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# Hemodynamic Changes with 1:1000 Epinephrine on Wrung-Out Pledgets Before and During Sinus Surgery

Annals of Otolaryngology, Rhinology & Laryngology  
1–7

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DOI: 10.1177/0003489420959107

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## Abstract

**Background:** Intranasal topical 1:1000 epinephrine has been used safely and effectively for hemostasis during endoscopic sinus surgery (ESS). Prior studies assessing hemodynamic changes after intranasal topical epinephrine application have only used soaking wet cottonoid pledgets, and have only assessed for hemodynamic changes before any surgery being performed.

**Objective:** The purposes of this study were to determine whether intranasal application of topical 1:1000 epinephrine with wrung-out cottonoid pledgets caused significant hemodynamic changes both before and during ESS, and whether it allowed for adequate hemostasis.

**Methods:** A prospective evaluation of 30 patients with eosinophilic chronic rhinosinusitis with nasal polyps (CRSwNP) undergoing complete bilateral ESS was conducted. Heart rate, blood pressure (systolic, diastolic, and mean arterial pressure), and electrocardiography changes were recorded at 0, 1, 2, and 5-minute intervals after placing wrung-out epinephrine-saturated pledgets, both before and at the end of ESS. No submucosal epinephrine injections were performed. Estimated blood loss (EBL) and major intraoperative complications were recorded for all cases.

**Results:** There were no significant hemodynamic changes or electrocardiographic abnormalities after placement of wrung-out epinephrine-soaked pledgets both before and after ESS. After bilateral ESS, there were actually mean decreases in heart rate and blood pressure parameters. Mean EBL was  $75.8 \pm 32.2$  mL, and no major intraoperative complications occurred.

**Conclusion:** Intranasal application of topical 1:1000 epinephrine via wrung-out cottonoid pledgets was effective for intraoperative hemostasis, and did not cause clinically significant alterations in hemodynamic parameters or cardiovascular events, either before or during ESS in patients with CRSwNP.

**Level of Evidence:** 4

## Keywords

topical epinephrine, hemostasis, nasal pledget, endoscopic sinus surgery, endoscopic skull base surgery

## Introduction

Intranasal topical 1:1000 epinephrine is commonly used to achieve hemostasis and to improve intraoperative visualization during endoscopic sinus surgery (ESS). Epinephrine can be administered intranasally either by submucosal injection or by topical mucosal application, commonly through cottonoid pledgets. Both methods have been shown to improve hemostasis.<sup>1</sup> However, submucosal injection results in higher plasma epinephrine concentrations than topically applied epinephrine.<sup>2,3</sup> Although rare, submucosal epinephrine injection is more likely to cause hemodynamic changes or cardiovascular events compared to topical epinephrine.<sup>4-6</sup> Additionally, inadvertent intravascular injection of epinephrine can lead to life-threatening cardiovascular events,<sup>7,8</sup> or even death.<sup>9</sup>

A number of studies have analyzed the safety of intranasal 1:1000 topical epinephrine, and very few adverse events have been reported.<sup>1,2,4,5,7,10-12</sup> With regard to study designs,

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retrospective chart reviews have been limited to reporting intraoperative and postoperative cardiovascular events, and while very rare on the order of 0.05%, they do not capture hemodynamic changes that occur after intranasal topical epinephrine application.<sup>7,10,11</sup> Epinephrine is metabolized rapidly both locally and systemically,<sup>13</sup> so to capture its effect on hemodynamic parameters after intranasal application, a prospective study measuring parameters in short successive time periods is required. While a few prospective studies have demonstrated safety with topical epinephrine application by nasal pledgets,<sup>4,6,12</sup> two of the studies actually did show hemodynamic parameter elevations after placement of completely soaked epinephrine pledgets.<sup>6,12</sup> Some authors have recommended wringing out epinephrine-soaked pledgets to minimize potentially dangerous systemic effects of epinephrine.<sup>1,5,10</sup> However, no prospective study has assessed hemodynamic changes after placement of wrung-out pledgets.

These prior studies also only assessed the effects of topical epinephrine before any sinonasal surgery being performed.<sup>4,6,12</sup> It is possible that exposure of sinonasal vascular beds during ESS could increase the risk of epinephrine absorption systemically,<sup>9</sup> so studying hemodynamic changes after topical epinephrine application during ESS would be beneficial. The purposes of this study were to determine whether intranasal application of topical 1:1000 epinephrine with wrung-out pledgets caused significant hemodynamic parameter changes both before and during ESS, and whether it allowed for adequate hemostasis.

## Methods

### Patient Population

Thirty adult patients who underwent complete bilateral ESS for eosinophilic chronic rhinosinusitis with nasal polyps (CRSwNP) were evaluated prospectively for hemodynamic changes after intranasal application of topical 1:1000 epinephrine before and during surgery. Institutional Review Board approval was obtained. All CRSwNP patients had polyps extending into the nasal cavity, and Lund-Mackay scores were collected. Structured histopathology reports were analyzed, and tissue eosinophilia was described as  $\geq 10$  eosinophils per high-power field.<sup>14</sup> Patients with significant cardiovascular disease with New York Heart Association (NYHA) class 3 or 4 disease, and known arrhythmias were excluded from the study. Patients were also excluded if they were pregnant, or if they had allergies to lidocaine, bupivacaine, or epinephrine.

### Experimental Procedure

Topical epinephrine was applied intranasally by  $0.5 \times 3$ -inch cottonoid pledgets (Codman and Shurtleff Inc, Raynham, MA). Pledgets were first completely soaked by immersing

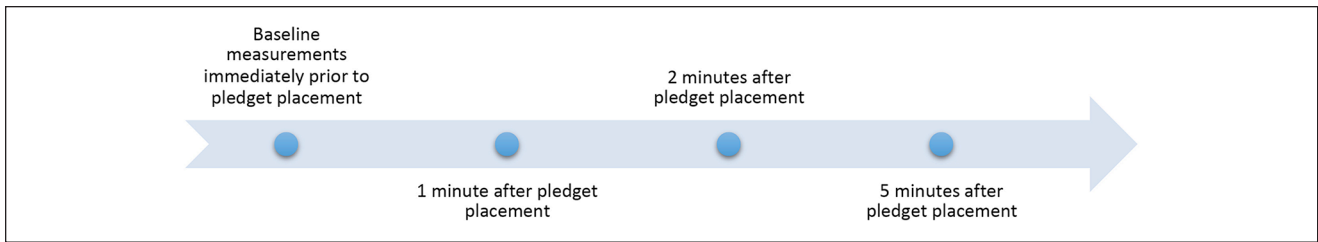
10 pledgets at a time in 30 mL of 1:1000 epinephrine for at least 5 minutes. Pledgets were then wrung out prior to intranasal placement by the senior author (JRC) in a standardized fashion, from one end of the pledget to the other.

*Patients received no anesthetic or anxiolytic medication prior to induction.* After induction with fentanyl, lidocaine, propofol, and rocuronium, patients were intubated, and their cardiovascular parameters were allowed to stabilize over 15 minutes. Next, epinephrine-soaked pledgets were wrung out and placed intranasally before any surgery was performed. When anatomy permitted, one pledget was placed into the middle meatus, and another into nasal cavity between the inferior turbinate and nasal septum. When nasal cavities were obstructed either by nasal polyps or a deviated septum, pledgets were placed intranasally in positions to maximize mucosal contact. A total of four pledgets were always placed preoperatively, two in each nasal cavity. Note that submucosal injection of epinephrine was never performed.

*Patients were then maintained with sevoflurane or isoflurane for the case duration. Neither nitrous oxide nor vasopressors were used in any cases. Urine output was maintained at greater than 0.5 mL/kg/hour.* Intraoperatively, wrung-out pledgets were placed into the operated sinus cavities after complete bilateral ESS. All patients underwent the same complete bilateral ESS, which included wide maxillary anrostomies, total ethmoidectomies with partial middle turbinate resections, wide sphenoidotomies, and Draf IIB frontal sinusotomies.<sup>15</sup> Six pledgets were always placed after completing ESS bilaterally, three on each side. Pledgets were placed so as to avoid pledget overlap and maximize contact between pledgets and traumatized tissue. Note that while epinephrine pledgets were used throughout the case for hemostasis as needed, no pledgets were placed on either side for at least 15 minutes prior to placement of the pledgets utilized for hemodynamic measurements. This was done to minimize the chance of any residual epinephrine locally or systemically from affecting hemodynamic measurements, since the half-life of epinephrine is 2 to 3 minutes.<sup>16</sup>

### Outcome Measures

The following baseline hemodynamic parameters were measured preoperatively and intraoperatively, immediately before pledgets were placed: heart rate (HR), systolic and diastolic blood pressure (SBP and DBP), mean arterial pressure (MAP), and electrocardiogram (ECG) abnormalities. Figure 1 demonstrates the timing of hemodynamic measurements from baseline to 1, 2, and 5 minutes, after which the pledgets were removed from the sinonasal cavities. The time between pledgets being placed preoperatively and intraoperatively was recorded for each patient. The type of maintenance general anesthetic used, and whether the



**Figure 1.** Flow diagram illustrating the basic study design of the timing of hemodynamic parameter measurements relative to intranasal pledget placement, both preoperatively and intraoperatively.

**Table 1.** Mean Baselines and Changes in Preoperative Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and Mean Arterial Pressure (MAP) After Placing Wrung-Out Epinephrine Pledgets.

	Mean Baseline, $\pm$ SD	Mean Change from Baseline at 1 Min, $\pm$ SD	P-Value	Mean Change from Baseline at 2 Min, $\pm$ SD	P-Value	Mean Change from Baseline at 5 Min, $\pm$ SD	P-Value
HR, bpm	75.8 $\pm$ 9.9	+1 $\pm$ 4.8	.261	+1.2 $\pm$ 6.2	.297	-1.6 $\pm$ 5.8	.133
SBP, mmHg	103.6 $\pm$ 14.9	+4.7 $\pm$ 9.4	<b>.013</b>	+0.8 $\pm$ 9.3	.649	-0.9 $\pm$ 6.4	.437
DBP, mmHg	58.2 $\pm$ 8.6	+2.8 $\pm$ 5.1	<b>.007</b>	+1.7 $\pm$ 6.1	.151	+0.03 $\pm$ 4.9	.970
MAP, mmHg	76.3 $\pm$ 10.8	+2.9 $\pm$ 8.3	.063	+0.4 $\pm$ 9.2	.828	-0.5 $\pm$ 7.5	.700

Note. The bold values are statistically significant values.

following medications were utilized during cases were also recorded: beta-blockers, dexmedetomidine, and remifentanyl. No arterial lines were utilized. Estimated blood loss (EBL) was recorded after every case, and was calculated by subtracting the known amount of saline irrigation used during surgery from the total amount of blood plus saline irrigation collected in a suction container during surgery. The following intraoperative complications were recorded as well: cerebrospinal fluid leak, orbital injury, arterial injury, or severe hemorrhage requiring blood transfusion. Potential arterial injuries included direct injuries to the internal carotid, anterior ethmoid, posterior ethmoid, or sphenopalatine arteries.

### Statistical Analysis

Preoperative and intraoperative baseline hemodynamic parameters were compared. Preoperative hemodynamic parameters at 1, 2, and 5 minutes after pledget placement were compared to their baseline measurements, and intraoperative hemodynamic parameters were analyzed in the same manner. Statistical analysis was carried out using paired two-tailed student’s t-tests. Separate t-tests were performed to compare the mean preoperative and intraoperative hemodynamic parameter changes between baseline and 1, 2, and 5-minute measurements. Statistical significance was set at  $P < .05$ . All statistical analyzes were performed using R software (version 3.6.1).

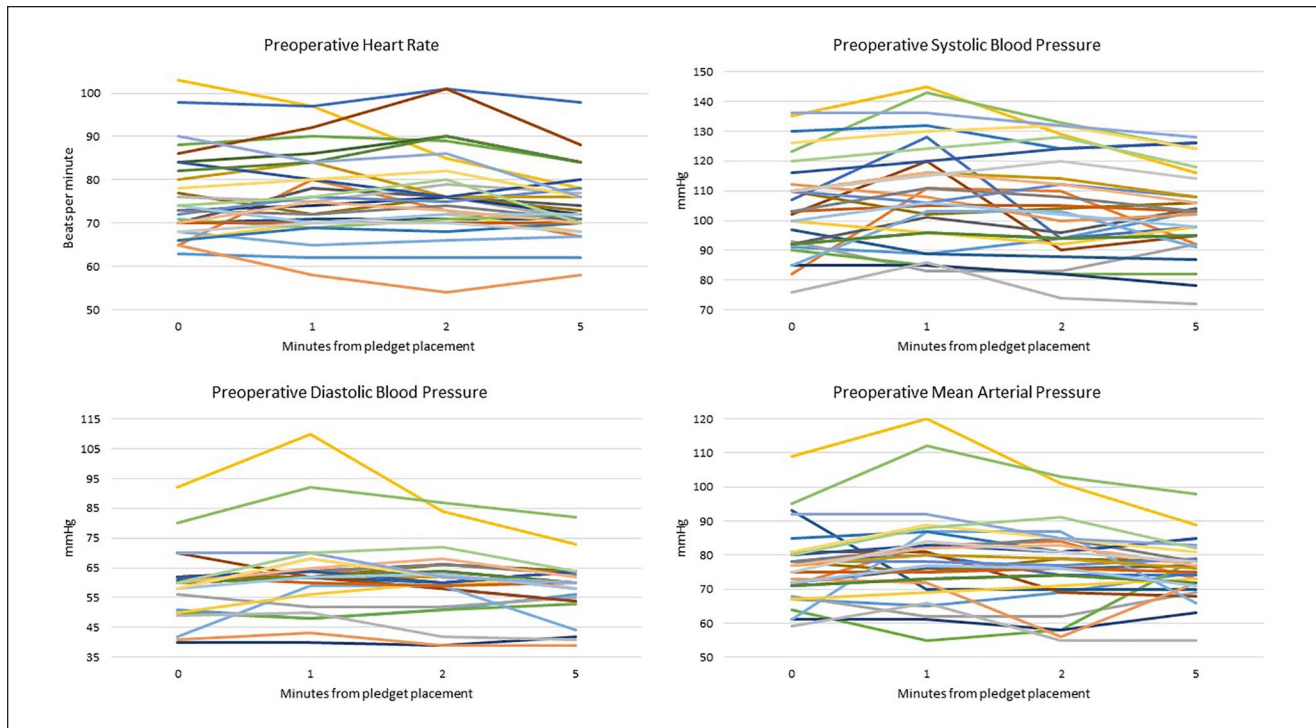
Data from these 30 patients were used to perform a power analysis using R software (version 3.6.1) and PASS (16.0.1). For hemodynamic parameters, a change greater

than 20% from the baseline measurements was considered clinically meaningful. The means of baseline hemodynamic parameters were estimated from data in this study, and the minimal clinically meaningful detectable difference for each hemodynamic parameter was calculated by multiplying mean baseline values by 20%. The standard deviation of the paired difference was also estimated from study data. The effect size was calculated as the difference/standard deviation. Note that because preoperative MAP had the smallest effect size (1.69) among all hemodynamic parameters, a sample size was sought that would achieve at least 80% power to detect that effect size. A sample size of six patients was determined to achieve at least 80% power to reject the null hypothesis of zero effect size when the population effect size was 1.69, and the significance level (alpha) was 0.05 using a two-sided paired t-test. Therefore, the data from the current study achieved adequate power, and additional data collection was not needed.

### Results

Of the 30 CRSwNP patients, all were eosinophilic, mean age was 55.4  $\pm$  16 years (Range, 18-80), and 57% were male. The mean Lund-Mackay score was 20.1  $\pm$  2.2. The mean elapsed time between preoperative and intraoperative hemodynamic parameter measurements was 132.6  $\pm$  22.4 minutes.

Table 1 shows the hemodynamic parameter changes after wrung-out epinephrine pledgets were placed preoperatively, after induction. Topical 1:1000 epinephrine largely led to no statistically significant alterations in any hemodynamic



**Figure 2.** Spaghetti plots demonstrating changes in preoperative heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) for all patients after placing wrung-out epinephrine pledgets.

**Table 2.** Mean Baselines and Changes in Intraoperative Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and Mean Arterial Pressure (MAP) After Placing Wrung-Out Epinephrine Pledgets.

	Mean Baseline, $\pm$ SD	Mean Change from Baseline at 1 Min, $\pm$ SD	P-Value	Mean Change from Baseline at 2 Min, $\pm$ SD	P-Value	Mean Change from Baseline at 5 Min, $\pm$ SD	P-Value
HR, bpm)	81 $\pm$ 9.9	-0.2 $\pm$ 3.1	.771	-1.2 $\pm$ 3.7	.098	-3.5 $\pm$ 4.9	<b>.001</b>
SBP, mmHg	114.8 $\pm$ 13.2	-3.4 $\pm$ 9	<b>.047</b>	-6.4 $\pm$ 9.8	<b>.001</b>	-11.9 $\pm$ 11.9	<b>&lt;.001</b>
DBP, mmHg	64 $\pm$ 10.8	-1.7 $\pm$ 5.2	.077	-4.1 $\pm$ 6.2	<b>.001</b>	-8.5 $\pm$ 6	<b>&lt;.001</b>
MAP, mmHg	82.2 $\pm$ 10.4	-1.9 $\pm$ 6.7	.123	-4.2 $\pm$ 7.8	<b>.006</b>	-8.6 $\pm$ 8.8	<b>&lt;.001</b>

Note. The bold values are statistically significant values.

parameters. There were slight transient increases in SBP and DBP of 4.6 and 2.8 mmHg, respectively, that were statistically significant at 1 minute. However, all parameter changes were non-significant at 2 and 5 minutes. Figure 2 is a spaghetti plot of all patients' hemodynamic parameter changes at successive time points after epinephrine pledgets were placed preoperatively.

Table 2 shows the hemodynamic parameter changes after wrung-out epinephrine pledgets were placed intraoperatively, after complete bilateral ESS. Interestingly, all hemodynamic parameters trended downward at 1, 2, and 5 minutes. Decreases in blood pressure parameters were statistically significant at nearly all time points, except for the MAP decrease at 1 minute. HR also decreased from baseline at each time point, but was only statistically significant at 5 minutes. Figure 3 is a spaghetti plot of all patients'

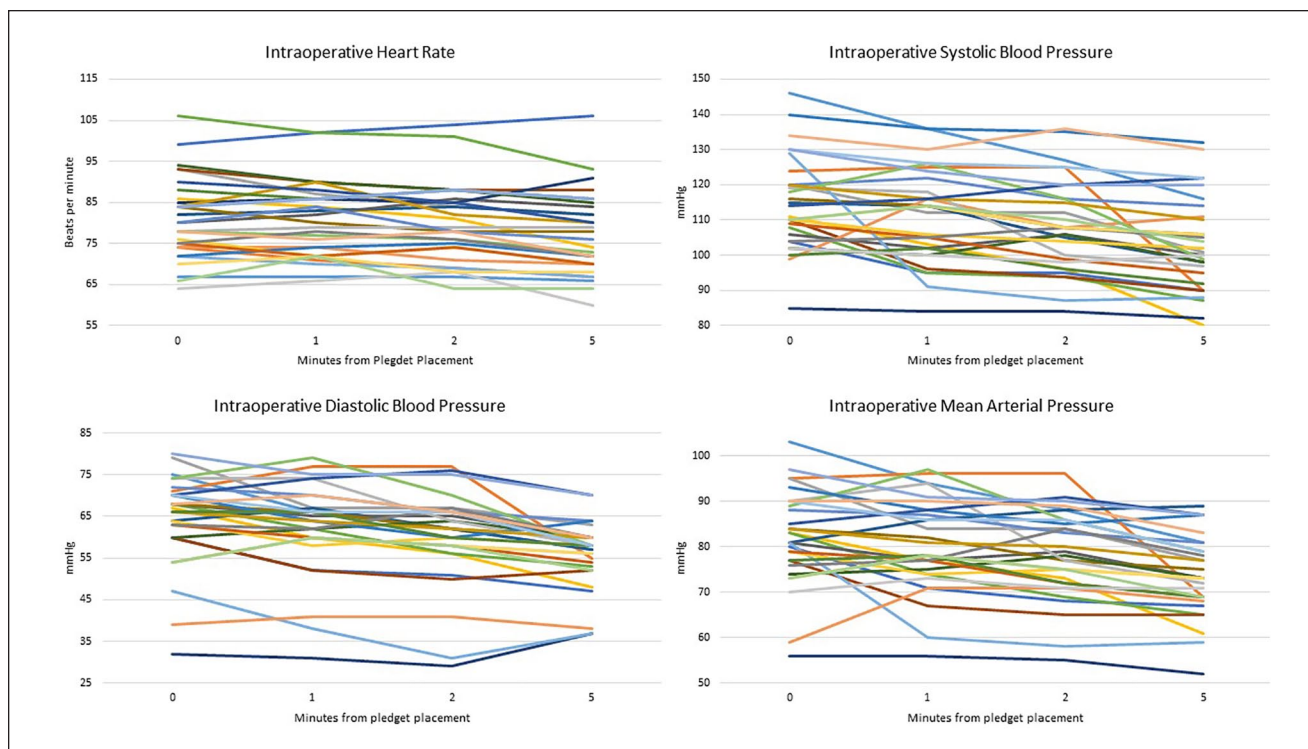
hemodynamic parameter changes at successive time points after epinephrine pledgets were placed after complete ESS.

No beta-blockers, or other vasodilatory or vasoconstrictive medications were necessary to treat hemodynamic changes encountered during the current study. There were no ECG abnormalities in any patients, and no cardiovascular events intraoperatively or postoperatively. Mean EBL was 75.8  $\pm$  32.2 mL, and there were no major intraoperative complications such as cerebrospinal fluid leak, orbital injury, arterial injuries, or severe hemorrhage requiring transfusion.

## Discussion

Topical 1:1000 epinephrine has been shown to be safe and effective for achieving hemostasis during ESS.<sup>5,7,8,10</sup> There





**Figure 3.** Spaghetti plots demonstrating changes in intraoperative heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) for all patients after placing wrung-out epinephrine pledgets.

are multiple reasons why intranasal application of topical 1:1000 epinephrine via pledgets may not cause significant hemodynamic changes. There could be limited systemic absorption of epinephrine due to more local vasoconstriction than what is seen with intramuscular or subcutaneous injections.<sup>17</sup> Limited systemic effects could also result from local epinephrine metabolism by adrenergic neurons, hepatic metabolism, or opposing pharmacodynamic effects of general anesthesia.<sup>13</sup> While a few studies have shown plasma levels of epinephrine to increase after topical intranasal application,<sup>1,18</sup> studies have yet to demonstrate exactly how plasma levels rise after nasal pledget placement. Studies on topical epinephrine absorption have varied considerably in design, with very few assessing topical epinephrine alone,<sup>2,3</sup> and none having assessed 1:1000 topical epinephrine specifically. The current study demonstrated that placing six wrung-out epinephrine pledgets, or nearly 6 mg of epinephrine,<sup>6,12,19</sup> in maximal direct contact with damaged sinonasal tissue resulted in no significant systemic hemodynamic changes. These findings reinforce findings from previous studies that topical 1:1000 epinephrine is safe to use during sinonasal surgery.

The current study had three key methodologic differences from previous studies on hemodynamic changes after intranasal topical epinephrine application. First, prior prospective studies on intranasal epinephrine application have only assessed hemodynamic changes after induction, before

any sinonasal surgery.<sup>4,6,12</sup> However, it is important to study whether injured mucosa and exposed bone could lead to increased systemic absorption of epinephrine. Interestingly, not only were there no significant intraoperative elevations in HR or blood pressure parameters, there were actually mean decreases in these parameters. Reasons for the relative vasodilatory systemic response could have been due to lower systemic epinephrine concentrations activating beta-2 receptors,<sup>20,21</sup> vasodilatory effects of the general anesthetic,<sup>22</sup> or perhaps the absence of surgical stimulation when pledgets were placed. Also interesting was that the decreases in hemodynamic parameters were more pronounced after surgery, compared to parameters measured before surgery. Preoperative hemodynamic measurements were largely unchanged at each time point, similar to other studies.<sup>4,6</sup> While the reasons for hemodynamic parameter changes in this study will require further research, it was important from a clinical perspective to show that epinephrine pledgets never led to significant HR or BP elevations, ECG abnormalities, or cardiac events, either preoperatively or intraoperatively. However, this was a small sample size, and surgeons should still use caution or avoid using topical epinephrine in patients with significant cardiovascular disease.<sup>4,7,11,12</sup>

Second, prior prospective studies assessing hemodynamic changes after intranasal epinephrine have also only utilized completely saturated pledgets. Yim et al showed

significant elevations in blood pressure parameters in 6/26 patients studied,<sup>12</sup> and Ahmed et al showed that 2/28 patients had significant SBP elevations after placing completely soaked epinephrine pledgets.<sup>6</sup> Kuhar et al recently showed that wrung-out pledgets contained a mean 0.931 mg of epinephrine,<sup>19</sup> which is about half the amount of epinephrine absorbed onto completely saturated pledgets.<sup>6,12</sup> This should lead to less epinephrine delivery to sinonasal mucosa and less systemic absorption, which should decrease the risk of hemodynamic changes and cardiovascular events.

The third unique methodologic aspect of this study was that it included only eosinophilic CRSwNP patients with significant mucosal inflammation based on severe nasal polyp burden and high Lund-Mackay scores. Patients also all underwent complete bilateral ESS. Therefore, patients had a maximal amount of exposed traumatized tissue in very inflamed and vascular wound beds, maximizing the potential effect of topical epinephrine. Yim et al and Ahmed et al only studied patients undergoing transsphenoidal surgery for skull base pathology, and excluded patients with inflammatory disease.<sup>6,12</sup> However, rhinologic surgery very frequently involves inflammatory conditions,<sup>23</sup> so it is important to appreciate the pharmacodynamic effects of topical 1:1000 epinephrine in these patients. Tangbunrueang et al recently published a study on topical versus injected epinephrine in 40 CRS patients undergoing ESS, 42.5% of whom had nasal polyps, but they did not study hemodynamic changes.<sup>24</sup> In the current study, it was encouraging to demonstrate no clinically significant hemodynamic parameter changes in patients undergoing complete ESS for eosinophilic CRSwNP, but future studies will be important to corroborate these findings.

This study also showed that wrung-out epinephrine pledgets provided excellent intraoperative hemostasis in all cases. The overall mean EBL during ESS was approximately 75 mL, which should be safe in patients undergoing ESS for CRSwNP, and was similar to the mean EBL in a systematic review of topical intranasal epinephrine used during sinonasal and skull base surgery (61.7-67.9 mL).<sup>10</sup> Note that no submucosal epinephrine injections were necessary in this study to achieve hemostasis, which brings into question whether epinephrine injection is needed during sinonasal surgery. Tangbunrueang et al recently showed in a double-blind randomized controlled study that injecting 1:100 000 epinephrine in addition to topical 1:1000 epinephrine provided no added benefit in intraoperative visualization, compared to topical epinephrine alone.<sup>24</sup> If topical epinephrine alone provides adequate hemostasis and visualization, with less potential for hemodynamic changes, perhaps submucosal epinephrine injection causes more risk than benefit in the majority of sinonasal surgeries.

There were limitations of the study as well. First, a larger sample size will be necessary to support or refute the findings from this study. However, while the sample size was

small, it was similar to previous studies,<sup>4,6,12,24</sup> and was adequately powered. A larger study would also be helpful in analyzing the effects of certain medical comorbidities on hemodynamic parameters intraoperatively, such as preoperative oral anti-hypertensive use, hepatic or renal dysfunction, coagulopathy, and thrombocytopenia. Another limitation was that adequate intraoperative hemostasis was based on EBL, without grading intraoperative visualization as has been utilized in prior studies.<sup>24,25</sup> However, the low mean EBL combined with no major intraoperative complications, suggested that adequate intraoperative visualization was achieved. Another potential limitation was that arterial lines were not used, as they were not indicated for the surgeries performed. Moment-to-moment hemodynamic changes could have potentially been missed, but measurements were taken in close succession to minimize this issue. Another limitation was that the study only assessed short-term hemodynamic responses to epinephrine pledgets, and one cannot determine whether there is any potential for persistent hemodynamic effects postoperatively. Future studies could examine whether some patients are at risk for persistent effects. A final limitation was that patients with significant cardiovascular risk factors were excluded. While this was felt to be in the best interest of patients, whether topical epinephrine is safe to use in patients with cardiovascular comorbidities cannot be determined from the current study. Caution should therefore still be used by surgeons in patients with significant cardiovascular disease.

## Conclusion

Intranasal application of topical 1:1000 epinephrine via wrung-out cottonoid pledgets was effective for intraoperative hemostasis, and did not cause clinically significant alterations in hemodynamic parameters or cardiovascular events, both before and during ESS in patients with CRSwNP.

## Acknowledgments

The authors would like to thank Natalie Craig, graphic designer, for assistance with formatting figures for this study.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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