Blood Loss During Endoscopic Sinus Surgery With Propofol or Sevoflurane

A Randomized Clinical Trial

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Importance: Total intravenous anesthesia (TIVA) with propofol has been associated with reduced operative time, decreased perioperative risks, and decreased intraoperative blood loss compared with inhalational anesthesia (IA). During endoscopic sinus surgery (ESS), reduced bleeding from the mucosal surfaces could improve visualization of the anatomy and decrease the risk of serious complications.

Objective: To compare blood loss during ESS between patients receiving TIVA with propofol and those receiving IA with sevoflurane.

Design, Setting, and Participants: Prospective, randomized study of 33 patients undergoing ESS in an academic medical center.

Interventions: Patients received either TIVA or IA.

Main Outcomes and Measures: The primary outcome was rate of blood loss in milliliters per hour. The secondary outcomes included the quality of visibility measured by the surgeon's numeric rating score, ease of anesthesia as measured by the anesthesiologist's numeric rating score, and total blood loss.

Results: The mean (SEM) blood loss per hour in the TIVA group was 78.5 (14) mL/h, and in the IA group it was 80.3 (17) mL/h (P = .93). A post hoc subgroup analysis found that in patients with a Lund-Mackay score of 12 or lower, the propofol TIVA group had a lower rate of blood loss compared with the sevoflurane IA group (mean blood loss, approximately 18 mL/h vs approximately 99 mL/h). The anesthesiologist's numeric rating score was significantly higher (indicating greater ease of performance) in the IA group than in the TIVA group. There was no statistically significant difference in the surgical numeric rating score between the 2 groups.

Conclusions and Relevance: In this comparative study, our results did not show any difference in blood loss and surgical conditions between the TIVA and IA groups. Even further study is not likely to show a difference in blood loss between TIVA and IA during ESS.

During endoscopic sinus surgery (ESS), bleeding from the mucosal surfaces can interfere with visualization of the anatomy and increase the risk of serious complications such as orbital or skull-base injury with resultant cerebrospinal fluid leak. In addition, reduction of bleeding could result in greater ease and thoroughness of the sinus surgery owing to better visibility.

There are multiple factors that contribute to blood loss during surgery, including, but not limited to, surgical and anesthesia technique. Historically, several ways have been used to minimize intraoperative bleeding. One of those is controlled hypotension (keeping the mean arterial pressure [MAP] between 50 and 60 mm Hg) achieved by the use of anesthetic agents alone or in combination with either sodium nitroprusside or esmolol drips. This technique, however, has been associated with increased morbidity and mortality. There is also good evidence that decreasing the MAP below 70 mm Hg can even increase intraoperative bleeding owing to local arteriolar vasodilation, which results from decreased blood flow to the tissues, increased local carbon dioxide concentration, and decreased pH. Other techniques that improve the surgical conditions during ESS include positioning the patient in the reverse Trendelenburg position, decongesting the nose, blocking the neurovascular bundles, and infiltrating the nasal mucosa with a local anesthetic with epinephrine.

In some studies, total intravenous (IV) anesthesia (TIVA) with propofol compared with inhalational anesthesia (IA) has been associated with reduced operative time and decreased perioperative risks. In studies from other surgical specialties, propofol has been shown to decrease in-
traoperative blood loss. The disadvantages associated with using a TIVA technique over an IA technique include increased chance of error in programming the pump and the danger of IV infiltration resulting in an unexpected lessening of anesthesia depth.

Our aim was to compare the rate of blood loss in patients undergoing ESS between a group receiving TIVA and one receiving IA in a prospective randomized clinical study.

**METHODS**

**PATIENTS**

We recruited 33 consecutive patients older than 18 years. Written informed consent was obtained from each patient who enrolled in the study. The trial was approved by the institutional review board of the University of Chicago and registered at clinicaltrials.gov (NCT01014728). One patient with asthma was not recruited because the attending anesthesiologist preferred to use an inhalation technique.

Included patients had chronic rhinosinusitis with or without nasal polyps, were scheduled to undergo elective ESS, and had American Society of Anesthesiologists (ASA) physical status of 1 (otherwise healthy patient) or 2 (patient with mild systemic disease). Exclusion criteria included pregnancy, any ASA designation greater than 2, and preoperative use of nonsteroidal anti-inflammatory medications or aspirin within the previous week. Patients were also excluded if they exhibited an abnormal coagulation profile (platelet count <50 × 10^9/L, partial thromboplastin time [PTT] >50 seconds, or international normalized ratio [INR] >1.3) on preoperative testing.

Patients were randomized in blocks of 4 to either receive TIVA with propofol or IA with sevoflurane. A randomized code was generated a priori. Patients were assigned to the next sequence at the time of surgery. We believed that it was impractical to blind the anesthesiologists.

**PROCEDURES AND TESTS**

Preoperatively, we drew blood for hemoglobin concentration, platelet count, prothrombin time, PTT, INR and platelet function assay (PFA-100). Platelet function was assessed using the platelet function analyzer, which monitors the blood flow through an aperture cut in a membrane coated with collagen and epinephrine (Col-Epi) or collagen and adenosine diphosphate (Col-ADP). The time for the platelets to occlude the membranes is measured in seconds, which is analogous to the bleeding time. The reason for using both of these tests is to increase the sensitivity, with Col-Epi being more sensitive than Col-ADP in detecting platelet function defects.

**ANESTHESIA TECHNIQUE**

Patients in both groups received 1 to 2 mg of midazolam and 1 to 3 μg/kg of fentanyl. Induction included 20 to 40 mg of lidocaine and 1 to 2 mg/kg propofol followed by 0.05 to 0.10 mg/kg of IV vecuronium. After induction, the TIVA group received an infusion of propofol (100-200 μg/kg/min), whereas the IA group received sevoflurane, 1% to 3%. Both groups received fentanyl. The patients’ MAPs were maintained at 70 to 80 mm Hg by adjusting either the propofol or the sevoflurane concentration within their range (1%-3% for sevoflurane and 100-200 μg/kg/min for propofol). If these modifications were not successful in achieving the target MAPs, then esmolol was added (10-20 mg every 5-10 minutes, as needed).

**SURGICAL CONSIDERATIONS**

Each patient was positioned supine with 6 degrees of reverse Trendelenburg for the entire procedure. Local vasoconstriction was performed first with bilateral endonasal application of oxymetazoline-soaked pledgets for 2 minutes followed by topical application of cocaine, 4%, to block the sphenopalatine and anterior ethmoid neurovascular bundles. Lidocaine, 1%, with 1:100,000 epinephrine was then injected into the lateral nasal wall mucosa in the osteomeatal unit and into the mucosa over the sphenopalatine recess and into all polyps. Patients who required a septoplasty and/or inferior turbinate somnoplasty had additional mucosal injections of local anesthesia into the septum and/or the turbinates. The computed tomographic (CT) scans of all patients were reviewed, and severity of sinus disease rated using the Lund-Mackay (LM) scoring system. In this system, the sinuses are scored according to their degree of opacification (0, no opacification; 1, partial opacification; or 2, obstruction), and the obstruction of the osteomeatal complexes is also scored (0, no obstruction; 2, obstruction). The LM score represents the total score of both the sinuses and bilateral osteomeatal complexes, with a minimum of 0 and a maximum of 24.

**OUTCOME MEASURES AND STATISTICAL ANALYSIS**

The primary outcome variable was estimated blood loss in milliliters per hour. This was calculated by subtracting the volume of total irrigation used during the case from the total amount of fluid in the suction canister at the end of surgery and dividing by surgical time in hours. We also calculated blood loss by collecting in suction canisters that contained 5 mL of 1:250,000 heparin. Hemoglobin concentration was measured from the suction canisters and the blood samples obtained from the patients at baseline. We calculated blood loss using the following formula: blood loss in milliliters = (hemoglobin concentration of the suction canister (grams per deciliter) × volume of the suction canister (milliliters)/serum hemoglobin concentration at time zero (grams per deciliter)).

An accurate power analysis could not be performed prior to starting the study because there is controversy in the literature. For this reason, the power analysis was inferred based on the estimated difference in the mean of blood loss between the groups (110 mL) and an estimated standard deviation of the mean between the 2 groups (150 mL). These assumptions led to N=40 as the number of subjects to be studied to meet the power calculation.

Secondary outcomes included surgeon assessment of bleeding and visibility and the anesthesiologist assessment of the ease of the anesthesia technique. The surgeon’s numeric rating scale (SNRS) rated the surgical conditions (mucosal bleeding and visibility) on a scale ranging from 0 to 10, with 0 defined as caudaveric conditions and 10 as severe bleeding requiring constant suction. The anesthesiologist also used a numeric rating scale (ANRS) to rate the ease of the anesthesia technique ranging from 0 to 10 (10 is best, 0 is worst). The ANRS was the general subjective score given by the anesthesiologist at the end of surgery and before emergence. It particularly focused on the ease of the anesthesia technique for both medication dispensation during surgery and hemodynamic control. The score was not influenced by emergence time because it was scored at the end of surgery and prior to extubation.

Data from the objective outcomes were normally distributed and were compared between groups using the unpaired t-test. Data from the subjective outcome measures were not normally distributed and were compared using the Mann-
Table 1. Demographic and Baseline Characteristics of Subjects in Both Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Intravenous (n = 18)</th>
<th>Inhalational (n = 15)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>41.3 (4.0)</td>
<td>43.4 (4.0)</td>
<td>.72</td>
</tr>
<tr>
<td>Men, No. (%)</td>
<td>9 (50)</td>
<td>8 (53)</td>
<td>.96</td>
</tr>
<tr>
<td>BMI</td>
<td>30.3 (1.7)</td>
<td>30.3 (2.0)</td>
<td>.77</td>
</tr>
<tr>
<td>Primary surgery, No. (%)</td>
<td>8 (44)</td>
<td>10 (66)</td>
<td>.80</td>
</tr>
<tr>
<td>Preoperative laboratory values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothrombin time, seconds</td>
<td>13.5 (0.2)</td>
<td>13.6 (0.3)</td>
<td>.87</td>
</tr>
<tr>
<td>Partial thromboplastin time, seconds</td>
<td>28.1 (0.4)</td>
<td>28.8 (0.7)</td>
<td>.43</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>1.60 (0.01)</td>
<td>1.10 (0.03)</td>
<td>.68</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.8 (0.4)</td>
<td>13.7 (0.5)</td>
<td>.90</td>
</tr>
<tr>
<td>Platelet count, ×10^3/µL</td>
<td>0.2294 (0.0128)</td>
<td>0.2519 (0.0144)</td>
<td>.36</td>
</tr>
<tr>
<td>PFA-100, mean, seconds</td>
<td></td>
<td></td>
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<tr>
<td>Col-ADP</td>
<td>142.75</td>
<td>127.93</td>
<td>.49</td>
</tr>
<tr>
<td>Col-Epi</td>
<td>95.75</td>
<td>83.29</td>
<td>.36</td>
</tr>
<tr>
<td>Lund-Mackay score</td>
<td>13.9 (1.3)</td>
<td>12.9 (1.1)</td>
<td>.53</td>
</tr>
<tr>
<td>Septoplasty, No. (%)</td>
<td>4 (22)</td>
<td>4 (26)</td>
<td>.95</td>
</tr>
</tbody>
</table>

Abbreviations: ANRS, anesthesia numeric rating score; SNRS, surgeon numeric rating score.

Of the 35 patients originally screened, 33 patients were actively enrolled in the study. One patient refused to enroll, and 1 patient with asthma was not randomized because the anesthesiologist believed that IA would be more appropriate. Eighteen received TIVA with propofol, and 15 received IA with sevoflurane. The demographic information, preoperative test results (prothrombin time, PTT, INR, hemoglobin level, platelet count, and PFA-100), and the LM CT scores were not significantly different between the 2 groups (Table 1). Furthermore, a comparable proportion of patients underwent septoplasty in each group. The mean (SEM) amount of fentanyl given in the IA group was 235 (82) µg, compared with 225 (75) µg in the TIVA group (P = .75). Only 1 patient in the TIVA group received esmolol. The MAP in the TIVA group (88 [30] mm Hg) vs that in the IA group (81 [10] mm Hg) was not significantly different (P = .36). The mean heart rate during surgery in the TIVA group (72 [13] bpm) vs IA group (75 [9] bpm) was not significantly different (P = .57). There were no complications, and all surgical procedures reached their intended end points.

We compared the results between estimated and calculated blood loss in the 13 subjects who had both. The mean estimated and calculated blood loss in these patients was 195 and 184 mL, respectively. This difference was not statistically significant (P = .81), thus supporting the validity of using estimated blood loss as the primary outcome for the study. We could not obtain both estimated and calculated blood loss in all patients because blood clotted in the canisters despite the addition of heparin prior to surgery, and so the laboratory could not make measurements in many patients. Our initial plan was to use both methods in every patient, but the clotting prevented us from doing so on a consistent basis.

Our results show no statistically significant difference in operative time, duration of anesthesia, estimated blood loss, and rate of blood loss per hour between the groups receiving TIVA or IA (Table 2). The mean (SEM) estimated rate of blood loss (milliliters per hour) for TIVA was 78.5 (14.0) mL/h, and for IA, it was 80.3 (17.0) mL/h (P = .93). The median anesthesia numeric rating score was 7.0 in the TIVA group and 8.9 in the IA group (P = .002), suggesting that the anesthesiologist thought that IA was an easier technique. The SNRS was not statistically different between the 2 groups (P = .46), suggesting that the anesthesia technique did not affect the performance of the surgical procedure (Table 2).
In this randomized clinical study, we found no significant difference in the primary outcome, rate of blood loss (in milliliters per hour), or the secondary outcomes, total estimated blood loss and subjective measurement of endoscopic visualization (SNRS), between patients who received TIVA with propofol vs IA with sevoflurane.

We therefore ran a futility analysis based on our data for the rate of estimated blood loss per hour of surgical time. Given the small difference we found in this parameter between groups (2.5%), and given the relatively large standard deviation obtained, 943 patients would be required in each group (total N = 1866) using a nonpaired t-test for the comparison, to show a statistically significant difference between the 2 techniques (α = 0.05) with a power of 0.8. We are suggesting, on the basis of our data, that a very large sample would be needed to show a significant difference between the 2 anesthesia techniques, which would not be clinically relevant; therefore, performing a new study or continuing our present study would be futile.

Studies in the literature have been conflicting regarding the effect of TIVA in ESS. Some results demonstrate a positive effect of TIVA on intraoperative blood loss and endoscopic visualization. These studies compared TIVA with propofol to sevoflurane or isoflurane. In contrast, our study is consistent with other studies that demonstrated no difference in estimated blood loss and subjective measurement of endoscopic visualization between the 2 techniques.

Manola et al compared TIVA vs IA with either sevoflurane or isoflurane. Their results showed that the blood loss and the surgeon’s visual endoscopic score with TIVA or sevoflurane were significantly better than with isoflurane. Similar to our results, they showed no statistically significant difference between the group that received TIVA with propofol and the group that received sevoflurane.

Some studies have indicated a better hemodynamic profile (controlled blood pressure and heart rate) in patients receiving TIVA with propofol than in patients receiving IA with sevoflurane or isoflurane. However, Yoo et al. in a more recent prospective randomized study of 60 patients, did not find any significant difference between the patients’ hemodynamic profile (mean blood pressure and heart rate) and the surgical grading scores between patients who received propofol/remifentanil, sevoflurane/remifentanil, or desflurane/remifentanil combination anesthesia drugs. Ankichetty et al. in a randomized controlled study involving 40 patients, reported no difference between controlled hypotension, blood loss, and operative field conditions between the group of patients who received TIVA and the group that received IA with isoflurane. Changes in the hemodynamic profile are not likely to have had any effect on our results because the MAP was maintained at 70 to 80 mm Hg in both groups.

Our study contradicts the findings of Ahn et al., who stratified patients into severity by LM score and administered TIVA to 20 patients and sevoflurane to 20 others. They also used the narcotic remifentanil (as opposed to fentanyl, which was used in our study) for both groups. They compared intraoperative mean hazard ratio, MAP, local anesthesia, duration of surgery, and rate of remifentanil infusion. In their groups, there was a significant difference between the mean hazard ratio (lower in the propofol group) vs the sevoflurane group. Only in the higher LM group (>12) did they find statistical significant difference between TIVA and sevoflurane in terms of both subjective and objective blood loss. They had significantly higher blood loss in milliliters per hour in the sevoflurane group. They concluded that because both groups received remifentanil, the propofol may be the reason for the good hemodynamic profile (lower heart rate) that could explain the decreased blood loss.

Our study did not show a statistically significant difference in either rate of blood loss (milliliters per hour) or the surgical numerical rating score between the 2 groups in patients with LM scores higher than 12. In the subset of patients with LM scores of 12 or lower, our patients receiving IA had a statistically significant higher rate of blood loss than the patients receiving TIVA. This differed from the results by Ahn et al., who reported no statistically significant difference in blood loss between the 2 groups in this subset of patients with milder disease.

In the study by Ahn et al. and in most other studies that report a beneficial effect of propofol, patients received remifentanil instead of fentanyl, which is infused continuously rather than in boluses. The pharmacokinetic profile of remifentanil may have added to the positive effect, with less bleeding in the TIVA/remifentanil...
group. This beneficial effect of remifentanil has been reported in the literature. In addition to having a shorter half-life and good hemodynamic profile, remifentanil has shown to offer a superior intraoperative hemodynamic stability during stressful surgical events, and only minor blood loss was found in a retrospective study comparing it with fentanyl.

There are several limitations to our study. The sample size was relatively small, but as shown by the futility analysis, a larger study would have been unlikely to lead to a meaningful positive result. The MAP and the heart rate were not different between the groups. This has been a controversial issue, with some studies reporting a benefit with the use of TIVA on intraoperative circulatory parameters; a recent prospective randomized study reported no difference in the circulatory parameters between TIVA and sevoflurane.

Given the controversy regarding the potential beneficial effect of remifentanil, our study would have better clarified this issue had we included a third group using propofol and remifentanil. This would have further decreased our sample size and would have increased the cost (remifentanil is 4 times more costly than fentanyl!). We would have been better served by using a validated scale of the surgical field, but this would not have affected the overall outcome.

Randomization is the most important factor in a study. The randomization worked well in that the groups were well matched for multiple parameters. Because it is difficult to blind this study, we chose not to. In addition, the lack of a difference between the 2 groups in terms of blood loss could be attributed to the other measures we took to reduce bleeding. These include controlling the MAP, using reverse Trendelenburg positioning, applying topical oxymetazoline before and during the procedure, and injecting local anesthetics with epinephrine.

In summary, our study results do not support a significant difference in rate of blood loss (in milliliters per hour) or subjective measure of endoscopic visualization between the group receiving TIVA with propofol and the group receiving IA with sevoflurane. These results can be considered in the preoperative discussion of anesthesia technique preferences between the surgeon and the anesthesiologist.