg was utilized to invigorate endotracheal intubation. Anesthesia was remained mindful of an equi-valent blend of propofol and alfentanil in an estimation of 75 µg/kg/min and 0.4 µg/kg/min, freely, and 60%–70% N<sub>2</sub>O in O<sub>2</sub>. Vecuronium boluses were utilized as anyone might expect to keep up muscle releasing up. Lactated Ringer's (LR) strategy was controlled at a rate of 4–6 mL/kg/h. Mechanical ventilation was switched according to keep up end-tidal CO<sub>2</sub> some place in the extent of 32 and 35 mmHg (normocapnia).

Hypotension was treated with a liquid bolus of LR blueprint 5–10 mL/kg intravenously. Hyper-tension was treated with intravenous nitroglycerin (NTG) boluses of 80 µg. As of anaesthesiologist's care, by altering the propofol/alfentanil implant-tation rate, the essentialness of anesthesia could be broadened or diminished. Tachycardia with hypertension was treated with 3 mL boluses of propofol and alfentanil, trailed by intravenous esmolol up to 0.5 mg/kg in isolated dosages. Bradycardia alone was seen with glycopyrrolate as required. Significant signs that included heartbeat, non-unmistakable circulatory strain and consistent electrocardiogram (ECG) were checked each 3 min. At the total of the helpful strategy, remaining neuromuscular barricade was turned with neostigmine 0.04–0.06 mg/kg in blend with glycopyrrolate 0.2 mg for each milligram of neostigmine. The propofol/alfentanil implantation was ceased. The trachea was extubated after watched flight course reflexes had returned and the patient was mindful with tasteful neuromuscular recuperation. Check circulatory strain and scenes of systolic hypertension, standard and astounding heartbeat, nasal pressing term, ventricular ectopy, ST section changes >1 mm, add up to estimations of NTG and esmolol, add up to whole of supplemental lidocaine with epinephrine and surveyed blood disaster were recorded. Around the total of the system, the nature of vasoconstriction was assessed on a size of 1–5, with 1 being unsatisfactory and 5 being prominent.

## 2.1. Statistical analysis

Randomized gatherings were graphically evaluated for adjust on gauge factors. Methylphenidate and cocaine bunches were looked at on the essential result of vasoconstriction quality appraisals of the clinical specialists and on other non-ordinarily conveyed consistent factors (pack min, number of lidocaine infusions, measurements of lidocaine, NTG, esmolol, evaluated blood misfortune, Working Room moment and percent hoisted post-pack pulse readings) with the two-sided Wilcoxon rank-entirety tests. The Cochran-Shelf Haenszel (CMH) test was utilized to think about gatherings on the nearness of systolic circulatory strain variations from the norm (>20% of gauge) while changing for the nearness of pre-pressing anomalies. 95% certainty interims on the evaluated treatment impacts were ascertained. As post-hoc optional examinations, the non-mediocrity of methylphenidate to cocaine on the essential results of vasoconstriction quality rating and blood misfortune utilizing one-followed Wilcoxon rank-whole tests with non-inadequacy deltas of 1 point for vasoconstriction quality rating and 24 mL for blood misfortune was likewise tried.

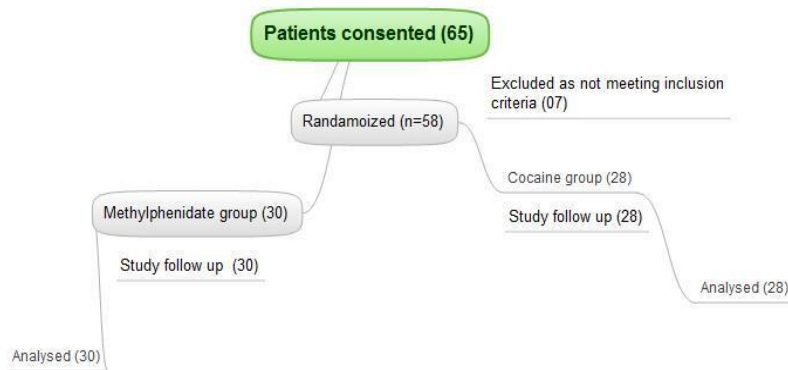
## 2.2. Sample size considerations

A randomized, open label balanced trial enlisting 100 patients and examined utilizing two-sided Wilcoxon rank-whole tried for 90% power at the 0.05 importance level to recognize contrasts of at least 1.0 focuses in the vasoconstriction quality appraisals by the clinical specialists. A noteworthiness level of 0.05 was utilized for all speculations. SAS factual programming was utilized for all information investigation. The East program from Cytel Partnership (Cambridge, Mama, USA) was utilized for the ceasing guideline part of the interval investigation.

Because of enrolment challenges, we directed a gathering successive between time investigation after 58 patients were selected to evaluate for viability and pointlessness utilizing a pre-characterized gamma spending capacity ( $\gamma = -5$  for adequacy and  $-2$  for worthless-ness). This gathering consecutive observing depended on the above-characterized test estimate counts: Maximum 100 patients to have 90% capacity to recognize a 1-point contrast in representation at the 0.05 level. The watched  $P$  estimation of 0.84 for the essential result crossed the pointlessness limit ( $P > 0.65$ ). Likewise, a restrictive power examination demonstrated that there was just a 2.5% possibility of discovering prevalence for either methylphenidate or cocaine on the off chance that we had proceeded with the first example size of 100, accepting that the treatment impact in later patients would be like the impact in the initial 58. We subsequently stopped the examination at 58 patients for “uselessness” i.e., guaranteeing no contrast between gatherings.

## 3. Results

65 patients were consented to participate in the study. Clinical investigator excluded 7 patients as the surgical plan involved more than a simple septoplasty. The measure taken among that seven excluded patients was that they were administered with cocaine. Among the 58 randomized patients, methylphenidate was administered for thirty patients and cocaine was administered for twenty-eight patients and the same was graphically represented in **Figure 1**. The demographic and preoperative data were compared with the respect to the randomized group which was represented in **Table 1**.



**Figure 1.** Patients consented, randomized and analyzed: a schematic representation.

**Table 1.** Baseline demographic and preoperative data of 58 patients undergoing nasal surgery.

Parameters	(X) methylphenidate <sup>1</sup> (n = 30)	(Y) Cocaine (n = 28)
Gender (% male)	59.7	54.9
Baseline heart rate (mean ± SD)	73.8 ± 12	78.6 ± 12
Frequency of abnormal <sup>x</sup> heart rates (median, 25%–75% IQR)	2 (0, 1)	0.5 (0, 3)
Mean baseline SBP (SD)	117.5 (18)	122.9 (17)
Pre-pack episodes of SHT (median, 25%–75% IQR) <sup>y</sup>	0 (0, 1)	0 (0, 1)
Pre-pack ventricular ectopy, n (%)	0 (0)	0 (0)
Pre-pack ST segment change, n (%)	2 (6.9)	0 (0)

SD—Standard deviation; IQR—Interquartile extend, <sup>1</sup>Statistical correlation at benchmark not done since it is a randomized trial, <sup>x</sup>Abdominal HR characterized as over 20% of gauge, <sup>y</sup>SHT—Systolic hypertension characterized as SBP above 20% of standard, ST segment change—A difference in excess of 1 mm from benchmark as watched and noted by the EKG screen; SBP—Systolic circulatory strain (mmHg).

### 3.1. Primary outcome

Methylphenidate did not show any improvement in the primary outcome of vasoconstriction rating when compared to cocaine, with a median score of 4 in each group with a *p* value of 0.85 which was obtained by Wilcoxon rank sum test and the same was represented in **Table 2**. Post-Hoc secondary analysis was run to show methylphenidate to be non-inferior compared to cocaine on vasoconstriction with a *p* value of 0.009 using one tailed Wilcoxon rank sum.

**Table 2.** Vasoconstriction in study patients rated by clinical investigator.

Rating	(X) methylphenidate group frequency (%)	(Y) Cocaine group frequency (%)
(Undesirable)	4 (13.8)	1 (3.8)
(Low)	1 (3.4)	1 (3.8)
(Normal)	5 (17.2)	8 (30.8)
(Worthy)	9 (31.0)	9 (34.6)
(Outstanding)	10 (34.5)	7 (26.9)
Ratings continuous Variable, median (Q1, Q3)	4 (3, 5)	4 (3, 5)

*P* = 0.85 comparing groups on ratings with Wilcoxon rank-sum test. *P* = 0.009 with one sided test for non-inferiority of methylphenidate vs cocaine (delta = 1 pt).

### 3.2. Secondary outcome

Among the randomized group studied, there was no difference studied in the frequency of ventricular ectopy, ST segment abnormalities, percent of a patient's heart rate readings, systolic blood pressure readings with a *p* value for every parameter studied which was well represented in **Table 3**.

**Table 3.** Variables observed and secondary outcomes in patients receiving methylphenidate/cocaine before nasal surgery.

Variable <sup>1</sup>	(X) methylphenidate ( <i>n</i> = 30)	(Y) Cocaine ( <i>n</i> = 28)	95% CI methylphenidate-Cocaine median <sup>3</sup>	<i>P</i> value <sup>4</sup>
Pack time in minutes	21 (12, 37)	15 (7, 27)	-2, 13	0.23
Number of lidocaine injections	2 (3, 4)	2 (2, 4)	1, 2	0.38
Lidocaine dose in cc of 1%	12 (11, 15)	10 (9, 13)	-2, 37	0.09
Nitro glycerine dose in µg	0 (0, 39)	0 (0, 0)	0, 0	0.16
Esmol dose in mg	0 (0, 0)	0 (0, 0)	0, 0	0.18
EBL in cc <sup>7</sup>	49 (26, 51)	61 (26, 100)	-50, 14	0.48
OR <sup>2</sup> minutes	129 (113, 181)	136 (124, 176)	-25, 20	0.59
% Abnormal <sup>8</sup> post pack heart rate readings	0 (0, 3.6)	0 (0, 0)	0, 0	0.98
% Abnormal <sup>8</sup> post pack heart rate readings systolic blood pressure readings	8 (0, 12)	0 (0, 8)	0.70	0.14
Post pack ventricular ectopy, <i>n</i> (%)	0 (0)	0 (0)	0, 0	0.98 <sup>5</sup>
Post pack ST segment change, <i>n</i> (%)	2 (8)	2 (9)	0, 0	0.59 <sup>6</sup>

<sup>1</sup>Data are median (25 percentile, 75 percentile) except if noted; <sup>2</sup>OR—operating room; <sup>3</sup>95% Certainty interm for middle distinction between gatherings; <sup>4</sup>Wilcoxon rank—sum test, except if noted; <sup>5</sup>Fisher's correct test; <sup>6</sup>Pearson chi-square test; <sup>7</sup>EBL—Estimated blood loss; <sup>8</sup>% abnormal is parent of a patient's readings falling 20% or more above baseline, ST segment change—A difference in excess of 1 mm from benchmark as watched and recorded by the EKG monitor, CI-Certainty interm.

In the randomized groups, no difference is noted in the incidence of at least one elevated post pack systolic blood pressure reading with a *p* value of 0.08 and relative risk of 2.7 (0.81, 8.9). The blood loss was 48 mL in methylphenidate group and 60 mL in cocaine group with a *p* value of 0.48 where Wilcoxon rank sum test was applied to study statistically and the same was represented in **Table 3**.

### 3.3. Blood loss

Methylphenidate was found to be non-linear to cocaine on the blood loss which was analyzed using one tailed Wilcoxon rank-sum test with a *p* value of 0.026 and the same was represented in **Table 3**. No relationship was identified between the predictions and the actual treatment applied. Being blinded study, investigator couldn't locate the treatment he has given.

### 3.4. Intraoperative adverse events

In the study conducted, intraoperative adverse events were recorded in eight cases. With the group administered with methylphenidate, hypotension is recorded with one case at the tenth minute from the drug administration. When it comes to hypertension, no such event is recorded with the study cases. When comes to Tachycardia, the event was noted in five cases where three are from methylphenidate group recorded at fifth minute and two from cocaine group recorded at baseline. When comes to bradycardia, two such cases were recorded with methylphenidate group, one at fifth minute and one at tenth minute.

## 4. Discussions

The vasoconstriction effects of topical 4% cocaine and 0.5% methylphenidate for nasal surgery is investigated in the present study. With the results obtained with both the drugs in the condition, it could be

said like both don't have a control in blood loss. No satisfactory results as measured by surgical criteria. However, similar pattern of adverse events and other complications were recorded with both the drugs. With all the analysis made among the two drugs, it is like, Methylphenidate is as effective as cocaine to administer as vasoconstrictor. The blood loss again is noted to be non-inferior with methylphenidate when compared to cocaine as studied in post-hoc non-inferiority analysis. Cocaine when administered in larger doses of 10% or 20%, severe side effects like intraoperative hypertensions, tachycardia, elevated pulse pressure, myocardial infarction were recorded<sup>[2,5-7,12]</sup>. The same when applied with lesser dose of 4%, we observed a well safe profile.

As systemic absorption takes place with topical application, it is recorded 35%–37% of cocaine is absorbed systematically when applied topically. It is been reported when cocaine 4% solution applied nasal on cottony pledgets, it's claimed to be sage for 20 min<sup>[2,13]</sup>. Fewer studies have also reported for cardio excitatory side effects with cocaine concentration of 4%. An acute myocardial infarction and cardiogenic shock has also recorded in patient's nasal surgery with an administration of 4% cocaine again. With application of 2% cocaine, sever hypertension and multiple ventricular ectopic beats and ST segment depression<sup>[14]</sup>.

There are lot many underlying mechanisms explained for cocaine for its effects towards Ischemia/infarction including coronary vasoconstriction, thrombosis and atherosclerosis. A small dose of cocaine 2 µg/kg administered intranasally ended up in constriction of the epicardial arteries and as well contributes a lot to potential local autoregulatory mechanism that would preserve the coronary blood flow.

The reuptake of norepinephrine is blocked because of the vasoconstrictor property of cocaine. The mechanism of methylphenidate could be explained as being a synthetic catecholamine, it stimulates alpha-1 adrenergic receptors. When it comes to norepinephrine release, a minor pharmacologic response is studied. A minimal effect has occurred with the beta-adrenergic receptors. Alpha-2 receptor is well stimulated than the Alpha-1 receptor with the dose of methylphenidate administered. A better preservation of coronary arterial perfusion could be possible as venoconstriction is greater than arterial vasoconstriction.

With the obtained results, we could conclude that methylphenidate is effective as cocaine subjectively rated by investigators and objectively by their effect on measured blood loss. No difference is noted in the amounts of other vasoconstrictors used in the treatment with intravenous esmolol, ephedrine or NTG. When it comes to the incidence of hypertension, changes in heart rate and arrhythmias, again, we couldn't make any differences between the drugs used. The results we obtained with the study found to be much consistent with the results of the previous investigators. 4% lidocaine with methylphenidate and 5% cocaine in nasal dilation, blood pressure and heart rate were studied and no differences were found among the two<sup>[9]</sup>. As that of cocaine 4%, topical nasal methylphenidate with 3% lidocaine found to be much sage and effective<sup>[10]</sup>. 5% lidocaine and methylphenidate solution were again compared with 10% cocaine spray which was a randomized double-blind trial where there was no difference in the visual analogy scale pain scores, nasal inspiratory peak flow recordings and incidence of adverse effects in the two groups<sup>[15]</sup>.

Restrictions in the investigation would be that nature of vasoconstrictor alone has examined accepted the same as abstract as it is an essential clinical practice in assessing the careful conditions. Then, endless supply of the medication, non-obtrusive circulatory strain estimation may miss fast pulse changes. The examination was not engaged to identify distinction in the double wellbeing results. So, when taken hemodynamic parameters, we couldn't finish up the security of methylphenidate to cocaine. To all the more likely clarify, certainty interim for the relative danger of hypertension ranges from 0.81 to 8.9 with a non-noteworthiness noted. A uselessness limit was crossed for the essential result, vasoconstriction quality. In the auxiliary examination, methylphenidate was noted to be slightest as successful as cocaine on both quality and seeping amid vasoconstriction. In the examination made, 4% cocaine was looked at towards methylphenidate while

there are part numerous preliminaries ran up with intriguing aftereffects of 2% tetracaine co-managed with epinephrine<sup>[16]</sup>. Trials are also there who tried the same with 1% xylometazoline and 0.05% oxymetazoline<sup>[17,18]</sup> as nasal decongestants. The future scope is that all these agents to be studied and compared with respect to cocaine in exploring the outcomes further.

## 5. Conclusions

Methylphenidate, as effective as cocaine, it could be replaced well necessarily as vasoconstrictor. Methylphenidate is not expensive and easily affordable. As like cocaine, methylphenidate do not have any administrative issues as well handling issues. Drug abuse here not a chance as it happens with cocaine. Methylphenidate could be used as conventional vasoconstrictor with respect to the concentration studied for adults in nasal surgery.

## Conflict of interest

The authors declare no conflict of interest.

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