ORIGINAL ARTICLE

The Hemostatic and Hemodynamic Effects of Epinephrine During Endoscopic Sinus Surgery

A Randomized Clinical Trial

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Objective: To assess the hemodynamic and hemostatic effects of 2 different concentrations of epinephrine in local anesthetic used during functional endoscopic sinus surgery (FESS). Injection of local anesthetic containing epinephrine during endoscopic sinus surgery, while providing hemostasis, has been associated with cardiac adverse effects such as tachycardia, hypertension, as well as arrhythmias.

Design: Double-blind, randomized clinical trial.

Setting: Tertiary referral center.

Patients: A total of 140 patients undergoing FESS randomly divided into 2 groups, with group 1 receiving lidocaine hydrochloride, 2%, with 1:100 000 epinephrine and group 2, lidocaine, 2%, with 1:200 000 epinephrine.

Main Outcome Measures: Baseline and postinjection hemodynamic parameters were recorded at 1-minute intervals for 5 minutes. Patient demographics, the extent of surgery, and the presence of polyps were recorded in both groups. Hemodynamic and hemostatic parameters and intraoperative blood loss were compared.

Results: Significant hemodynamic fluctuations were noted following injection of lidocaine, 2%, with 1:100 000 epinephrine (group 1). Increases in heart rate and systolic, diastolic, and mean arterial blood pressure were noted in group 1 patients. The increase was found to be significant ($P < .001$) in the first and second minutes after injection and decreased to baseline level by the fifth minute. This fluctuation was not noted in group 2 patients, who received lidocaine, 2%, with 1:200 000 epinephrine. Using a standardized scale to assess surgical bleeding, no statistical difference in the 2 groups was observed ($P > .05$).

Conclusion: Submucosal injection of lidocaine, 2%, with 1:200 000 epinephrine during FESS does not lead to hemodynamic fluctuations or increased intraoperative bleeding compared with lidocaine, 2%, with 1:100 000 epinephrine.

Trial Registration: clinicaltrials.gov Identifier: NCT00852410

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SINCE THE EARLY DEVELOPMENT of functional endoscopic sinus surgery (FESS) in the early 1970s, this minimally invasive technique has gained increasing popularity among otolaryngologists.[1,2] The aim of this surgery is to clear the air cells of disease and improve ventilation of the paranasal sinuses, thereby reducing the severity and frequency of infections.[1,2] The major limiting factors for endoscopic approaches to paranasal sinuses and the skull base are its complex anatomy and the high vascularity.[1,2] Often, a slight hemorrhage is sufficient to dramatically reduce visibility, creating a poor surgical field. This is particularly problematic in patients with severe infections and the presence of extensive nasal polyposis. Thus, obtaining adequate hemostasis is of utmost importance during surgery to improve the surgical field and prevent complications.

The ideal technique to obtain vasoconstriction during FESS is not clear. Vasoconstriction is typically achieved by the combination of topical application and local infiltration of anesthetic containing epinephrine.[3-5] Topical vasoconstriction can be achieved by using epinephrine, oxymetazoline hydrochloride, and, less frequently, cocaine hydrochloride.[3-6] Most otolaryngologists also advocate the use of submucosal infiltration of local aesthetic containing epinephrine to further obtain hemostasis and

Table 1. Quality of Surgical Field

Grade	Assessment
0	No bleeding, cadaveric conditions
1	Slight bleeding, no suctioning required
2	Slight bleeding, occasional suctioning required
3	Slight bleeding, frequent suctioning required. Bleeding threatens surgical field a few seconds after the suction is removed.
4	Moderate bleeding, frequent suctioning required, and bleeding that threatens surgical field directly after suction is removed
5	Severe bleeding, constant suctioning required. Bleeding appears faster than can be removed by the suction; surgical field severely threatened, and surgery usually not possible.

reduce postoperative pain.[3-5] The traditional areas of infiltrations are the area of sphenopalatine foramen, the anterior insertions of the middle turbinate, and the pterygopalatine foramen.[6-8]

Although epinephrine during FESS provides excellent hemostasis, it can also be coupled with potential adverse effects, such as hypertension, hypotension, tachycardia, and arrhythmias. Furthermore, these complications could cause some serious adverse effects in susceptible patients.[9,10] In a recent study, Cohen-Kerem et al[11] compared the effectiveness of topical 1:1000 epinephrine vs injected local anesthetic containing 1:100 000 epinephrine during FESS. In this study, it was reported that submucosal injection of local anesthetic with epinephrine facilitated improved surgical condition; however, increased hemodynamic fluctuations were noted after infiltrations. In a follow-up study, we have designed a double-blind randomized controlled trial (RCT) assessing the hemodynamic and hemostatic effects of 2 different concentrations of epinephrine with local anesthesia during FESS. We hypothesize that (1) submucosal infiltrations of a lower concentration of epinephrine containing local anesthetic will reduce the hemodynamic fluctuations noted after injection, thereby creating a safer operative environment, and (2) the use of lowered concentration of epinephrine will not result in increased intraoperative bleeding.

METHODS

INCLUSION AND EXCLUSION CRITERIA

A total of 140 patients aged 18 to 70 years undergoing elective FESS for recurrent acute sinusitis, chronic sinusitis, or nasal polyposis were enrolled in the study. The hospital ethics committee at St Joseph's Health Centre (Toronto, Ontario, Canada) approved the study, and informed consent was obtained from all patients prior to enrollment. Our exclusion criteria included age younger than 18 years, history of coronary artery disease, bleeding disorders, and use of antihypertensive medications. All enrolled patients were categorized as class I or class II according to the American Society of Anesthesiologists criteria.

RANDOMIZATION

All patients considered for the study were randomized and assigned to 1 of the 2 study groups. Assignment to groups was performed by computer-generated random numbers. The randomization process was performed by a third party; the patients, surgeons, anesthetists, and operating room personnel were not aware of the group assignment for each patient.

Table 2. Patient Demographics and Baseline Data

Characteristic	Group (Dosage)[a]	
	1 (Lidocaine Hydrochloride, 2%, With 1:100 000 Epinephrine)	2 (Lidocaine Hydrochloride, 2%, With 1:200 000 Epinephrine)
Patients, No.	70	70
Age, mean ± SD, y	39.1 ± 11.1	41.1 ± 12.3
Male sex, No. (%)	35 (50)	34 (49)
Polyps, No. (%)	38 (54)	36 (51)
Bilateral surgery, No. (%)	49 (70)	49 (70)
Baseline parameter, mean ± SD		
HR, bpm	75.4 ± 18.7	77.4 ± 14.7
SBP, mm Hg	107.3 ± 17.5	102.2 ± 15.4
DBP, mm Hg	61.1 ± 11.2	59 ± 12.8
MAP, mm Hg	76.5.1 ± 11.8	73.4 ± 12.1

Abbreviations: bpm, beats per minute; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure.
[a] $P > .05$.

GENERAL ANESTHESIA

All surgical procedures were performed with the patient under standard general anesthesia administered by the same anesthesiologist. Premedication was limited to midazolam hydrochloride (0.5-1 mg) and fentanyl citrate (1-2 µg/kg). General anesthesia and paralysis were obtained using propofol (1-2 mg/kg) and rocuronium bromide (1-2 µg/kg). Maintenance of anesthesia was achieved with sevoflurane, nitrous oxide, and intermittent doses of fentanyl citrate, 0.5 µg/kg, as required.

SURGICAL PROCEDURE

The same 2 surgeons (A.M. and I.J.W.) performed all procedures using similar techniques for dissections. All patients enrolled had endoscopic dissections of maxillary, ethmoid, and sphenoid sinuses. Before the injection of the study drug, all patients received topical 1:1000 epinephrine for decongestion of the nasal mucosa. Baseline heart rate (HR) and blood pressure (BP) were recorded in all patients. Patients randomized to group 1 received lidocaine hydrochloride, 2%, with 1:100 000 epinephrine (n=70), and patients randomized to group 2 received lidocaine, 2%, with 1:200 000 epinephrine (n=70). A total of approximately 4 mL of the study solution was injected bilaterally. Data for the following patient parameters were collected during the procedure using a Datex-Ohmeda monitor (GE, Fairfield, Connecticut): HR, electrocardiograph for arrhythmias, systolic and diastolic BP (SBP and DBP, respectively), and mean arterial pressure (MAP) measured from a BP cuff. These parameters were monitored by the anesthesiologist throughout the procedure and were repeated at 1-minute intervals for 5 minutes. The patient demographics, the extent of surgery, and the presence of nasal polyps were recorded for further analysis. At the end of each procedure, the extent of blood loss was assessed using the validated scale shown in **Table 1**.[12,13] The same 2 surgeons (A.M. and I.J.W.) assessed and scored the surgical field during all procedures. The assessment considered the feasibility of performing the procedure and the effectiveness of hemostasis.

Table 3. Mean (SD) Hemodynamic Parameters at Baseline and Postinjection of Study Drugs at 1-Minute Intervals

Group (Dosage)	Time, min					
	0	1	2	3	4	5
1 (Lidocaine hydrochloride, 2%, with 1:100 000 epinephrine)						
HR, bpm	75.4 (18.7)	86.8 (18.2)[a]	82.3 (18.2)[b]	78.6 (18.0)	76.7 (18.9)	75.0 (17.1)
SBP, mm Hg	107.3 (17.5)	127.5 (27.0)[a]	128.0 (28.7)[a]	118.2 (26.5)[b]	110.2 (20.3)	104.8 (19.8)
DBP, mm Hg	61.1 (11.2)	72.7 (15.0)[a]	70.6 (14.5)[a]	65.5 (15.0)[b]	61.3 (14.1)	57.2 (13.1)
MAP, mm Hg	76.5 (11.8)	91.0 (17.6)[a]	89.7 (17.1)[a]	83 (17.1)[b]	77.6 (14.5)	73.1 (13.7)
2 (Lidocaine hydrochloride, 2%, with 1:200 000 epinephrine)						
HR, bpm	77.4 (14.7)	77.9 (14.5)	76.0 (14.0)	76.0 (13.9)	75.3 (13.4)	75.1 (13.5)
SBP, mm Hg	102.2 (15.4)	107.1 (15.8)	106.6 (15.6)	104.1 (15.8)	102.5 (16.9)	102.6 (17.3)
DBP, mm Hg	59.0 (12.8)	58.8 (10.7)	59.9 (10.0)	58.4 (10.7)	57.7 (9.8)	56.6 (10.7)
MAP, mm Hg	73.4 (12.1)	74.9 (11.3)	75.4 (11.1)	73.6 (11.5)	72.6 (11.1)	71.3 (11.9)

Abbreviations: bpm, beats per minute; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure.
[a] $P<.001$ compared with baseline measurement.
[b] $P<.01$.

Table 4. Difference in the Mean Change Hemodynamic Parameters at 1, 2, and 5 Minutes Between the 2 Groups

Variable	Mean Difference (95% CI)					
	At 1 Minute	*P* Value	At 2 Minutes	*P* Value	At 5 Minutes	*P* Value
HR, bpm	10.18 (6.22 to 14.13)	<.001	7.40 (2.96 to 11.86)	<.001	1.06 (–2.85 to 4.97)	.59
SBP, mm Hg	17.46 (10.67 to 24.24)	<.001	18.77 (11.54 to 26.00)	<.001	–0.42 (–6.00 to 5.16)	.88
DBP, mm Hg	12.64 (9.01 to 16.27)	<.001	9.52 (6.06 to 12.98)	<.001	0.66 (–2.90 to 4.22)	.71
MAP, mm Hg	14.02 (9.80 to 18.23)	<.001	12.36 (8.23 to 16.49)	<.001	0.15 (–3.59 to 3.88)	.94

Abbreviations: bpm, beats per minute; CI, confidence interval; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure.

STATISTICAL ANALYSIS

Data are presented as mean (SD) for the continuous variables and as frequency (percentage) for the discrete variables. Analysis of covariance by adjusting for baseline measurements was used to test for the difference between the groups in the HR and BP at 1, 2, and 5 minutes. Paired *t* test was used to test for the increase from baseline in the hemodynamic parameters for the 2 groups. Fisher exact test was used to test for differences in the proportions of bleeding grades between the 2 groups. All tests are 2-tailed, and $P \leq .05$ was considered to be statistically significant. Using the first 30 patients, an estimate of standard deviation was determined based on a difference of a change of 10 beats per minute (bpm) in the HR. To detect this difference statistically, with 80% power, 64 patients were needed. Data were analyzed using SAS statistical software (version 9.1; SAS institute Inc, Cary, North Carolina).

RESULTS

A total of 140 patients fulfilled the criteria for enrollment in the study. The patient demographics, extent of surgery, the presence of polyps, and the baseline hemodynamic parameters were similar (**Table 2**). **Table 3** summarizes the hemodynamic changes noted following submucosal injection of the study drugs in the 2 groups. In the group 1 patients, who received lidocaine, 2%, with 1:100 000 epinephrine, we noted an increase in HR at 1 and 2 minutes after injection, and the levels plateaued down to the baseline level after 5 minutes. The increases from baseline at the 1- and 2-minute postinjection marks were found to be statistically significant ($P<.001$). This increase was not noted in group 2 patients, who received lidocaine, 2%, with 1:200 000 epinephrine. In fact, minimal fluctuations were observed following submucosal injections of the local anesthetic. A similar pattern was noted in SBP, DBP, and mean BP measurements in the 2 groups (Table 3). In group 1, an increase in SBP, DBP, and mean BP were noted in the first 2 minutes, and a gradual decrease to baseline was noted by the fourth and fifth minutes. These measurements were found to be statistically significant ($P<.001$). Minimal fluctuations were noted again in group 2 patients receiving lower doses of epinephrine. No statistical significance was noted in the hemodynamic parameters in group 2 patients. No arrhythmias were noted in either group during the procedure.

Following injection of the study drug, increases in the HR of 10.2 and 7.4 bpm were noted after 1 and 2 minutes in group 1 compared with group 2 (**Table 4**). Similarly, SBP had an estimated increase of 17.5 mm Hg more, on average, in group 1 compared with group 2 after 1 minute and and increase of 18.8 mm Hg after 2 minutes. There were no differences in the mean change scores between the 2 groups by the 5-minute postinjection mark. A statistical difference between the 2 groups was still present in SBP, DBP, and MAP at the 3-minute postinjection mark.

Assessment of blood loss was performed using a standardized validated scale shown in Table 1. This scale has been used extensively in medical literature to assess blood loss in surgical patients. In this study, we found all the

Table 5. Bleeding Grades in the 2 Study Groups[a]

Group	Bleeding Grade, No. (%)			
	1	2	3	4
1	9 (12.9)	35 (50.0)	24 (34.3)	2 (2.9)
2	3 (4.3)	36 (51.4)	30 (42.9)	1 (1.4)

[a] $P = .25$.

patients to have bleeding scores of 1 to 4 (**Table 5**). We found no statistical difference ($P = .25$) between the 2 study groups in bleeding.

COMMENT

The efficacy and the safety of epinephrine during FESS is a topic of considerable debate. To characterize the hemodynamic and hemostatic properties of injected epinephrine during FESS and to determine the optimum dose to provide a safer operative condition for both the surgeon and the patient, we compared 2 different concentrations of injected epinephrine used with local anesthetic. In this study, we have shown that the hemodynamic fluctuations noted during the first few minutes after injection of lidocaine, 2%, with 1:100 000 epinephrine can be prevented using lidocaine, 2%, with 1:200 000 epinephrine. This could prevent further cardiac complications in susceptible patients and, therefore, would lead to safer operative conditions.

Among the major limiting factors of FESS is the complexity of the nasal anatomy as well as its high vascular supply.[1-3] Excellent hemostasis is mandatory to improve endoscopic visualization, allowing identification of the anatomical structures and thereby preventing catastrophic complications. Vasoconstriction has traditionally been performed via combination of topical and injectable decongestants.[3-6] Injectable techniques typically involve a local anesthetic containing epinephrine at various concentrations.[5-8] These solutions are typically injected at the anterior insertion of the middle turbinate, the region of sphenopalatine foramen, and the greater palatine foramen, where most nasal vascular supplies are found.[6-8]

The choice of topical vs injected decongestants, the injection site, and the concentrations used are quite variable among otolaryngologists. Numerous reports have shown that injection of epinephrine, even in therapeutic doses, can lead to increased HR and stroke volume, resulting in arrhythmia in susceptible patients.[9,10] The incidence of cardiovascular toxic adverse effects has been shown to increase in a dose-dependent manner.[9,10]

Anderhuber et al[14] were the first group to analyze the systemic absorption of injected epinephrine during FESS. A significant increase in the plasma catecholamine level was noted after injection with associated hemodynamic fluctuations.[14] In a more recent study, Cohen-Kerem et al[11] investigated the pharmacokinetic effect of topical and injected epinephrine during FESS. In this study, substantial hemodynamic fluctuations were noted following the use of injected epinephrine. However, injection of epinephrine containing local anesthesia did facilitate improved surgical conditions when compared with topical epinephrine.[11] The hypotensive effects of epinephrine at subtherapeutic concentrations were recently evaluated in a series of reports by Yang et al.[15,16] This mechanism was attributed to the preferential stimulation of the β2 receptors at lower concentrations.[15,16] In our study, no hypotensive episodes were observed following injection of the study drugs. We attribute this to the use of a higher concentration of epinephrine preferentially stimulating the α and β1 receptors, thereby manifesting the vasoconstrictive effect.

To assess intraoperative blood loss, we chose a validated grading scale proposed by Boezaart et al[13] (Table 1). This method of assessing blood loss has been criticized for compressing the grading scores and its inability to differentiate subtle bleeding differences.[17] Nair et al[17] have proposed further subdividing grade 3 score to allow for this differentiation. In our study, we also found that scores were mostly 2 and 3, with no scores on the extreme ends of the scale. Nevertheless, we chose this method over alternative methods, such as measuring blood loss, because we believe it provides an objective measure that directly portrays the surgical field seen by the surgeon. Using this scale, we found no statistical differences between the 2 groups ($P = .25$).

In conclusion, preventing hemodynamic fluctuations is the key factor in avoiding cardiac complications during FESS. We have shown in this double-blind RCT that injection of lidocaine, 2%, containing 1:200 000 epinephrine reduces the hemodynamic fluctuations noted after injection without compromising surgical conditions when compared with lidocaine, 2%, containing 1:100 000 epinephrine.

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