

Real-time hemodynamic effects of 1:100,000 and 1:200,000 injectable epinephrine and placement of topical 1:1000 epinephrine pledgets in patients undergoing endoscopic sinus and skull-base surgery: a randomized, prospective study

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Background: Intranasal injection of epinephrine and placement of topical epinephrine pledgets are methods to improve visualization during endoscopic sinonasal surgery. Studies comparing the hemodynamic effects of these vasoconstrictors using intraoperative arterial line monitoring are lacking.

Methods: Twenty-eight patients undergoing endoscopic skull-base surgery were enrolled in a prospective, randomized study. Patients were randomized to have either 2 mL of 1:100,000 or 2 mL of 1:200,000 epinephrine injected intranasally. Hemodynamic parameters, including pulse, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP), were collected using intraoperative arterial line monitoring for 5 minutes. Afterward, 1:1000 topical epinephrine-soaked pledgets were placed in both groups, and the same parameters were collected for another 5 minutes.

Results: There was no statistical difference in change in pulse, SBP, DBP, and MAP between the 1:100,000 and 1:200,000 epinephrine groups. However, epinephrine injections did cause an increase in all hemodynamic parameters when compared with baseline ($p < 0.05$). Topical epinephrine pledgets placed after injection of epinephrine did not have any significant hemodynamic effects, except

for 2 of 28 patients who had a >75 -mmHg increase in SBP. No preoperative characteristics were identified that predicted sensitivity to epinephrine.

Conclusion: There is no statistical difference in changes in hemodynamic parameters between injecting epinephrine 1:100,000 compared with 1:200,000 during endoscopic sinonasal surgery. In a subset of patients, placement of topical 1:1000 epinephrine pledgets had significant hemodynamic elevation requiring intervention and thus should be used judiciously depending on patient comorbidities. © 2019 ARS-AAOA, LLC.

Key Words:

endoscopic sinus surgery; endoscopic skull-base surgery; sinus surgery; epinephrine; randomized clinical trial

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Endoscopic sinus surgery (ESS) and its associated techniques are used in the treatment of many sinonasal and skull-base pathologies. The endoscopic approach is a minimally invasive procedure that has been associated with higher rates of total disease resection, low risk of postoperative complications, and reduced hospital length of stay.^{1–3} However, surgical field visualization is dependent on achieving adequate intraoperative hemostasis.⁴ As

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a result, many studies have focused on identifying perioperative techniques to reduce intraoperative blood loss. Some of the most common strategies include optimizing patient positioning, use of preoperative steroids, and localized and topical epinephrine administration.⁵⁻⁷

Epinephrine is an adrenergic agonist widely used in ESS due to its vasoconstrictive properties.^{4,8} Although epinephrine is administered locally for endonasal procedures, research has shown that even localized intranasal epinephrine application and injection can still lead to systemic absorption.⁹ This phenomenon has been linked to undesired systemic cardiovascular side effects, with recent studies indicating that intranasal epinephrine administration may induce hemodynamic dysregulation, resulting in hypertension and tachycardia.^{10,11}

The combination of epinephrine injection followed by topical epinephrine-soaked pledget placement is a commonly used technique prior to ESS. However, there is currently limited research evaluating the safety profile of intranasal epinephrine administration on systemic hemodynamic parameters. In particular, there has not been a randomized, prospective clinical trial that has characterized how varying concentrations of epinephrine affect cardiovascular response using arterial line monitoring. Arterial line monitoring allows us to review unexpected real-time hemodynamic changes that a normal blood pressure cuff may not measure. Prospective trials will play an important role in identifying epinephrine concentrations that are efficacious but also limit cardiovascular complications.

To provide further clarity on this issue, we describe the findings of a randomized, prospective trial on the hemodynamic changes associated with injectable epinephrine and topical epinephrine placement. Hemodynamic parameters were assessed in real time using arterial line monitoring. Differing concentrations of epinephrine were used to assess for a dose-related hemodynamic response.

Patients and methods

This randomized, prospective study included all patients undergoing transsphenoidal pituitary surgery from February 1, 2018 to September 30, 2018 at a single institution. Patients with a history of chronic rhinosinusitis or previous sinus surgery were excluded from participation. Data collection was commenced with approval by the institutional review board of the Baylor College of Medicine.

On the day of surgery, induction was standardized with weight-based intravenous administration of fentanyl, lidocaine, rocuronium, and propofol, followed by intubation. An arterial line was placed by anesthesiology immediately after intubation. Maintenance anesthesia was obtained with sevoflurane to achieve a minimum alveolar concentration (MAC) between 1 and 2. Cefazolin and clindamycin were given as prophylactic antibiotics. Fourteen of the patients were randomized into the 1:100,000 injectable epinephrine group, and the remaining 14 patients were placed into the 1:200,000 concentration group. Every

4 patients were assigned to one group, and the next 4 patients were assigned to another group. This was the randomization process. Identical volumes of both analgesic solutions (2 mL) were drawn into a syringe and injected around the surgical site. One milliliter of solution was injected near the attachment of the middle turbinate and along the anterior aspect of the uncinate process on each side. Hemodynamic parameters, including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP), were recorded via an arterial line using the Epic (Verona, WI) electronic medical record anesthesia workspace. Hemodynamic parameters were first collected prior to injection for a baseline measurement, and then after injection at 30 seconds, 1 minute, 2 minutes, 3 minutes, 4 minutes, and 5 minutes. Additional time was given if hemodynamic parameters were significantly different than baseline.

Three 0.5 × 3-inch cottonoid pledgets soaked in 1:1000 epinephrine were then placed into each nasal passage. As described in Yim et al,¹² measurements were taken prior to initiating the study by weighing the pledgets on a scale that showed the average amount of topical epinephrine absorbed by 6 cottonoid pledgets to be approximately 12 mL (12 mg). Six wrung-out pledgets absorbed, on average, 7 mL (7 mg) of topical epinephrine. Completely soaked pledgets were deliberately used to achieve maximum possible effect, as well as to mimic common practice patterns. HR, SBP, DBP, and MAP were again collected after pledget placement at the same time intervals described previously. Interventions to control hemodynamic status were instituted as necessary for patient safety purposes. All of our data collection was performed prior to the patient's head being placed in a neurosurgical pinned head frame. Thus, we avoided any potential hemodynamic effects caused by this process.

Based on our previous study, our main outcome measure was a change in systolic blood pressure (SBP). To calculate our main outcome of change in SBP, the greatest change in SBP over the 5 minutes of measurement was used. A power analysis was performed assuming that the 1:200,000 group would undergo an SBP change of 10 vs the 1:100,000 group, which would undergo an SBP change of 20, with a standard deviation of 10 for both groups. Assuming a power of 0.75 and a significance value of 0.05, each sample would need 14 patients, which is the number we used in this study.

Statistical analysis

Excel version 16.11 (Microsoft Corp, Redmond, WA) was used for statistical analysis. Changes to hemodynamic parameters were compared with baseline for each patient using a paired *t* test. Differences in hemodynamic parameters between the 1:100,000 vs 1:200,000 epinephrine groups were compared using two-sample *t* tests. *p* < 0.05 was considered statistically significant.

TABLE 1. Demographics and patients' characteristics in the 2 treatment groups

Baseline comparison between groups	1:200,000	1:100,000	<i>p</i> value ^a
Number of patients	14	14	
Age ($\pm$ SD)	52 $\pm$ 17	48 $\pm$ 12	0.5
Males (%)	5 (36)	6 (43)	0.71
Hypertension (%)	5 (36)	6 (43)	0.71
Cardiovascular history (%)	1 (7)	0 (0)	0.32
Taking antihypertensive medications (%)	5 (36)	6 (43)	0.71
Hemodynamic parameters before intervention ($\pm$ SD)			
HR (bpm)	77 $\pm$ 20	78 $\pm$ 15	0.87
SBP (mmHg)	104 $\pm$ 14	122 $\pm$ 26	0.037
DBP (mmHg)	62 $\pm$ 12	70 $\pm$ 17	0.22
MAP (mmHg)	76 $\pm$ 13	87 $\pm$ 19	0.085

^aComputed using t test for mean and z test for proportions.

DBP = diastolic blood pressure; HR = heart rate; MAP = mean arterial blood pressure; SBP = systolic blood pressure; SD = standard deviation.

Results

There were a total of 28 patients who met inclusion criteria and enrolled in this study. The average age of the patients was 49 (range, 21-76) years. There were 11 males and 17 females. All demographic information is presented in Table 1. Changes in hemodynamic values for HR, SBP, DBP, and MAP were tracked for all patients after

epinephrine injection and pledget placement (Table 2). Increases in HR and SBP were observed after injection of epinephrine ($p < 0.05$). On average, HR increased by 6.3 beats per minute (bpm) 30 seconds after epinephrine administration. This was followed by a sudden decrease to 4 bpm below baseline before returning to normal after 4 minutes. Average SBP spiked to 15.7 mmHg above baseline after 2 minutes and returned to baseline after 3 minutes

TABLE 2. Changes in hemodynamic parameters after injection of epinephrine compared with baseline aggregated across all groups*

	Δ HR (bpm)	<i>p</i> value	Δ SBP (mmHg)	<i>p</i> value	Δ DBP (mmHg)	<i>p</i> value	Δ MAP (mmHg)	<i>p</i> value
Epinephrine injection								
30 s	6.30	<0.001 ^a	9.75	0.027 ^a	1.34	0.627	3.90	0.213
1 min	3.14	0.102	15.71	0.003 ^a	5.29	0.147	8.52	0.027 ^a
2 min	-4.00	0.012 ^a	12.43	0.014 ^a	-1.89	0.540	2.64	0.428
3 min	-3.71	0.016 ^a	2.18	0.571	-1.50	0.683	-0.51	0.865
4 min	-2.84	0.058	-4.41	0.246	-7.93	0.002 ^a	-6.99	0.015 ^a
5 min	-2.46	0.093	-9.00	0.037 ^a	-8.86	0.001 ^a	-9.14	0.002 ^a
Application of pledget								
30 s	1.78	0.096	3.73	0.303	1.75	0.489	2.41	0.371
1 min	1.74	0.204	5.62	0.257	3.36	0.241	4.11	0.215
2 min	0.85	0.753	8.80	0.197	4.29	0.229	5.79	0.192
3 min	-1.15	0.459	10.80	0.119	4.66	0.144	6.71	0.107
4 min	0.63	0.802	10.36	0.153	3.77	0.273	5.97	0.183
5 min	0.08	0.749	2.32	0.537	1.40	0.471	1.71	0.418

*Values reported as the mean.

^aStatistically significant difference.

bpm, beats per minute; DBP = diastolic blood pressure; HR = heart rate; MAP = mean arterial blood pressure; SBP = systolic blood pressure; SD = standard deviation.

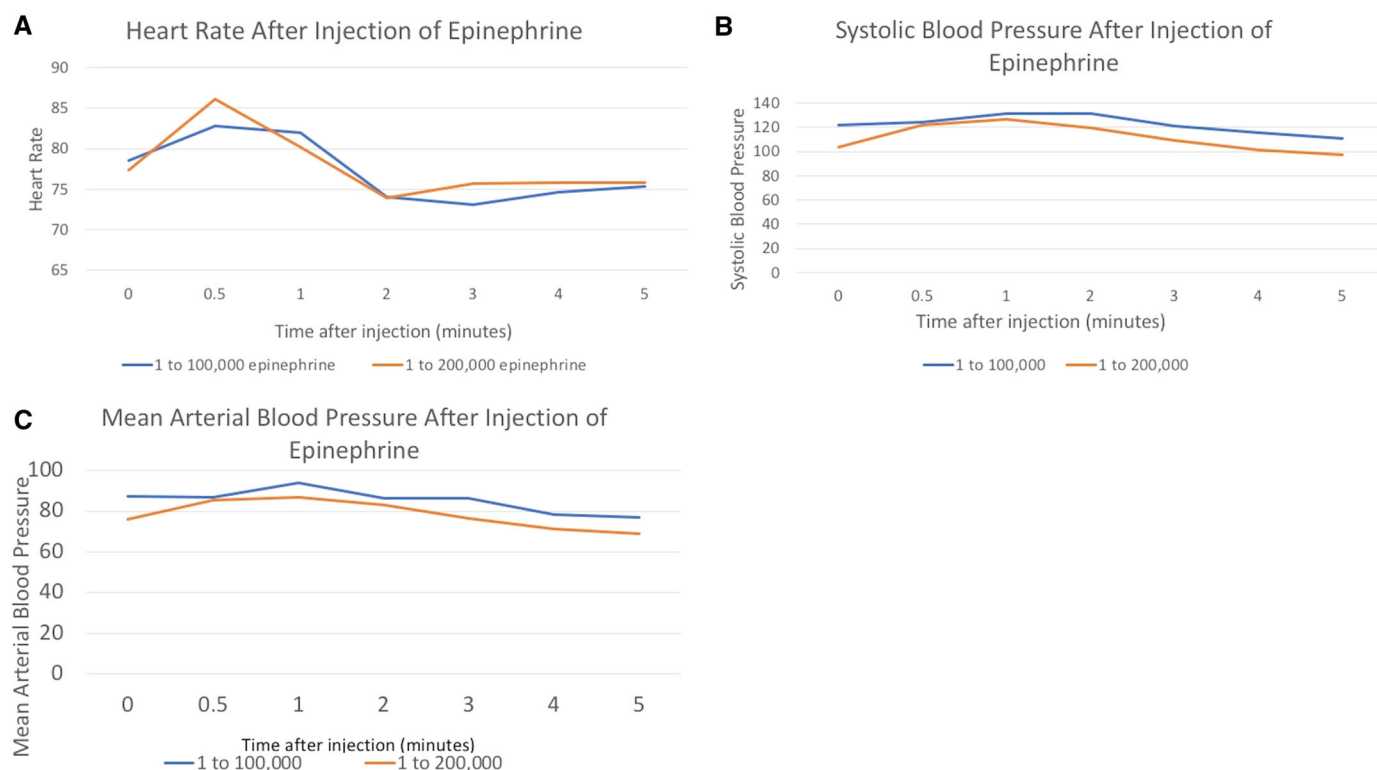


FIGURE 1. After injection of lidocaine with epinephrine, there was no statistical difference in average heart rate (A), average systolic blood pressure (B), or average mean arterial pressure (C) between patient groups administered 1:100,000 vs 1:200,000 epinephrine injections.

(Table 2). No significant differences in any hemodynamic parameters were observed after epinephrine-soaked pledget placement.

Hemodynamic variables were compared between the 1:100,000 and 1:200,000 injectable epinephrine groups. There was no statistically detectable difference in any of the changes in hemodynamic parameters between these 2 groups after epinephrine injection (Fig. 1). After injections were performed, topical epinephrine pledgets (1:1000) were placed in bilateral nasal cavities in both groups. There was also no significant difference in HR, SBP, and MAP after placement of topical epinephrine pledgets (1:1000) between patients who received 1:100,000 injectable epinephrine vs 1:200,000 injectable epinephrine.

Variations in the patients' SBPs were observed after the administration of epinephrine. In particular, there was an SBP increase of >40 mmHg after epinephrine injection in 6 of the 28 patients. Four of these patients were in the 1:200,000 group, whereas 2 were in the 1:100,000 group. Moreover, 2 of 28 patients had a >75-mmHg SBP increase after the application of topical 1:1000 epinephrine. One of the 2 patients had both a >40-mmHg SBP increase after epinephrine injection and a >75-mmHg increase after pledget placement. The SBP trends of these 7 "responder" patients are plotted separately in Figure 2. Review of patient data, including age, sex, medical history, and medications, was unsuccessful in identifying any characteristics that may predispose these individuals to epinephrine sensitivity.

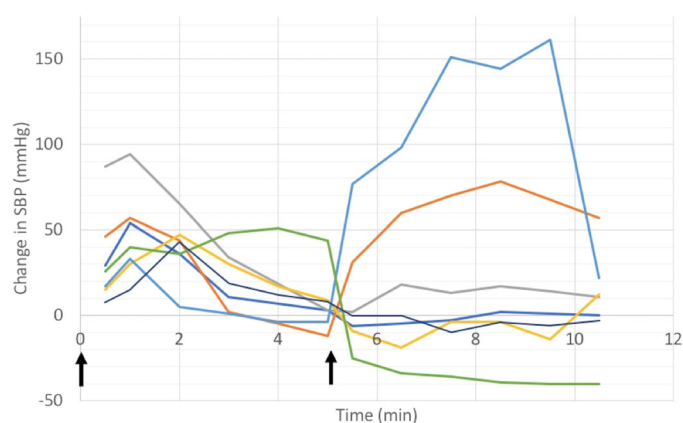


FIGURE 2. Spaghetti plot for 7 patients who had either a >40-mmHg increase in SBP after injectable epinephrine or a >75-mmHg increase in SBP after application of pledget. The first black arrow is when epinephrine was injected, and the second black arrow is when the epinephrine-soaked pledget was administered. Only 1 patient was sensitive to both injectable epinephrine and topical epinephrine. SBP = systolic blood pressure.

Discussion

Epinephrine is used as a vasoconstrictor to decrease bleeding and improve visualization prior to ESS. Correctly attributing hemodynamic changes to epinephrine administration can be challenging due to confounding variables that influence epinephrine absorption or placement, including formation of scar tissue from previous surgeries, presence

of a highly vascular tumor, and/or acute/chronic mucosal inflammation. In this study, we examined patients undergoing transsphenoidal pituitary resection to help control for many of these variables. Pituitary masses rarely disrupt the anatomy of the nasal cavity or influence epinephrine administration.¹³ Moreover, pituitary tumors have not been found to predispose patients to paranasal sinus disease that may affect epinephrine mucosal absorption.¹⁴ Thus, controlling for these factors enabled us to more accurately examine the effect of intranasal epinephrine injection and pledget placement on systemic hemodynamic parameters. To the best of our knowledge, the present investigation is among the first to evaluate the effects of varying injectable epinephrine concentrations and pledget placement on blood pressure and HR using real-time hemodynamic tracking in a randomized, prospective study.

Existing literature investigating the effect of epinephrine on hemodynamic parameters can be stratified by type of epinephrine administration. When evaluating the effect of injectable intranasal epinephrine, there is evidence that injectable epinephrine may elevate blood pressure and HR. Gunaratne et al found increases in HR, SBP, DBP, and MAP associated with 1:100,000 epinephrine injection.¹⁰ Wormald et al also noted increases in HR and MAP with 1:80,000 epinephrine injection into the pterygopalatine fossa.¹¹ Our study confirms that intranasal epinephrine injection of both 1:100,000 and 1:200,000 epinephrine can cause a statistically significant increase in HR and SBP ($p < 0.05$). In particular, HR and SBP rise within the first 3 minutes of administration before returning to baseline thereafter. This is consistent with the existing literature. This elevation is likely caused by intranasal injections puncturing and introducing epinephrine into adjacent blood vessels, which traverse back to the heart and mediate hemodynamic changes.

Identifying a concentration of epinephrine that provides adequate vasoconstriction but limits cardiovascular side effects is a clinically relevant issue. De Moraes et al found that 1:100,000 compared with 1:200,000 injectable epinephrine had no perceivable impact on hemodynamic status during third molar extraction.¹⁵ However, when looking specifically at endonasal injections prior to ESS, Moshaver et al found that lidocaine with 1:200,000 epinephrine had less of a hemodynamic effect than lidocaine with 1:100,000 epinephrine in a prospective, randomized, controlled trial.¹⁶ In our study we found no significant difference in hemodynamic parameters when comparing 1:100,000 and 1:200,000 concentrations ($p > 0.05$), even though both solutions increased blood pressure and HR when compared with baseline. There are several key differences in the methods that may explain the alternative findings in our study compared with the landmark study. Our surgeries were performed on patients without chronic sinusitis in order to prevent any confounding factors associated with inflammation and infection. We also injected a total of 2 mL compared with 4 mL per patient. In the Moshaver study, topical epinephrine pledgets were placed and removed

before injection of epinephrine, whereas we performed these in reverse order. Our study also had intra-arterial line monitoring to provide more accurate blood pressure monitoring compared with the blood pressure cuff. Based on our findings, either concentration of injectable epinephrine will elicit an increase in hemodynamics, but no significant difference between the concentrations. Our data suggest that using a dose of 2 mL of injectable 1:100,000 epinephrine may achieve more vasoconstriction and less bleeding without an increase in hemodynamic effects when compared with 1:200,000 epinephrine.

When evaluating hemodynamic changes associated with epinephrine-soaked pledgets, there have been mixed reports. Korkmaz et al performed a large retrospective review of 1140 patients who received 1:1000 topical epinephrine and found no intraoperative cardiovascular complications and a lack of significant hypertensive episodes.¹⁷ Similarly, Gunaratne et al conducted a prospective study and found no hemodynamic parameter changes associated with placement of 1:1000 pledgets.¹⁰

There are, however, several studies that reported topical epinephrine sensitivity in a small portion of patients. Orlandi et al observed 2 patients who had cardiovascular complications after topical epinephrine placement.¹⁸ Our group previously found that 6 of 26 patients had severe spikes in SBP after topical treatment.¹² Our current results provide further supporting evidence that topical epinephrine may induce significant hemodynamic changes in a subset of sensitive individuals. Two of 28 patients in this study had an SBP increase of >75 mmHg after pledget placement. There were no confounding factors identified in these patients, similar to our previous study.¹² We observed a lower percentage of responders in this study compared with our previous study.¹² In the current study, injectable epinephrine was administered first before topical epinephrine, which may have blunted or blocked absorption of the topical epinephrine. However, this was difficult to assess as we did not measure the amount of epinephrine absorbed in the bloodstream. This should be performed in future studies. Cohen-Karem et al found that sinonasal injectable epinephrine combined with 1% lidocaine may reduce the patient's stress response, which may prevent higher catecholamine levels.¹⁹ This may also explain why there were only 2 of 28 responders, compared with 6 of 26 in our previous study. Overall, use of topical epinephrine could be life-threatening and this should be recognized prior to placement of pledgets, especially in patients with cardiovascular disease.

This phenomenon of epinephrine response was also seen in 6 of 28 of our patients after intranasal epinephrine injections, regardless the concentration. No confounding factors were identified. Although we made sure to withdraw the syringe before injection to prevent significant intravascular injection, one explanation could be inadvertent increased intra-arterial injection in these 6 patients. Only 1 of these 6 patients also was sensitive to topical epinephrine placement. It is unclear what etiology sensitizes patients

to epinephrine. Some emerging research has identified differences in epinephrine response based on patient demographics and medical history. Van Berge-Landry et al found that different ethnic groups may have varying sensitivities to epinephrine administration.²⁰ Trovik et al reported that adrenergic sensitivity may fluctuate for patients with insulin-dependent diabetes.²¹ However, none of these confounding factors played a role in our patient population. Future work should be directed at identifying patient characteristics that predispose them to epinephrine sensitivity.

In future studies, measuring the serum concentration of epinephrine may be helpful in assessing the true absorption of both injectable and topical epinephrine. This study was performed by injecting epinephrine first and then placing topical epinephrine pledgets. This order is sometimes performed in reverse by some otolaryngologists and could potentially alter the hemodynamic findings. The current study was performed using patients presenting for transsphenoidal pituitary resection. This patient population was chosen to control for confounding factors, such as chronic mucosal inflammation and presence of large vascular tumors. We acknowledge that epinephrine absorption may differ with alternative pathologies.

Conclusion

Epinephrine administration is commonly used for hemostasis and visualization during ESS. Although epinephrine-induced vasoconstriction may improve surgical field visualization, the perioperative complications associated with epinephrine must be monitored closely, especially in sensitive populations. This study has revealed that injectable intranasal epinephrine can significantly increase hemodynamic parameters such as HR and SBP. Both 1:100,000 and 1:200,000 solutions of injectable epinephrine were found to elevate HR and blood pressure, even though there was no detectable difference when comparing the 2 groups. A subset of patients were found to have a pronounced cardiovascular response to injectable epinephrine and another subset had a response to topical 1:1000 epinephrine pledgets, which caused SBP spikes of >40 and 75 mmHg, respectively. This warrants the conclusion that epinephrine must be used judiciously depending on patient comorbidities and sensitivity in patients undergoing endonasal skull-base surgery. However, the patients included in our study had healthy mucosa, and this may not apply to patients with diseased mucosa. 

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