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REVIEW ARTICLE

Greater palatine canal injections reduce operative bleeding during endoscopic sinus surgery: a systematic review and meta-analysis

Se Hwan Hwang[1,2] · Sung Won Kim[1] · Soo Whan Kim[1] · Byung Guk Kim[1] · Jin Hee Cho[1] · Jun Myung Kang[1,2]

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Abstract

Objectives The use of greater palatine canal (GPC) injections of a local anesthetic and a vasoconstrictor to decrease surgical bleeding during endoscopic sinus surgery (ESS) is controversial. We investigated the role of a preoperative GPC injection to minimize intraoperative bleeding during ESS in patients with chronic sinusitis through a meta-analysis of the relevant literature.

Data sources PubMed, SCOPUS, and the Cochrane database.

Review methods We screened the relevant literature published before May of 2018. Five articles that compared the pre-operative GPC injection (treatment group) with a placebo or no treatment (control group) were included for this analysis of the outcomes, which included an endoscopic grade of nasal bleeding and intraoperative hemodynamic stability during ESS.

Results The endoscopic grade in the treatment group was significantly reduced when compared with the control group. No significant adverse effects were reported in the enrolled studies. The subgroup analyses of these results compared the concentrations of adrenalin (1:80,000 or 1:100,000), and adrenalin 1:80,000 showed significant effects on intraoperative bleeding when compared to adrenalin 1:100,000.

Conclusion This study demonstrated that GPC injections of local anesthesia with 1:80,000 adrenaline for ESS effectively reduced intraoperative bleeding. Additionally, this procedure showed no significant adverse effects, such as hemodynamic instability. However, the standardized dosing needs further investigation and more trials.

Level of evidence Ia.

Keywords Adrenalin · Endoscopic sinus surgery · Bleeding · Adverse effect · Meta-analysis

Introduction

Endoscopic sinus surgery (ESS) is the procedure of choice for the surgical management of chronic rhinosinusitis (CRS) or nasal polyps [1]. However, given the vascularity of the paranasal sinuses, particularly in infectious states, even a small amount of hemorrhage can greatly affect visibility and thus the overall surgery. There is a multitude of techniques used by sinus surgeons to diminish hemorrhaging intra-operatively. However, no ideal management has yet been developed to decrease intraoperative bleeding during sinus surgery [2].

The sphenopalatine artery is the main feeding vessel to the lateral wall and to most of the septum. Blocking this artery is believed to reduce the amount of bleeding, thereby improving the surgical field during ESS. The block involves injecting a local anesthetic with adrenaline through the greater palatine canal (GPC). Several recent studies found positive effects of greater palatine canal injections on intra-operative bleeding during ESS [3]. However, the injection of this agent into the GPC to induce the vasoconstriction of the sphenopalatine artery is not commonly performed by sinus surgeons [4]. Given that ESS is considered to be a popular operation and that intraoperative bleeding is an important

✉ Jun Myung Kang
entkjm@catholic.ac.kr

1 Department of Otolaryngology-Head and Neck Surgery, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

2 Department of Otolaryngology-Head and Neck Surgery, College of Medicine, Bucheon St. Mary's Hospital, The Catholic University of Korea, 327 Sosa-ro, Bucheon-si, Gyeonggi-do 14647, Republic of Korea

factor that increases the risk of complications in patients who undergo nasal surgeries, it is essential that surgeons follow efficient practices for reducing intra-operative morbidity. The goal of this review was to evaluate the effects of GPC injections and whether they improve the outcomes of sinus surgery.

Materials and methods

Search strategy and study selection

An electronic database search (Pubmed, SCOPUS, Google scholar, Embase, and the Cochrane Register of Controlled Trials) using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was conducted with the goal of identifying all available studies related to an intraoperative SPGB from inception of application of greater palatine canal injections and written in English up to May of 2018. The following search terms were used: 'greater palatine canal', 'chronic sinusitis', 'endoscopic sinus surgery', 'pterygopalatine fossa', 'vasoconstrictor', 'infiltration', 'bleeding,' and 'surgical field.'

Two independent reviewers screened all abstracts and titles for the candidate studies and discounted the studies not associated with pre-operative GPC injections. The full texts of potentially relevant studies were used if the decision for inclusion could not be made from the abstract alone. Prospective controlled trials that satisfied the next inclusion criteria were eligible for review: trials that studied patients undergoing endoscopic sinus surgery and intraoperative GPC injections of local anesthesia with a vasoconstrictor. Studies were not deemed for inclusion if, in addition to sinus surgery, patients underwent procedures such as septal and turbinate surgery or if reports were duplicated. Additionally, studies were excluded from the analysis if the outcomes of interest were not clearly provided with quantifiable data, or if it was impossible to evaluate the appropriate data from the published results. Figure 1 summarizes the search strategy used to identify studies selected for the meta-analysis.

Data extraction and risk of bias assessment

Data from eligible studies were extracted using standardized forms and were checked by two independent reviewers. The analyzed outcomes were: endoscopic grading related to nasal bleeding [3–7], intraoperative hemodynamic stability (mean arterial blood pressure (MAP), heart rate, the concentration of end-tidal CO_2) [3, 4, 8], and the events of adverse effects related to GPC injections. These outcomes were compared with the treatment group (including GPC injection) versus the control group (patients that used no treatment or saline injection) during the operation and the postoperative period.

We selected data with respect to patient number, endoscopic bleeding-related grading scale, quantity of intraoperative hemodynamic stability, event of side effects, and the *p* value reported as a comparison of the treatment group with a control group from the studies marked for inclusion. This was done to determine the influence of the GPC injection on operative bleeding and adverse effects.

Analyses for statistics

The statistical analysis of the included studies was conducted using the R program (R Software Foundation, Vienna, Austria). In the case of quantitative variables, the meta-analysis was conducted using the standardized mean difference

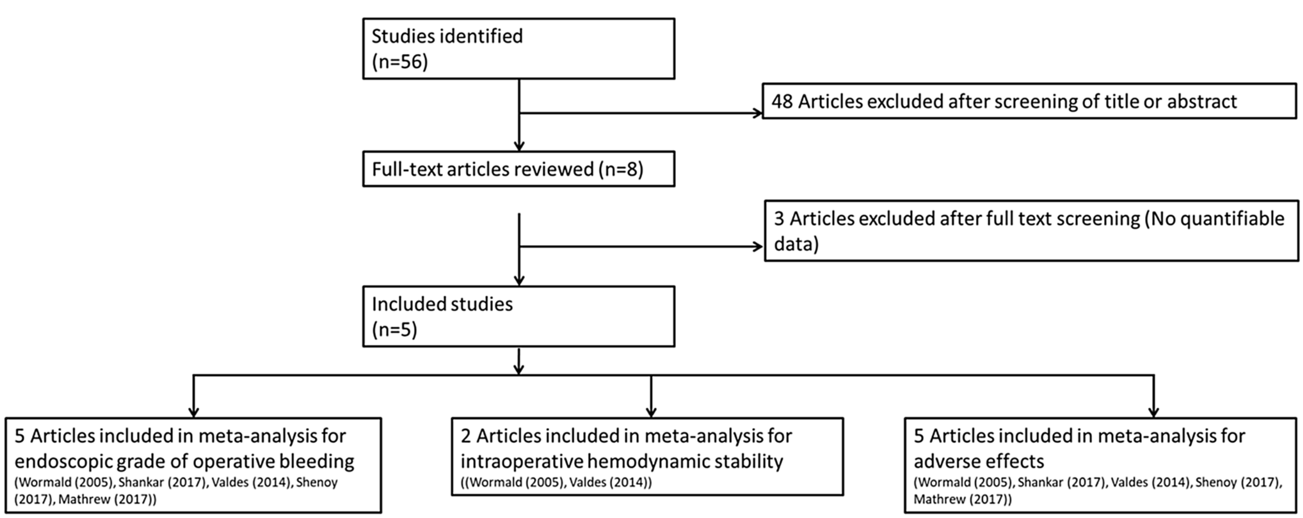

Fig. 1 Study selection diagram

(SMD). The SMD was adopted as a summary statistic to standardize the results of the studies to an equal scale when the studies measured the equal outcome but assessed it in various methods. This method was selected to analyze endoscopic bleeding grade and intraoperative hemodynamic stability because there was no single standardized scale used in all studies. We used a funnel plot and the Egger's test concurrently to identify potential publication bias. In addition, we used the Duval and Tweedie's trim and fill to compensate the summed effect size with respect to publication bias. Heterogeneity was calculated with the I^2 test and the measure ranged from 0 (no heterogeneity) to 100 (maximum heterogeneity). When significant heterogeneity among outcomes was found (defined as $I^2 > 50$), the random-effects model was used. Subgroup analysis was also performed in this version. Those outcomes that did not present a significant level of heterogeneity ($I^2 < 50$) were analyzed with the fixed-effects model. Additionally, to estimate the effect of individual study in the overall meta-analysis results, sensitivity analyses were conducted. These analyses were performed by repeating the meta-analyses while omitting a different study each time.

Results

In our study, out of 56 potentially eligible articles, 48 articles were extracted after screening titles and abstracts. Eight articles were screened with full-text review and five articles with 183 participants were finally eligible for our review (Table 1). Risk of bias assessments and study characteristics are described in Table 2. Publication bias was not analyzed because the five trials enrolled were not enough to analyze a funnel plot.

Effect of preoperative GPC injections on endoscopic grading of bleeding, intraoperative hemodynamic stability, and side effects compared with the control group

The endoscopic grading of bleeding (SMD = −0.42; confidence interval 95% (CI) [−0.70, −0.14]) was statistically lower in the treatment group than in the control group (Fig. 2). There were no significant differences between the two groups in the intraoperative MAP (SMD = −0.02;

Table 1 Summary of studies included in the meta-analysis

Study (year)	Sample size	Comparison	Outcome measure analyzed
Wormald et al. [3]	31	2 mL of 2% lidocaine and 1:80,000 adrenalin versus control	Endoscopic grading of operative bleeding Intraoperative mean arterial blood pressure Intraoperative heart rate Concentration of end-tidal CO_2
Shankar et al. [5]	22	2 mL of 2% lidocaine and 1:80,000 adrenalin versus control	Endoscopic grading of operative bleeding
Valdes et al. [4]	65	2 mL of xylocaine 1 percent with 1:100,000 adrenaline versus control	Endoscopic grading of operative bleeding Intraoperative mean arterial blood pressure Intraoperative heart rate Concentration of end-tidal CO_2
Shenoy et al. [6]	33	2 mL of 2% lidocaine with 1:80,000 adrenaline versus control	Endoscopic grading of operative bleeding
Mathew et al. [7]	32	2 mL of 2% xylocaine with 1:80,000 adrenaline	Endoscopic grading of operative bleeding

Table 2 Individual randomized controlled trial (RCT) methodological quality

Study (year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Free of selective reporting	Risk of bias of randomized studies
Wormald et al. [3]	Yes	Yes	Yes	Yes	Yes	Yes	Risk of bias (low risk)
Shankar et al. [5]	No	No	No	Yes	Yes	Yes	Risk of bias (high risk)
Valdes et al. [4]	Yes	Yes	Yes	Yes	Yes	Yes	Risk of bias (low risk)
Shenoy et al. [6]	Unclear	Unclear	Yes	Yes	Yes	Yes	Risk of bias (unclear risk)
Mathew et al. [7]	Yes	Yes	Yes	Yes	Yes	Yes	Risk of bias (low risk)

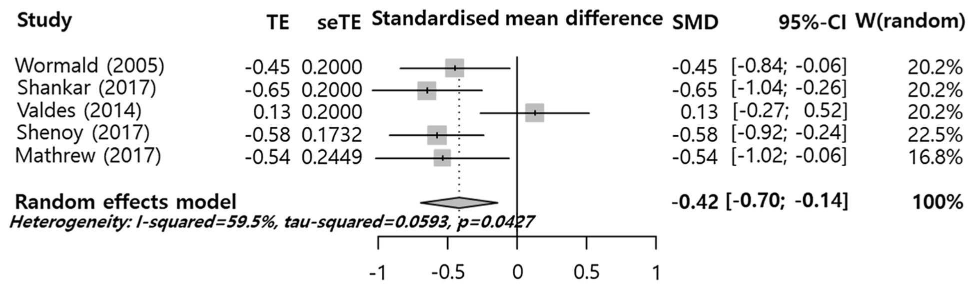

Fig. 2 Preoperative greater palatine canal injection of vasoconstrictor versus placebo: standard mean difference of endoscopic grade of nasal bleeding. *TE* treatment effect, *seTE* standard error of treatment effect

confidence interval 95% (CI) [−0.30, 0.27]), heart rate (SMD = −0.16; confidence interval 95% (CI) [−0.44, 0.11]), and concentration of end-tidal CO_2 (SMD = −0.01; confidence interval 95% (CI) [−0.29, 0.26]) (Fig. 3). Significant inter-study heterogeneity ($I^2 > 50\%$) was found at the endoscopic grading ($I^2 = 59.5\%$) except for intraoperative hemodynamic stability ($I^2 = 0\%$) (Figs. 2, 3).

The overall analysis did not consider the adrenaline concentration (1:80,000 versus 1:100,000 adrenalin). This omission is reflected in the high heterogeneity (more than 50%) of the results obtained by all studies. Only a single study [4] used a vasoconstrictor with 1:100,000 adrenaline and the others injected 1:80,000 adrenaline in the canal. In the subgroup analyses, the effect sizes differed considerably depending on the adrenaline concentration. The greater palatine injection with 1:80,000 adrenaline effectively improved the operative field visibility (SMD = −0.56; 95% CI [−0.75; −0.36]), but the injection with 1:100,000 adrenaline did not show significant effects (SMD = 0.13; 95% CI [−0.27; 0.52]). Therefore, this factor might be influencing the analyzed outcomes.

There were no severe adverse effects related to the vasoconstrictor or the injection procedure, such as severe hemodynamic instability needed for treatments. Valdes et al. [4] reported palatal discomfort caused by the topical administration post-operatively in 8 of 65 patients. Shenoy et al. [6] showed that 3 of 33 patients developed tachycardia immediately following the infiltration, but it subsided within 5–6 min without any active intervention. However, because these adverse effects were not consistent among the enrolled studies, there was not enough data to conduct the meta-analysis.

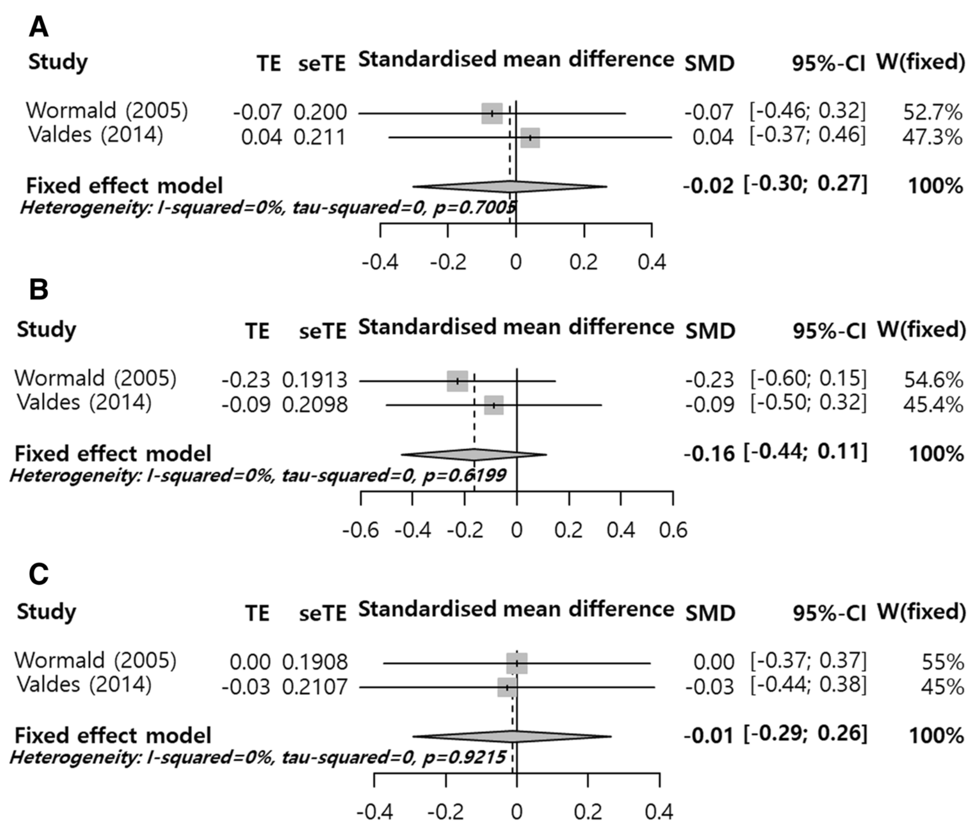

Fig. 3 Preoperative greater palatine canal injection of vasoconstrictor versus placebo: standard mean difference of intraoperative mean arterial pressure (**a**), heart rate (**b**), and concentration of end-tidal CO_2 (**c**)

Sensitivity analysis

Sensitivity analyses were conducted to assess the differences between the pooled estimates of endoscopic grading of bleeding and intraoperative hemodynamic stability by repeating the analyses while omitting a different study each time. The final results were consistent with those above (Fig. 4).

Discussion

The outcome of ESS depends on many factors, one of the most important being a clean surgical field during the procedure [9]. Because the sinonasal area has rich vascularization and narrow space, bleeding in the presentation of oozing, either slowly or quickly, usually causes unrealizable blood loss, is enough to limit the visual field, and increases the risk of several complications, like those in the skull base or orbital damage [10]. Additionally, bleeding increases the operation time due to multiple stops during surgery for suctioning and packing [11, 12]. In particular, because increased inflammation and vascularity are usually observed in cases of chronic rhinosinusitis, increased intraoperative bleeding was expected in these cases similar with the previous results of the positive correlation with bleeding during primary ESS [12].

GPC injections with vasoconstrictors and local anesthesia have been shown in many articles [3, 5–7, 13, 14]. Vasoconstrictors infiltrated into this space act on the third part of the maxillary artery as it enters the pterygopalatine fossa, which seems to lead to the vasospasm of the maxillary artery and decreases the amount of blood flow into the sphenopalatine artery, which causes a reduction in the blood flow to the nasal cavity mucosa [6]. With this mechanism, the reduction of blood loss provided good intraoperative endoscopic visibility despite having risks for tachycardia and hypertension. In addition, a sphenopalatine ganglion block with a local anesthetic also reduced the mucosal blood flow of the nasal sinuses and the turbinates as a result of blocking the effect of vasodilatory parasympathetic fibers of the sphenopalatine ganglion [15]. This procedure was used to control bleeding by many endoscopic sinus surgeons, but there was no universal consensus regarding its efficacy in achieving a good surgical field. There are studies that support a definite decrease in bleeding adopting these techniques as well as those which contradict the efficacy of the procedure [3–8]. Therefore, we evaluated the effect of GPC injections on the endoscopic bleeding grade and the adverse effects related to this procedure.

In our study, five studies were enrolled for review and meta-analysis. Wormald et al. [3] conducted the first prospective, blind, randomized controlled trials that evaluated the usefulness of the preoperative infiltration of epinephrine and lidocaine into the pterygopalatine fossa. They enrolled the 55 patients (24 women and 31 men) with a median age of 50 years (range 20–78 years) undergoing ESS due to CRS with ($n=25$) or without nasal polyp ($n=23$) and fungal sinusitis ($n=7$). Computer-generated randomization was used to determine which side the patient would receive their pterygopalatine fossa injection and which side of the nose would be operated on first. They revealed a significant improvement in the surgical field on the intervention side. There were no significant differences in heart rate, MAP, and end-tidal CO_2 concentration between both sides. Since then, several studies have reported similar experiences, with

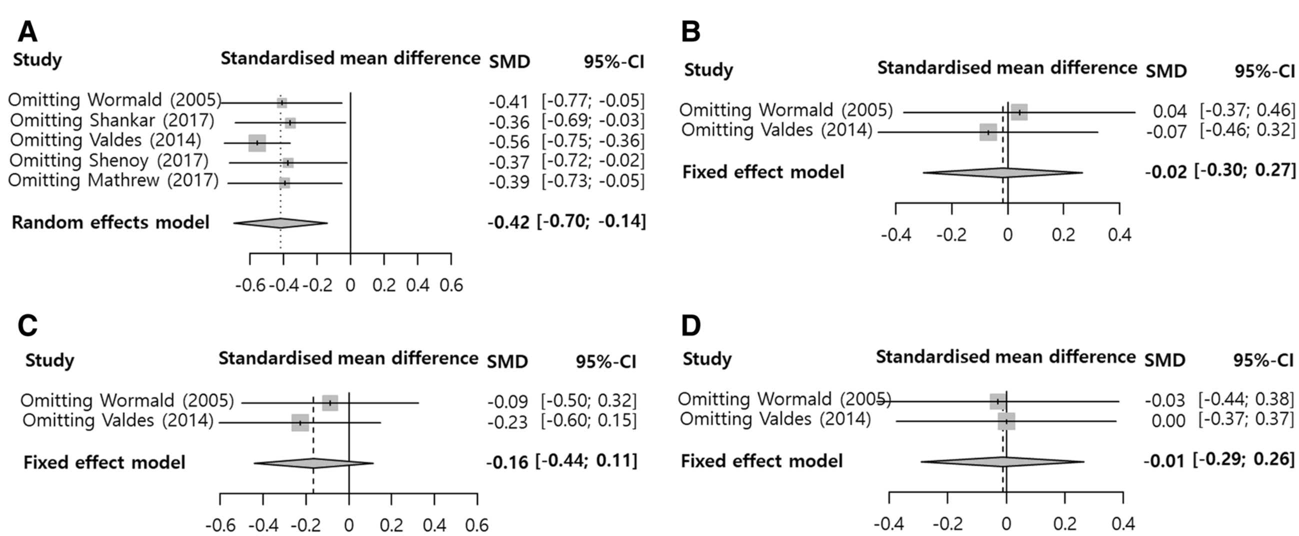

Fig. 4 Sensitivity analysis of endoscopic grade of nasal bleeding (**a**), intraoperative mean arterial pressure (**b**), heart rate (**c**), and concentration of end-tidal CO_2 (**d**)

particular reference to favorable surgical fields [5–7]. Shanker et al. [5] enrolled 55 patients (27 women and 28 men) with age range from 20 to 40 undergoing ESS due to CRS (not defined about the existence of nasal polyp). Randomization method was not defined. Their study showed a significant decrease in the operative bleeding on the blocked side.

In the study by Shenoy et al. [6], 68 patients (30 women and 38 men) with a mean age of 33 years (range 23–33 years) undergoing ESS due to CRS with ($n = 38$) or without nasal polyp ($n = 27$) and fungal sinusitis ($n = 3$) were included for assessing the effectiveness of GPC infiltration. The side of infiltration was selected randomly and the surgeon doing the procedure was blinded as to which side was infiltrated. There was a statistical significant improvement in the surgical field on the infiltrated side with almost 25–30% improvement in the surgical field. They recommended that the use of pterygopalatine fossa infiltration with lignocaine and adrenaline gives a comparatively better surgical field during ESS.

Mathew et al. [7] performed a randomized controlled trial assessing the effectiveness of pterygopalatine fossa infiltration of 2% xylocaine with adrenaline in controlling operative bleeding during ESS. They enrolled 32 patients (14 women and 18 men) with a mean age of 39 years undergoing ESS due to CRS with ($n = 17$) or without nasal polyp ($n = 13$) and fungal sinusitis ($n = 2$). The side of infiltration was selected by block randomization and the surgeon doing the procedure was blinded as to which side was infiltrated. There was a statistically significant improvement in the surgical field on the infiltrated side.

By contrast, in Valdes et al.'s study [4], 45 patients (15 women and 30 men) with a mean age of 48 years (range 29–74 years) undergoing ESS due to CRS with or without nasal polyp (patient number per disease was not defined) were included. Computer-generated randomization was used to determine the side on which the patient would receive the pterygopalatine fossa injection. There was no statistically significant difference in the surgical field grade between the injected and non-injected sides. They suggested that pterygopalatine fossa injection prior to functional endoscopic sinus surgery did not decrease intraoperative surgical field bleeding despite a safe procedure.

Through the systemic review, we identified that most of the enrolled studies found the favorable effect of GPC infiltration on the operative bleeding during ESS except a single study. Due to the inconsistency findings form the review, we conducted the meta-analysis for statistically summated results. Based on this analysis, we found that the endoscopic grading of bleeding significantly improved in the treatment group compared to the control group. A preoperative injection of a vasoconstrictor and local anesthesia into GPC inhibited the local tissue bleeding by decreasing the amount of blood flow into the sphenopalatine artery and blocking effect of the vasodilatory parasympathetic fibers of the sphenopalatine ganglion [5, 6, 15], which could explain the result that preoperative GPC injection appears to be a beneficial tool in improving ESS. Decreased blood flow in the nasal cavity would theoretically be expected to present high clinical effectiveness on surgical bleeding. Contrary to our expectation, the effect size for the assessments with respect to the endoscopic grading of bleeding was approximately 0.5, which would indicate that this effect was clinically small or moderately efficient during the ESS [16]. For this reason, a comparison of the results in all of the enrolled studies was conducted for the same patients. For example, the treatment group was one side and the control group was the other side. Therefore, infiltration to one side may gradually diffuse to the opposite side and also cause vasoconstriction on the other side via the extensive vascular anastomosis in the nasal mucosa. This could alter the results by falsely showing low bleeding on the control side [5]. This tendency was consistent with the results in the enrolled studies, which showed a small but significant reduction in bleeding during ESS using GPC injection [3, 5–7].

Additionally, subgroup analyses according to the concentration of adrenaline were used to reduce the heterogeneity and to evaluate for factors that could influence the results. The GPC injections had a different effect on surgical field bleeding according to the concentration of adrenaline. In the five studies, one study [4] with 1:100,000 adrenaline reported no significant difference between the injected and non-injected sides in terms of the endoscopic bleeding grade. By contrast, the other four studies administered 1:100,000 adrenaline, which showed that the GPC injection effectively, significantly decreased the surgical field bleeding and dropped the heterogeneity by 0% [3, 5–7]. Based on this subgroup analysis, the concentration of adrenaline would be the considerable factor to influence the outcome.

Adrenaline is known to be effective in preventing or minimizing blood loss during surgical procedures due to its vasoconstrictive effects. Additionally, it can reduce the absorption and systemic toxicity of local anesthesia [17]. Previously, it was shown that higher concentrations of adrenaline had a favorable effect on the prevention of bleeding [18]. However, adrenaline has significant side effects, such as the potential dose-related cardiac effects. It would be necessary to administer a minimum adrenalin dose to produce adequate hemostasis with minimal toxicity. Among the enrolled five studies, two doses of adrenaline, such as 1:80,000 and 1:100,000, were administered to provide the local bleeding control during ESS, although the only the study of Vales et al. used 1:80,000 adrenaline. Our analysis found that the severity of bleeding was influenced favorably by the increase of adrenaline concentration. Although Vales et al. could not explain the cause of the difference in result regarding surgical bleeding between their study and other studies [4], we could explain this discrepancy of results with a concentration of adrenaline.

Additionally, the increase in adrenaline concentration showed no significant side effects on blood pressure and the heart rate during surgery. In this meta-analysis, the side effects related to adrenalin or topical administrations were reported in two studies. Valdes et al. [4] reported postoperative palatal discomfort caused by the topical administration in eight of 65 patients. One study [6] presented that 3 of 33 patients complained transient tachycardia for several minutes not requiring any treatment. Considering the above mentioned, these results may suggest that the adverse effects of preoperative GPC injection would be minimal. However, whether the surgeon would use the dosage of administration of adrenaline should depend on the patient-specific medical factors and clinical requirements.

This study has some limitations. First, due to the characteristics of meta-analysis which performs systemic reviews of published studies, narrow standardization criteria would make the meta-analysis offer weak evidence for the use of treatments due to the lack of the enrolled studies. The previous many meta-analysis adopted wide inclusion criteria which enrolled all available trials at the time, regardless of the difference in treatments administered, and intended to perform a more powerful and precise estimation of the true effect size [19–22]. Therefore, this study also included analyses with broad standardization criteria (different local anesthetics and dose of epinephrine) that assessed the reduction in intraoperative bleeding. However, this study included only five studies and the sample size was small. These factors may have caused bias. Second, this analysis is performed based on the statistical measurements of the figure in the articles. So external factors such as patient characteristics or demographic factors, surgeon skill, pre, intra- and postoperative care, facility capacity and so on could not be reflected in the analysis, which could be the inevitable limitation. Considering these limitations, a large-sample, randomized, controlled clinical study should be performed to provide further evidence on the efficacy of the greater palatine canal (GPC) injections in ESS.

We concluded that GPC injections of local anesthesia with 1:80,000 adrenaline have a favorable effect on the prevention of bleeding. However, the effects of different adrenalin concentrations on clinical effects and vital criteria, such as heart rate and blood pressure during surgery, were not sufficiently observed. There were uncontrolled external factors and inclusion of some biased trials in our study. Considering the above mentioned, additional clinical trials are needed to confirm the results of this study and to establish preoperative guidelines.

Conclusion

This study demonstrated that preoperative GPC injections of local anesthesia with a vasoconstrictor regarding ESS reduced intraoperative bleeding effectively and that 1:80,000 was the adequate dose of adrenaline for the GPC injections. However, the standardized dosing needs further investigation and more trials need to be analyzed.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

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