Original contribution

The effect of intravenous tranexamic acid on blood loss and surgical field quality during endoscopic sinus surgery: a placebo-controlled clinical trial☆,☆☆

Mahzad Alimian MD (Assistant Professor of Anesthesiology and Intensive Care)*, Masood Mohseni MD (Assistant Professor of Anesthesiology and Intensive Care)

Department of Anesthesiology, Rasul Akram Hospital, Tehran University of Medical Science, Tehran, Iran

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Abstract

Study Objectives: To evaluate the effects of intravenous (IV) tranexamic acid on blood loss and surgical field quality during functional endoscopic sinus surgery (FESS).

Design: Randomized, double-blinded, controlled trial.

Setting: Operating room and postoperative recovery area of a university-affiliated hospital.

Patients: 84 consecutive, adult, ASA physical status 1 and 2 patients undergoing FESS.

Interventions: Patients were randomized to receive either IV tranexamic acid 10 mg/kg (TA group) or sterile water 0.1 mL/kg (placebo group) as a bolus dose immediately after induction of anesthesia.

Measurements: Amount of blood loss and bleeding and satisfaction scores were obtained from the surgeon.

Main Results: Blood loss in the TA group was 184 ± 64 mL and in the placebo group, 312 ± 75 mL on average (P < 0.01). The median (range) bleeding score in the TA group was significantly lower than the placebo group [2 (1-3) vs 2.5 (2-4); P < 0.0001]. The surgeon was more satisfied with the surgical field in the TA group than the placebo group [median score: 4 (3-5) vs 3 (1-5), P < 0.001].

Conclusion: Intravenous tranexamic acid effectively reduces bleeding and improves the surgical field during FESS.

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1. Introduction

Bleeding during functional endoscopy sinus surgery (FESS) remains a challenge for both surgeons and anesthesiologists [1]. Although major blood loss during FESS is rare, maintaining an optimal surgical field is crucial for the surgeon; even a small amount of blood may disturb the endoscopic view, increasing the likelihood of complications, lengthening the operative procedure, and possibly resulting in incomplete surgery [2].
Several techniques have been suggested to improve the surgical field in sinus surgery. Bipolar diathermy, packing, topical vasoconstrictors, and induced hypotension are among the most commonly used techniques [2-4]. Of these, diathermy may result in local tissue damage and subsequent bleeding [2]. Topical vasoconstrictors may result in hemodynamic instability, especially in patients with a history of hypertension or ischemic heart disease. Induced hypotension exposes patients to more anesthetic drugs and consequently their side effects. Furthermore, none of these drugs consistently provides a desirable bloodless field for the surgeon.

Earlier studies have confirmed the favorable effects of antifibrinolytics, including tranexamic acid, on bleeding tendency in patients undergoing cardiac, major orthopedic, transplantation, and prostate surgeries [5,6]. Of particular interest is the increasing use of tranexamic acid by oral surgeons in the form of mouthwash for dental extractions [7,8] and in the management of epistaxis with hereditary hemorrhagic telangiectasia [9,10]. Only two studies have reported the efficacy of topical [11] and oral [12] forms of tranexamic acid in achieving hemostasis and improving the surgical field in nasal surgeries, including FESS. In this study, the efficacy of intravenous (IV) tranexamic acid in reducing bleeding associated with nasal surgery (ie, FESS) was examined.

2. Materials and methods

2.1. Patients

This prospective study was approved by the Tehran University Ethics Committee and written, informed consent was obtained from all patients. Between June 2008 and February 2009, a total of 84 ASA physical status 1 and 2 patients, aged 19 to 64 years, and undergoing FESS for chronic sinusitis, were enrolled in the study. Patients receiving anticoagulants or having a bleeding diathesis were excluded. Patients were randomly allocated to receive either 10 mg/kg of IV tranexamic acid (Rasht Pharmaceutical Co., Rasht, Iran; TA group) or sterile water 0.1 mL/kg (placebo group) as a bolus dose immediately after induction of anesthesia.

2.2. Anesthesia and surgery protocols

All patients were premedicated with oral oxazepam 10 mg two hours before surgery, then IV fentanyl 4 μg/kg and lidocaine 1.5 mg/kg three to 5 minutes before intubation. After the application of 100% oxygen at 5 L/min for 5 minutes, anesthesia was induced with propofol 2.0 mg/kg and atracurium (0.5 mg/kg). After tracheal intubation, anesthesia was maintained with propofol 100 μg/kg/min, remifentanil 0.1 μg/kg/min, and atracurium. Controlled mechanical ventilation with an initial tidal volume of 10 mL/kg and respiratory rate of 10 breaths/min was adjusted to maintain normocapnia. At the end of anesthesia, muscle relaxation was reversed with neostigmine 0.04 mg/kg and atropine 0.02 mg/kg. Before induction of anesthesia, all patients received isotonic crystalloid 3.0 mL/kg for volume expansion. During surgery, maintenance fluids were standardized for patients based on their weight, and blood loss was replaced with Ringer’s lactate in a 3:1 ratio. None of the patients required transfusion of blood products.

The same anesthesia and surgical teams performed all procedures using the same technique. Based on the study protocol, none of the patients received preoperative or intraoperative local vasoconstrictors. Cutting forceps and grabbing instruments were used, but a microdebrider was not used for any procedure included in the study.

2.3. Assessment of blood loss, surgical field quality, and other covariates

Intraoperative blood loss was estimated by the attending anesthesiologist at the end of surgery by accounting for loss of blood and irrigation fluid in the 25 mL-graded suction canister, and nasopharyngeal packing (measured weight of packing on the electronic scale). Moreover, at the end of a surgery, the surgical field was graded in terms of bleeding by the surgeon using the scale used by Boezaart et al in 1995 (Table 1) [13]. The surgeon’s satisfaction with surgical field quality was also graded in a 5-item Likert scale, where 1 = poor and 5 = excellent. Hemodynamic parameters, including systolic and diastolic arterial blood pressure (BP), and heart rate (HR) were recorded at 15-minute intervals. Prothrombin time, partial thromboplastin time, and complete blood count were measured before surgery and 6 hours postoperatively.

The occurrence of possible side effects of treatment such as nausea and vomiting was evaluated in the post-anesthesia care unit (PACU). Patients stayed in the hospital

<table>
<thead>
<tr>
<th>Grade</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No bleeding (cadaveric conditions).</td>
</tr>
<tr>
<td>1</td>
<td>Slight bleeding: no suctioning required.</td>
</tr>
<tr>
<td>2</td>
<td>Slight bleeding: occasional suctioning required.</td>
</tr>
<tr>
<td>3</td>
<td>Slight bleeding: frequent suctioning required. Bleeding threatens surgical field a few seconds after suction is removed.</td>
</tr>
<tr>
<td>4</td>
<td>Moderate bleeding: frequent suctioning required and bleeding threatens surgical field directly after suction is removed.</td>
</tr>
<tr>
<td>5</td>
<td>Severe bleeding: constant suctioning required; bleeding appears faster than can be removed by suction; surgical field severely threatened and surgery usually not possible.</td>
</tr>
</tbody>
</table>

Table 1: Boezaart et al grading scale for scoring of surgical field bleeding [13]
for at least 24 hours, and then returned three days after surgery to have the nasopharyngeal packing removed. Postoperative epistaxis and clinical evidence of thrombus development were recorded at the time of discharge and three days postoperatively.

2.4. Blinding

Randomization was performed by the hospital pharmacy using a table of random numbers. The hospital pharmacy provided the medications (tranexamic acid or sterile water) in similar syringes labeled only with each patient’s record number. The surgeon, anesthesiologist, and anesthetic technician who were involved in the surgery and patient care were blinded to the nature of the study assignments.

2.5. Statistical analysis

Data are presented as means (standard deviation), medians (ranges), or percentages, as appropriate. Baseline characteristics of the two groups were analyzed with Student’s t-test for continuous data and Chi-square test for categorical analysis. Repeated measures of BP and HR were analyzed with repeated measures analysis of variance. Ranked data, including bleeding and satisfaction scores, were compared between groups with the Mann-Whitney U test. All comparisons were two-tailed. P-values < 0.05 were considered statistically significant. Statistical analyses were performed with SPSS version 11.0 software (SPSS, Inc., Chicago, IL, USA).

2.6. Power analysis

Calculation of required sample size was performed with respect to bleeding score using a nomogram. For sample size estimation, we calculated a standardized difference for our target variable (bleeding score) using the \([\frac{(p_1-p_2)}{\sqrt{p_m(1-p_m)}}]\) formula, where \(p_m = (p_1+p_2)/2\), \(P = \text{Boezaart bleeding score}\), and \(p_1\) and \(p_2\) = 0.6 and 0.2, respectively. The assigned \(p_1\) value was considered based on an overall literature review and \(p_2\), on the basis of an unpublished earlier pilot study. With a power of 80% and \(\alpha\) level of 0.05 for two-tailed statistical analysis, a sample size for each group of at least 42 patients each (total of 84 pts) was calculated as being appropriate.

3. Results

A total of 84 patients (49 men and 35 women) with a median age of 35 years (range, 19–64 yrs) were enrolled in the study. No significant differences were noted between the groups regarding demographic data and coagulation profile (Table 2). Fig. 1 shows similar trends in mean arterial pressure and HR in the two groups (\(P > 0.05\)).

### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>TA group</th>
<th>Placebo group</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>33 (13)</td>
<td>35 (12)</td>
<td>0.54</td>
</tr>
<tr>
<td>Male gender (N; %)</td>
<td>25 (59.5)</td>
<td>24 (57.1)</td>
<td>0.99</td>
</tr>
<tr>
<td>Platelet count (1,000/mm(^3))</td>
<td>263 (58)</td>
<td>271 (79)</td>
<td>0.81</td>
</tr>
<tr>
<td>Preoperative PT (sec)</td>
<td>12.2 (1.3)</td>
<td>12.1 (1.1)</td>
<td>0.67</td>
</tr>
<tr>
<td>Preoperative PTT (sec)</td>
<td>31.3 (2.9)</td>
<td>32.1 (3.2)</td>
<td>0.43</td>
</tr>
<tr>
<td>Postoperative PT (sec)</td>
<td>12.4 (1.7)</td>
<td>12.5 (1.5)</td>
<td>0.87</td>
</tr>
<tr>
<td>Postoperative PTT (sec)</td>
<td>34.2 (3.1)</td>
<td>33.4 (2.7)</td>
<td>0.67</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>84.2 (27.1)</td>
<td>91.1 (19.2)</td>
<td>0.21</td>
</tr>
<tr>
<td>Bleeding score (N; %)</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9 (21.4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>27 (66.3)</td>
<td>21 (50.0)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6 (14.3)</td>
<td>18 (42.9)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0 (0)</td>
<td>3 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Satisfaction score (N; %)</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0 (0)</td>
<td>2 (4.8)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0 (0)</td>
<td>4 (9.5)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>9 (21.4)</td>
<td>16 (38.1)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>18 (42.9)</td>
<td>16 (38.1)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>15 (35.7)</td>
<td>4 (9.5)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as means (standard deviation). The TA group received intravenous tranexamic acid 10 mg/kg as a bolus dose immediately after induction of anesthesia. The placebo group received sterile water 0.1 mL/kg as a bolus dose immediately after induction of anesthesia. PT = prothrombin time, PTT = partial thromboplastin time.

Blood loss in the TA group was 184 ± 64 mL and in the placebo group, 312 ± 75 mL (\(P < 0.01\)). In the surgeon’s opinion, the median (range) bleeding score in the TA group was significantly lower than that of the placebo group [2 (1-3) vs 2.5 (2-4); \(P < 0.0001\)]. The data showed that in 21.4% of patients given tranexamic acid, no suctioning was required during the surgery compared with none of the patients in the placebo group. Moderate bleeding requiring frequent suctioning occurred in 7.1% of the placebo group [median score: 4 (3-5) vs 3 (1-5); \(P < 0.001\)].

In the first three days after surgery, epistaxis requiring intervention was reported only in one patient in the placebo group. There were no significant changes in patients’ postoperative coagulation parameters (Table 2). None of the study patients showed signs or symptoms of thromboembolic events. Early postoperative nausea but not vomiting was reported in 14.3% of the TA and 9.5% of the placebo group (\(P > 0.05\)).

4. Discussion

The results of this study verify the efficacy of IV tranexamic acid in rendering a bloodless surgical field during FESS. This finding was independent of demographic...
characteristics or hemodynamic variables. To prevent the introduction of confounding factors, all operations were performed by the same surgical team using the same technique. This is in accordance with earlier studies appreciating the use of topical[11] and oral[12] tranexamic acid in nasal surgery.

Tranexamic acid inhibits fibrinolysis by blocking the lysine binding sites of plasminogen to fibrin. It has been proposed that therapeutic plasma concentrations of tranexamic acid (5 -10 mg/L) may be achieved with an IV bolus dose of 10 mg/kg followed by an infusion of 1.0 mg/kg/hr during extracorporeal circulation in cardiac surgery[14], and the therapeutic concentration of tranexamic acid is maintained for approximately three hours[15]. Considering the relatively short duration of FESS, we assumed that a single bolus dose of TA 10 mg/kg would fulfill our therapeutic goal.

The reported side effects of tranexamic acid mainly include nausea, vomiting, and possibly arterial or venous thrombosis. Early postoperative nausea was reported in less than 15% of our TA group patients, which did not differ significantly from the placebo group. Clinical evidence of arterial or venous thrombosis was not detected in any of our patients. Of note, the risk of thrombosis, although theoretically possible, has not been confirmed in any randomized controlled studies[5]. Moreover, isolated case reports considered much higher doses of tranexamic acid and mostly continued the medication in the postoperative period, rather than as a single low-dose treatment[5].

In addition to estimating the amount of blood loss, we used a validated scale to evaluate surgical field quality and satisfaction of the surgical team. The latter measurement modalities even more accurately reflected the efficacy of hemostatic interventions, in that the direct objective of anesthesia in FESS is to render an optimal surgical field rather than to reduce blood loss. Recently, a multi-center standardized reliability analysis verified the interobserver and intraobserver reliability of the Boezaart scale[16].

4.1. Limitations

We did not address the severity of sinus disease in our patients because our surgical team does not routinely use validated relevant scales such as the Kennedy staging system. However, all patients in this survey were first-time candidates of two-sided FESS due to chronic sinusitis.

In regard to the efficacy and safe therapeutic profile of tranexamic acid, we recommend its use in otherwise healthy candidates for sinus surgery. Further large-scale clinical trials are required to address the optimal dose and application method.

Acknowledgment

We would like to thank our surgeon, “Dr Shabahang Mohammadai”, and his assistants for their contribution to this study.

References

IV tranexamic acid reduces bleeding in FESS


