Clinical Investigation

Phenylephrine as an alternative to cocaine for nasal vasoconstriction before nasal surgery: A randomised trial

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ABSTRACT

Background: Cocaine is often used topically to provide the profound vasoconstriction required for nasal surgery; however, it has been associated with intraoperative cardiac adverse effects. We compared cocaine with phenylephrine as an alternative to ascertain their relative efficacy as vasoconstrictors in nasal septoplasty. **Methods:** Adult patients, presenting for elective nasal septoplasty, of American Society of Anaesthesiologists physical status I–III, were randomised to either 0.5% phenylephrine or 4% cocaine. The primary outcome was quality of vasoconstriction on a 5-point scale (1=unacceptable, 5=excellent), rated by the surgeon at the end of the procedure. **Results:** Twenty-nine patients received phenylephrine and 26 received cocaine. The median rating for quality of the vasoconstriction was 4.0 (good) in both the phenylephrine and cocaine groups (P=0.84). Median blood loss was 50 ml in the phenylephrine group and 62.5 ml in the cocaine group (P=0.49). In secondary analyses, phenylephrine was shown to be non-inferior to cocaine on both quality of vasoconstriction (non-inferiority delta of 1 point, P=0.009) and estimated blood loss (non-inferiority delta of 25 ml, P=0.028). The frequency of ventricular ectopy, ST segment changes or blood pressure changes after nasal packing was not significantly different between the two groups. **Conclusion:** Phenylephrine in a concentration of 0.5% is not different from 4% cocaine on the quality of vasoconstriction in septoplasty. Given the abuse potential of cocaine and the added administrative burden associated with its handling, phenylephrine might serve as an alternative.

Key words: Cocaine, hypertension, local anaesthetics, nasal surgery, neo-synephrine, phenylephrine

INTRODUCTION

Cocaine has maintained a unique position among local anaesthetics as the only one that provides both analgesia and vasoconstriction. The combination of these attributes makes it particularly popular in otolaryngologic and plastic surgery where intense vasoconstriction is required for procedures involving the nasal mucosal surfaces to reduce blood loss and improve visibility in the surgical field.[1] Unfortunately, cocaine is associated with substantial perioperative morbidity, including myocardial ischaemia and infarction, cardiomyopathy, hypertensive crisis, cerebrovascular accidents, aortic dissection and arrhythmias.[2-7] This is especially a concern with elderly patients and those with known cardiovascular compromise.[8] In addition, cocaine is a controlled substance with a potential for abuse. Handling and storing controlled substances involves added administrative costs and risks of error. For these reasons, an alternative vasoconstrictor might be preferable if proven to be effective and safe.

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The combination of phenylephrine, a pure alpha-receptor agonist, and lidocaine has been shown to be as effective as cocaine,[9,10] and may be safer, providing analgesia and vasoconstriction for awake nasotracheal intubation. As a result, at many centres, the phenylephrine–lidocaine combination has virtually replaced cocaine for nasotracheal intubation. This example suggests that phenylephrine may be effective for providing surgical homeostasis in rhinologic surgery. However, the use of phenylephrine for this purpose has not been fully characterised, and cocaine continues to be used by some clinicians. While the potential for abuse and the dilemma of handling a controlled drug is not an issue with phenylephrine, the use of this drug is not without side effects. Reported side effects ranged from minor things like rebound hyperaemia up to even mortality when unmeasured doses of topical phenylephrine were used, and the resulting hypertension was mistreated with long-acting beta-blockers.[11] Our primary study objective was to test the hypothesis that phenylephrine is more effective than cocaine in patients undergoing nasal septoplasty. Secondarily, we assessed whether phenylephrine is associated with no worse side effects than cocaine.

METHODS

The Institutional Review Board approved this study. All patients gave written informed consent. Any patient of age between 18 and 65 years and of American Society of Anaesthesiologists (ASA) physical status I–III, presenting for elective nasal septoplasty, was eligible. Exclusion criteria included a history of a known coronary artery disease or uncontrolled hypertension, defined as diastolic blood pressure higher than 110 mmHg measured on three separate occasions.

Randomisation and blinding

Patients were randomised to receive either 0.5% phenylephrine (Neo-Synephrine; Bayer Healthcare, Pittsburgh PA, USA) or 4% cocaine based on computer-generated codes (SAS statistical software, PLAN procedure, with randomly sized blocks) and using opaque sealed envelopes. Neither patients nor physicians (anaesthesiologists or surgeons) were aware of group assignments. Both study drug solutions were prepared in our pharmacy, identically tinted blue, dispensed in 5-ml vials, and labelled study drug 1 and study drug 2.

Study protocol and anaesthetic management

Following induction of anaesthesia and intubation, the surgeon packed the nasal cavity with either phenylephrine (Neo-Synephrine; Bayer Healthcare) or cocaine-soaked pledgets using the whole 5 ml of the solution provided. The surgeon was also allowed to use a mixture of lidocaine 0.5% and epinephrine 10 μg/ml, if needed, to supplement the vasoconstriction achieved by the study drug. We used the same anaesthetic technique for all patients. Patients were premedicated with intravenous midazolam (1 mg) and glycopyrrolate (0.2 mg). General anaesthesia was induced with a mixture of propofol (9 mg/ml) and alfentanil (45.5 μg/ml) in a dose of about 2 mg/kg of propofol and 9 μg/kg of alfentanil. Vecuronium 0.1 mg/kg was used to facilitate endotracheal intubation. Anaesthesia was maintained with the same mixture of propofol and alfentanil in a dose of 75 μg/kg/min and 0.4 μg/kg/min, respectively, and 60%–70% N_2O in O_2. Vecuronium boluses were used as needed to maintain muscle relaxation. Lactated Ringer's (LR) solution was administered at a rate of 4-6 ml/kg/h. Mechanical ventilation was adjusted to maintain end-tidal CO_2 between 32 and 35 mmHg (normocapnia).

Hypotension, defined as systolic blood pressure below 20% of preoperative baseline, was treated with a fluid bolus of LR solution 5-10 ml/kg and/or ephedrine 5-10 mg intravenously. Hypertension, defined as an increase in systolic blood pressure above 20% of the preoperative baseline, was treated with intravenous nitroglycerin (NTG) boluses of 80 μg. Depth of anaesthesia was increased or decreased by adjusting the propofol/alfentanil infusion rate at the anaesthesiologist's discretion. Tachycardia (20% above baseline) with hypertension was treated with 3-ml boluses of propofol and alfentanil, followed by intravenous esmolol up to 0.5 mg/kg in divided doses. Bradycardia alone was treated with glycopyrrolate as needed. Vital signs that included heart rate, non-invasive blood pressure and continuous electrocardiogram (ECG) analysis were checked every 3 min. At the end of the surgery, residual neuromuscular blockade was reversed with neostigmine 0.04-0.06 mg/kg in combination with glycopyrrolate 0.2 mg for every milligram of neostigmine. The propofol/alfentanil infusion was discontinued. The trachea was extubated after protective airway reflexes had returned and the patient was awake with adequate neuromuscular recovery. We recorded baseline blood pressure and episodes of systolic hypertension, baseline and abnormal heart rate, nasal packing duration, ventricular ectopy, ST segment changes >1 mm, cumulative dose of NTG

and esmolol, total amount of supplemental lidocaine with epinephrine and estimated blood loss. At the end of the procedure, the surgeon was asked to rate the quality of vasoconstriction on a scale of 1-5, with 1 being unacceptable and 5 being excellent. Both the anaesthesiologist and the surgeon were asked to guess what the study drug had been.

Statistical methods

Randomised groups were descriptively assessed for balance on baseline variables. We compared the phenylephrine and cocaine groups on the primary outcome of vasoconstriction quality ratings of the surgeons and on other non-normally distributed continuous variables (pack minutes, number of lidocaine injections, doses of lidocaine, NTG, esmolol, estimated blood loss, Operating Room minutes and percent elevated post-pack heart rate readings) with the two-sided Wilcoxon rank-sum tests. The Cochran–Mantel–Haenszel (CMH) test was used to compare groups on the presence of systolic blood pressure abnormalities (>20% of baseline) while adjusting for the presence of pre-packing abnormalities. Ninety-five percent confidence intervals on the estimated treatment effects were calculated. As *post-hoc* secondary analyses, we also tested the non-inferiority of phenylephrine to cocaine on the primary outcomes of vasoconstriction quality rating and blood loss using one-tailed Wilcoxon rank-sum tests with non-inferiority deltas of 1 point for vasoconstriction quality rating and 25 ml for blood loss.

Sample size considerations

The study was designed to include 100 patients for 90% power at the 0.05 significance level to detect differences of 1.0 or more points in the vasoconstriction quality ratings by the surgeons (primary outcome) in the randomised groups using a two-sided Wilcoxon rank-sum test. A significance level of 0.05 was used for all hypotheses. SAS statistical software (Cary, NC, USA) was used for all data analysis. The East program from Cytel Corporation (Cambridge, MA, USA) was used for the stopping rule part of the interim analysis.

Due to enrolment difficulties, we conducted a group sequential interim analysis after 55 patients were enrolled to assess for efficacy and futility using a pre-defined gamma spending function (gamma = −4 for efficacy and − 2 for futility). This group sequential monitoring was based on the above-defined sample size calculations: maximum 100 patients to have 90% power to detect a 1 point difference in visualisation at the 0.05 level. The observed *P* value of 0.84 for the primary outcome crossed the futility boundary (*P*>0.65). In addition, a conditional power analysis showed that there was only a 2.5% chance of finding superiority for either phenylephrine or cocaine if we had continued with the original sample size of 100, assuming that the treatment effect in later patients would be similar to the effect in the first 55. We therefore halted the study at 55 patients for "futility," i.e. claiming no difference between groups.

RESULTS

Sixty patients consented to participate in the study. Five patients were excluded as per the surgeon's request as the surgical plan involved more than a simple septoplasty. The excluded patients received cocaine according to the surgeon's usual practice. Of the 55 randomised patients, 29 received phenylephrine treatment and 26 received cocaine treatment [Figure 1]. The randomised groups were comparable with respect to demographic and preoperative data [Table 1]. When compared to 4% cocaine, 0.5% phenylephrine did not improve the primary outcome of surgeon vasoconstriction rating, with a median [quartiles] score of 4[3,5] in each group (*P*=0.84 Wilcoxon rank-sum test) [Table 2]. Although not superior in our primary analysis, phenylephrine was shown in a *post-hoc* secondary analysis to be non-inferior (i.e., not worse) to cocaine on vasoconstriction rating using a non-inferiority delta of 1 point with a one-tailed Wilcoxon rank-sum test (*P*=0.009).

Table 1: Baseline biologic data of 55 patients undergoing nasal surgery

Characteristic	Phenylephrine[1] (*n*=29)	Cocaine (*n*=26)
Gender (% male)	58.6	53.8
History of hypertension (%)	3.4	11.5
History of arrhythmia (%)	0	0
Baseline heart rate (mean±SD)	72.7±11	77.5±11
Frequency of abnormal* heart rates (median, 25%-75% IQR)	2 (0, 3)	0.5 (0, 3)
Mean baseline SBP (SD)	116.4 (18)	121.8 (17)
Pre-pack # episodes of SHT (median, 25%-75% IQR)[γ]	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 range, [1]Statistical comparison at baseline not done since it is a randomised trial[12], *Abnormal HR defined as above 20% of baseline, [γ]SHT – systolic hypertension defined as SBP above 20% of baseline, ST segment change – A change of more than 1 mm from baseline as observed and recorded by the EKG monitor; SBP – Systolic blood pressure (mmHg)

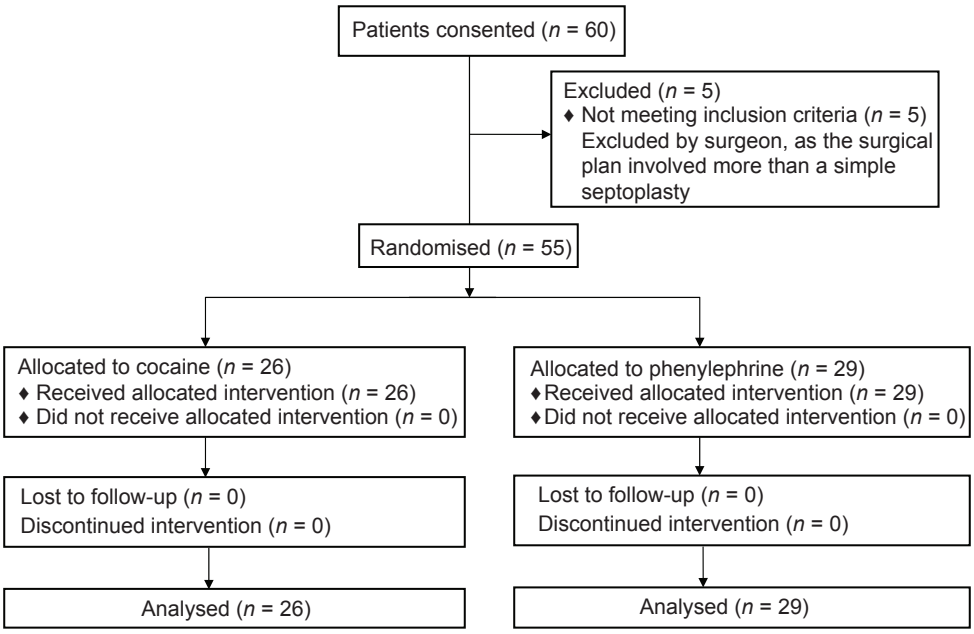

Figure 1: Flow chart indicating number of patients consented, randomised and analysed

Table 2: Surgeons' ratings of vasoconstriction in study patients

Rating	Phenylephrine group frequency (%)	Cocaine group frequency (%)
1 (Unacceptable)	4 (13.8)	1 (3.8)
2 (Poor)	1 (3.4)	1 (3.8)
3 (Average)	5 (17.2)	8 (30.8)
4 (Good)	9 (31.0)	9 (34.6)
5 (Excellent)	10 (34.5)	7 (26.9)
Rating as continuous variable, median [Q1, Q3]	4 [3, 5]	4 [3, 5]

P=0.84 comparing groups on ratings with Wilcoxon rank-sum test, *P*=0.009 with one-sided test for non-inferiority of phenylephrine vs. cocaine (delta=1 pt)

There was no detected difference between randomised groups in the frequency of ventricular ectopy (*P*=0.99), ST segment abnormalities (*P*=0.99), or the percent of a patient's heart rate readings (*P*=0.99) or systolic blood pressure readings (*P*=0.15) which were elevated at least 30% above baseline [Table 3].

There was also no difference between randomised groups in the incidence of at least one elevated post-pack systolic blood pressure reading [31% for phenylephrine vs. 12% for cocaine, relative risk (95% CI) of 2.7 (0.81, 8.9), *P*=0.08]. Median [quartiles] blood loss was 50 [25, 75] ml in the phenylephrine and 62.5 [25, 100] ml in the cocaine group (*P*=0.49 Wilcoxon rank-sum test) [Table 3].

Again in a *post-hoc* secondary analysis, and using 25 ml as a non-inferiority buffer, phenylephrine was shown to be non-inferior to cocaine on the amount of blood loss, using a one-tailed Wilcoxon rank-sum test (*P*=0.028). There was no relationship detected between their predictions and the actual treatment. Neither anaesthesiologists nor surgeons were significantly better than chance at guessing which treatment had been given.

DISCUSSION

In this study, we compared the effects of topical 4% cocaine and 0.5% phenylephrine as mucosal vasoconstrictors for nasal septoplasty. Our results did not find either of the two drugs to be superior in controlling blood loss or producing a satisfactory surgical field as measured by surgical criteria, with a similar profile of side effects and complications. Only in *post-hoc* non-inferiority analyses did we find phenylephrine to be non-inferior to cocaine on the quality of vasoconstriction and estimated blood loss. The use of cocaine has been associated with reported serious side effects. Various authors have cited deleterious effects of cocaine absorption from the nasal mucosa. These have included intraoperative hypertension, transient ventricular tachycardia, increase in pulse pressure product, myocardial infarction in patients with normal coronaries, non-ST segment elevation infarction (NSTEMI) and other serious toxic reactions.[2,5-7,13]

The above reports are associated with the use of mostly higher concentrations of cocaine, i.e., 10% or 20%. Four percent cocaine, as we use in our practice and in our study, on the other hand, is thought

Table 3: Intraoperative variables and secondary outcomes in patients receiving phenylephrine or cocaine before nasal surgery

Variable[1]	Phenylephrine (*n*=29)	Cocaine (*n*=26)	95% CI Phen-Coc median[3]	*P* value[4]
Pack time in minutes	20 (11,36)	14 (6,26)	−3, 12	0.22
Number of lidocaine injections	2 (2,3)	2 (1,3)	0, 1	0.37
Lidocaine dose in cc of 1%	11 (10,14)	9 (8,12)	−02, 3.6	0.08
Nitroglycerine dose in μg	0 (0,40)	0 (0,0)	0, 0	0.17
Esmolol dose in mg	0 (0,0)	0 (0,0)	0, 0	0.19
EBL in cc[7]	50 (25,50)	62 (25,100)	–50, 15	0.49
OR[2] minutes	130 (115,180)	135 (125,175)	–25, 20	0.58
% Abnormal[8] post-pack heart rate readings	0 (0,3.7)	0 (0,0)	0, 0	0.99
% Abnormal[8] post-pack systolic blood pressure readings	7 (0,11)	0 (0,9)	0, 7.1	0.15
Post-pack ventricular ectopy, *n* (%)	0 (0)	0 (0)	0, 0	0.99[5]
Post-pack ST segment change, *n* (%)	2 (7)	2 (8)	0, 0	0.58[6]

[1]Data are median (25th percentile, 75th percentile) unless noted; [2]OR – Operating room; 395% confidence interval for median difference between groups; [4]Wilcoxon rank-sum test, unless noted; [5]Fisher's exact test; [6]Pearson Chi-square test; [7]EBL – Estimated blood loss; [8]% abnormal is percent of a patient's readings falling 20% or more above baseline, ST segment change – A change of more than 1 mm from baseline as observed and recorded by the EKG monitor; CI – Confidence interval

to have a better safety profile. Studies on cocaine absorption have shown that less than 35%–37% of topically applied cocaine is absorbed systemically and claimed that a 4% solution of cocaine applied to the nasal mucosa on cottonoid pledgets for up to 20 min is safe.[2,14] That said, cocaine at concentrations of 4% or less has also been reported to cause cardio excitatory side effects. Makaryus *et al.* described a case of acute myocardial infarction and cardiogenic shock in a patient undergoing a sphenoidectomy and septoplasty with 4% topical cocaine preparation prior to the procedure.[15] El-Din *et al.* described severe hypertension and multiple ventricular ectopic beats and ST segment depression following application of intranasal 2% cocaine.[4]

Several mechanisms have been suggested for cocaine's role in cardiac ischaemia/infarction, including coronary vasoconstriction, thrombosis and accelerated atherosclerosis. It has been elegantly described by Lange *et al.*[3] that doses of cocaine, as small as 2 μg/kg, intranasally administered resulted in constriction of the epicardial arteries which was further attributed to overwhelming of the local autoregulatory mechanisms that preserve the coronary blood flow. Cocaine's vasoconstrictor properties are the result of its well-described abilities to block the re-uptake of norepinephrine.

Phenylephrine, on the other hand, is a synthetic catecholamine that stimulates principally alpha-1 adrenergic receptors by a direct effect, with only a minor pharmacologic response caused by norepinephrine release. There is a minimal effect on beta-adrenergic receptors. The dose of phenylephrine necessary to stimulate alpha-1 receptors is far less than the dose that stimulates alpha-2 receptors. The resulting venoconstriction is greater than arterial vasoconstriction, which allows for better preservation of coronary arterial perfusion. It is noteworthy that a systematic review of topical vasoconstrictors in nasal sinus surgery strongly discouraged the use of topical phenylephrine if possible.[16] However, this was based on the report of nine cases of phenylephrine-associated morbidity and mortality which had prompted the Phenylephrine Advisory Committee to the New York State Department of Health to issue guidelines for phenylephrine use in the operating room.[11] In these cases, it was apparent that the dose of phenylephrine was excessive and frequently not measured or controlled and that a long-acting beta-blocker was used to treat hypertension resulting in pulmonary oedema.

Our evidence suggests that 0.5% phenylephrine is as effective as 4% cocaine, both when rated subjectively by surgeons and objectively by their effect on measured blood loss. We did not find any differences in the amounts of additional vasoconstrictor used by the surgeon, treatment with intravenous esmolol, ephedrine or NTG. Furthermore, we did not find any differences between the two drugs in the incidence of hypertension, changes in heart rate, effects on ST segments and arrhythmias under the conditions of this study. This is consistent with the results of prior investigators. Sessler *et al.* measured the nasal dilating effects of 4% lidocaine with 0.5% phenylephrine against those of 5% cocaine and found no differences between the two.[9] They also noted no differences in blood pressure and heart rate in the two groups of volunteers. Topical nasal phenylephrine in 0.25% concentration with 3% lidocaine has been

shown to be safe and effective (as 4% cocaine) as a vasoconstrictor prior to blind nasal intubation.[10] Moreover, Smith *et al*. compared 5% lidocaine and 0.5% phenylephrine (co-phenylcaine) solution, with 10% cocaine spray in a randomised double-blind trial in patients undergoing transnasal fibreoptic laryngoscopy. They found no differences in the Visual Analog Scale pain scores, nasal inspiratory peak flow recordings and incidence of adverse effects in the two groups.[17]

There were some limitations to this study. Our assessment of the quality of vasoconstriction was subjective. We chose this method because it approximates clinical practice for evaluating the surgical conditions. In addition, non-invasive blood pressure measurement may miss rapid blood pressure changes, which may have occurred immediately after a drugs' application or injection. The study was adequately powered to detect differences in visualisation of 1 point or more, should they exist. However, we caution that the study was not powered to detect difference in the binary safety outcomes. We therefore cannot make firm conclusions about the relative safety of phenylephrine versus cocaine on haemodynamic parameters. For example, although non-significant, our confidence interval for the relative risk of hypertension ranges from 0.81 to 8.9. Although we crossed a futility boundary for the primary outcome of vasoconstriction quality rating, in secondary analyses, phenylephrine was at least as effective as cocaine (i.e., non-inferior) on both vasoconstriction quality and bleeding. We only compared 4% cocaine to 0.5% phenylephrine. However, recent trials have shown promising results of 2% tetracaine in combination with epinephrine,[18] 0.1% xylometazoline[19] and 0.05% oxymetazoline[20] as nasal decongestants. Thus, future research should be directed at comparing all these agents side by side in a randomised fashion with a well-planned comparative analysis.

CONCLUSION

Phenylephrine is as effective as cocaine as a local mucosal vasoconstrictor. Since phenylephrine also lacks the costs and administrative issues associated with the use of controlled drugs in the operating rooms, it may serve as an acceptable vasoconstrictor alternative at the studied concentration and dose for adults presenting for nasal surgery.

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