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Meta-Analysis
Orthognathic Surgery

The efficacy of tranexamic acid for orthognathic surgery: a meta-analysis of randomized controlled trials

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Abstract. The efficacy of tranexamic acid in orthognathic surgery remains controversial. We conducted a systematic review and meta-analysis to explore the influence of tranexamic acid on blood loss for orthognathic surgery.

We performed a search of PubMed, Embase, Web of science, EBSCO, and Cochrane library databases through October 2017 for randomized controlled trials (RCTs) assessing the effects of tranexamic acid versus placebo on orthognathic surgery. Meta-analysis was performed using the random-effects model.

Six RCTs were included in the meta-analysis. Overall, compared with placebo in orthognathic surgery, tranexamic acid administration results in significantly decreased blood loss [mean difference (MD) = −159.73; 95% confidence interval (CI) = −236.42 to −83.03; $P < 0.0001$], and higher postoperative haemoglobin (MD = 0.71; 95% CI = 0.11 to 1.31; P = 0.02), but has no remarkable impact on postoperative haematocrit (MD = 1.23; 95% CI = −1.22 to 3.69; P = 0.33) and operation time (MD = −2.35; 95% CI = −18.05 to 13.36; P = 0.77). In addition, patients with orthognathic surgery need decreased amounts of irrigant fluid (MD = −229.23; 95% CI = −399.63 to −58.83; P = 0.008) after using tranexamic acid.

We concluded that tranexamic acid promotes the bleeding control in orthognathic surgery.

Key words: tranexamic acid; orthognathic surgery; blood loss; systematic review; meta-analysis.

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Orthognathic surgery is a well-known procedure to correct different types of dentofacial deformities and aims to readjust the anatomic and functional relationships through surgical manipulation of facial skeletal components[1–3]. Blood loss is one of the main concerns for maxillofacial surgeons[4,5]. Some patients may need blood transfusion during or after orthognathic surgery[6]. Because the maxillomandibular area is highly vascularized, significant intraoperative bleeding may occur[7,8].

Blood transfusion may result in transmission of various blood-borne diseases, infections, and other complications (e.g., transfusion-related acute lung injury)[2,9,10]. Various pharmacologic agents have been developed to reduce intraoperative blood loss and blood transfusion, and they include tranexamic acid and aprotinin, etc.[11,12]. The lysine analog inhibitor tranexamic acid has been reported to be effective in reducing perioperative blood loss in various surgical procedures, and no adverse effects are reported[13,14].

Topical application of tranexamic acid in the maxillary sinus is able to decrease intraoperative blood loss in endoscopic sinus surgery[14]. Preoperative intravenous bolus administration of tranexamic acid is reported to reduce blood loss during bimaxillary osteotomy[15]. Patients with bleeding trauma have decreased rate and volume of packed red blood cell transfusion, and reduced hospital and intensive care unit lengths of stay after using tranexamic acid[16].

However, some studies have reported that the use of tranexamic acid shows no significant influence on blood loss, and postoperative haematocrit for orthognathic surgery[15,17]. Considering these conflicting results, we performed a systematic review and meta-analysis of RCTs to investigate the efficacy of tranexamic acid in orthognathic surgery.

Materials and methods

Ethical approval and patient consent were not required because this was a systematic review and meta-analysis of previously published studies. The systematic review and meta-analysis were conducted and reported in adherence with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[18].

Search strategy and study selection

Two investigators independently searched the following databases (from inception to October 2017): PubMed, Embase, Web of science, EBSCO, and Cochrane library. The electronic search strategy was conducted using the following key words: 'tranexamic acid' and 'orthognathic surgery'. We also checked the reference lists of the screened full-text studies to identify other potentially eligible trials.

Inclusive selection criteria were as follows: (1) the population were patients with orthognathic surgery; (2) intervention treatments were tranexamic acid versus placebo; (3) study design was RCT.

Data extraction and outcome measures

We extracted the following information: author, number of patients, age, weight, and preoperative haemoglobin, etc. Data were extracted independently by two investigators, and discrepancies were resolved by consensus. We contacted the corresponding author to obtain the data when necessary. The primary outcome was blood loss. Secondary outcomes included postoperative haemoglobin, postoperative haematocrit, operation time and amount of irrigation fluid.

Quality assessment in individual studies

Methodological quality of the included studies was independently evaluated using the modified Jadad scale[19]. There were three items for the Jadad scale: randomization (0–2 points), blinding (0–2 points), dropouts and withdrawals (0–1 points). The scoring of the Jadad Scale varied from 0 to 5 points. An article with Jadad score of ≤ 2 was considered to be of low quality. If the Jadad score was ≥ 3, the study was thought to be of high quality[20].

Statistical analysis

We estimated mean differences (MDs) with 95% confidence interval (CI) for continuous outcomes (blood loss, postoperative haemoglobin, postoperative haematocrit, operation time, amount of irrigation fluid). A random-effects model was used regardless of heterogeneity. Heterogeneity was reported using the I^2 statistic, and $I^2 > 50\%$ indicated significant heterogeneity[21]. Whenever significant heterogeneity was present, we searched for potential sources of heterogeneity via omitting one study in turn for the meta-analysis or performing subgroup analysis. Publication bias was not evaluated because of the limited number (<10) of included studies. All statistical analyses were performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

Results

Literature search, study characteristics and quality assessment

A detailed flowchart of the search and selection results was shown in Fig. 1. A total of 674 potentially relevant articles were identified initially. Six RCTs that met our inclusion criteria were finally included in the meta-analysis[13,15,17,22–24].

The baseline characteristics of the six eligible RCTs in the meta-analysis are summarized in Table 1. The six studies were published between 2009 and 2015, and sample sizes ranged from 32 to 61 with a total of 288. Two included RCTs involving tranexamic acid irrigation[17,22], two included RCTs involving oral tranexamic acid[13,15], one included an RCT involving intravenous infusion of tranexamic acid[24], and the remaining included an RCT involving tranexamic acid 10 mg/kg as a bolus preoperatively followed by 1 mg/kg as a maintenance dose intraoperatively[23].

Among the six studies included here, five studies reported blood loss[13,15,17,22,23], two studies reported postoperative haemoglobin[15,23], three studies reported postoperative haematocrit[15,17,23], six studies reported operation time[13,15,17,22–24], and two studies reported amount of irrigation fluid[17,22]. Jadad scores of the six included studies varying from 3 to 5, and all six studies were considered to be high-quality according to quality assessment.

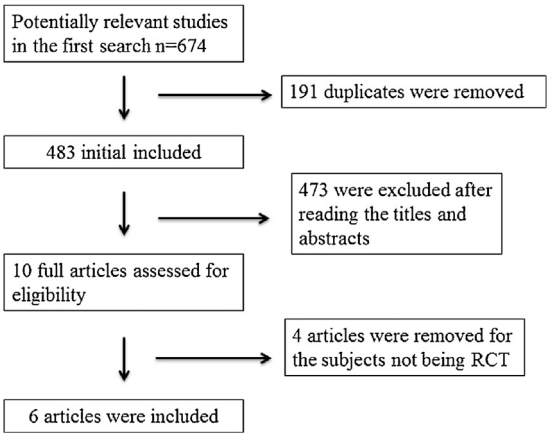

Fig. 1. Flow diagram of study searching and selection process.

Table 1. Characteristics of included studies.

No.	Author	Tranexamic acid group						Control group						Jadad scores
		Number	Age (years)	Male (*n*)	Weight (kg)	Preoperative haemoglobin (mg/dL)	Methods	Number	Age (years)	Male (*n*)	Weight (kg)	Preoperative haemoglobin (mg/dL)	Methods	
1	Eftekharian 2015	28	21.64 ± 3.81	14	62.25 ± 10.48	13.89 ± 1.43	Tranexamic acid irrigation with normal saline (1 mg/mL),	28	22.71 ± 6	13	59.90 ± 8.20	13.70 ± 1.54	Matched placebo	4
2	Christabel 2014	25	24.16 ± 4.524	–	–	12.64 ± 1.516	10 mg/kg body weight of tranexamic acid infusion	24	23.21 ± 4.363	9	–	12.35 ± 1.737	Matched placebo	4
3	Sankar 2012	25	23.20 ± 4.30	8	49.90 ± 12.10	–	Tranexamic acid 10 mg/kg as a bolus preoperatively followed by 1 mg/kg as a maintenance dose intraoperatively	25	24.30 ± 3.70	9	53.80 ± 10.60	–	Matched placebo	4
4	Karimi 2012	16	22.80 ± 12.80	6	62.60 ± 18.90	–	Tranexamic acid (20 mg/kg) intravenously	16	23.90 ± 12.20	7	61.80 ± 19.30	–	Matched placebo	3
5	Kaewpradub 2011	20	26.25 ± 5.01	5	55.02 ± 12.64	–	0.05% Tranexamic acid irrigation	20	25.55 ± 7.11	11	58.60 ± 13.51	–	Matched placebo	4
6	Choi 2009	32	23.90 ± 6.10	10	56.30 ± 9.30	–	Bolus of tranexamic acid (20 mg/kg)	29	22.80 ± 4.50	11	57.7 ± 11.7	–	Matched placebo	5

Data are represented as mean ± standard deviation.

Primary outcome: blood loss

This outcome data was analysed with a random-effects model, and the pooled estimate of the five included RCTs suggested that, compared to placebo in orthognathic surgery, tranexamic acid treatment could significantly reduce blood loss (MD = −159.73; 95% confidence interval (CI) = −236.42 to −83.03; $P < 0.0001$), with significant heterogeneity among the studies ($I^2 = 73\%$, heterogeneity P = 0.005) (Fig. 2).

Sensitivity analysis

Significant heterogeneity was observed among the included studies for blood loss, but there was still remarkable heterogeneity when performing sensitivity analysis by omitting one study in each turn or subgroup analysis based on the different approaches of taking tranexamic acid.

Secondary outcomes

Compared to placebo in orthognathic surgery, tranexamic acid treatment led to significantly higher postoperative haemoglobin (MD = 0.71; 95% CI = 0.11 to 1.31; P = 0.02; Fig. 3) but showed no notable influence on postoperative haematocrit (MD = 1.23; 95% CI = −1.22 to 3.69; P = 0.33; Fig. 4) and operation time (MD = −2.35; 95% CI = −18.05 to 13.36; P = 0.77; Fig. 5). In addition, tranexamic acid treatment resulted in decreased amounts of irrigation fluid during orthognathic surgery (MD = −229.23; 95% CI = −399.63 to −58.83; P = 0.008; Fig. 6).

Discussion

Orthognathic surgery can trigger significant intraoperative blood loss and may require blood transfusion with an increased risk of transmission of blood-borne pathogens, allergic reactions, and other complications[8,25–27]. Numerous methods have been advocated to reduce intraoperative blood loss and blood transfusion[22,28]. Tranexamic acid is well known as a synthetic analogue of lysine to produce an antifibrinolytic effect by reversibly inhibiting the lysine-binding sites on plasminogen and plasmin molecules, as well as preventing degradation of fibrin[29–32]. Previous studies have reported that intraoperative administration of tranexamic acid can significantly decrease intraoperative and postoperative blood loss and blood transfusion in various surgical procedures[33].

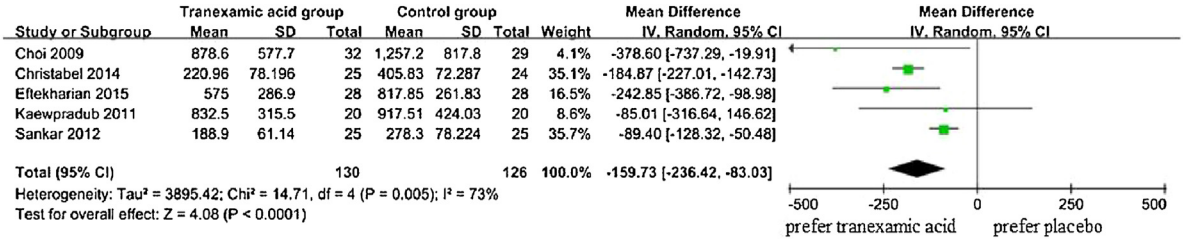

Fig. 2. Forest plot for the meta-analysis of blood loss (mL).

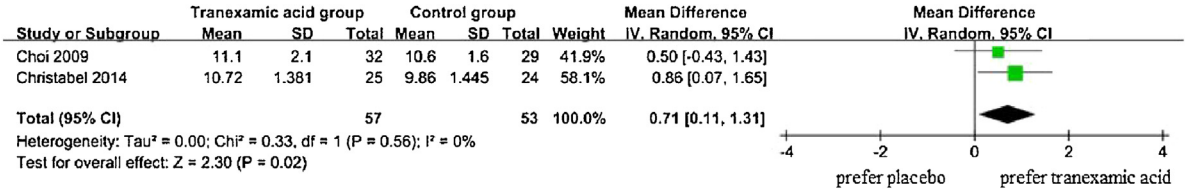

Fig. 3. Forest plot for the meta-analysis of postoperative haemoglobin (mg/dL).

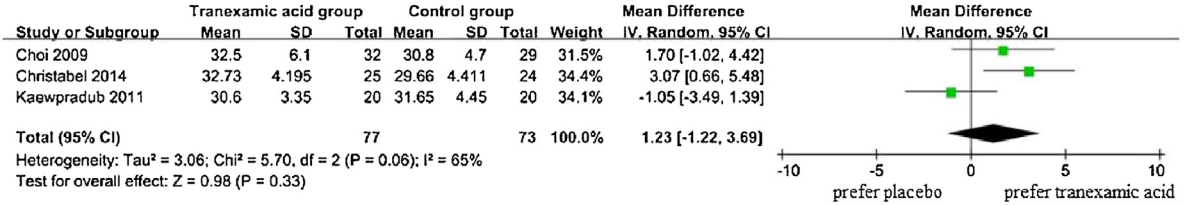

Fig. 4. Forest plot for the meta-analysis of postoperative haematocrit (%).

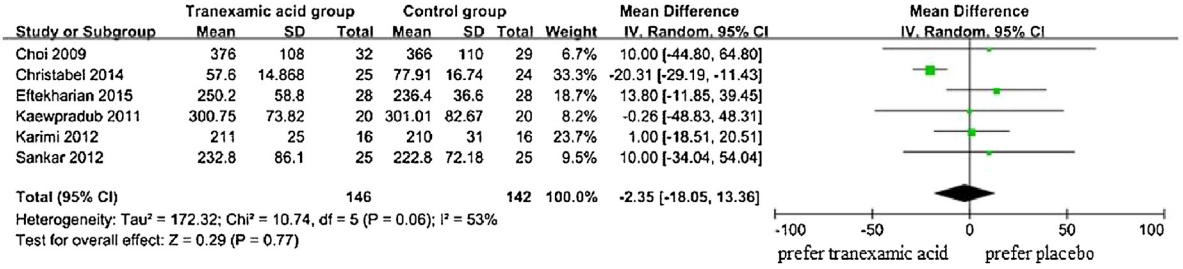

Fig. 5. Forest plot for the meta-analysis of operation time (min).

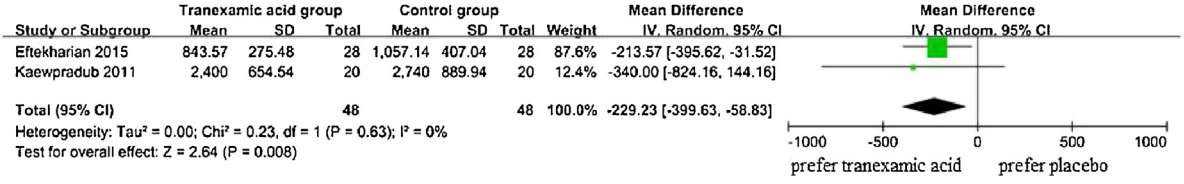

Fig. 6. Forest plot for the meta-analysis of amount of irrigation fluid (mL).

Topical application of tranexamic acid is both target-directed and potentially effective in reducing intraoperative and postoperative bleeding, because topical application can directly mark the source of bleeding and increase the antifibrinolytic activity[34]. The recommended amount of topical tranexamic acid during endoscopic sinus surgery to reduce intraoperative bleeding is 1000 mg (20 mL)[16]. Patients with surgical removal of third molars have diminished blood loss after tranexamic acid administration[35]. One recent meta-analysis included four RCTs. The results found that tranexamic acid can effectively reduce intraoperative blood loss in patients with orthognathic surgery, but show no remarkable influence on postoperative levels of haemoglobin and haematocrit[36]. Six RCTs were included in another meta-analysis, and the results concluded that tranexamic acid is associated with reduced intraoperative blood loss by an average of 171 mL and decreased operating time by an average of 15 min for orthognathic surgery[37]. In our meta-analysis, patients with orthognathic

surgery had significantly decreased blood loss and amount of irrigation fluid, improved postoperative haemoglobin, but there was no influence on postoperative haematocrit or operation time.

Regarding the sensitivity analysis, there is still significant heterogeneity after performing sensitivity analysis by omitting one study in turn or subgroup analysis. There may be several reasons for this. Firstly, the approaches of tranexamic acid include intravenous infusion, oral method, irrigation or their combination. Secondly, different operation time and detailed surgical procedures may affect the heterogeneity. Thirdly, serum concentrations of drug, and the duration of irrigating solution may affect the efficacy of topical tranexamic acid[38,39]. For instance, intraoperative administration of 1% tranexamic acid irrigation solution results in a significant decrease in intraoperative blood loss during orthognathic surgery[22], but there is no significant efficacy after using 0.05% tranexamic acid irrigation solution[17]. Irrigation solution cannot be reduced after applying 1% tranexamic acid for the surgery[22]. Finally, different methods used to calculate blood loss may result in inconsistencies.

The intravenous dose of tranexamic acid (10–20 mg/kg) is found to significantly reduce intraoperative blood loss during orthognathic surgery[15,23], but is limited by the increased risk of thromboembolic complications after systemic administration of this medication[39]. The optimal dose of tranexamic acid for orthognathic surgery remains elusive. Other adverse events include nausea, diaorrhea, and occasionally orthostatic reaction, but they are uncommon[40]. Topical application of tranexamic acid facilitates 70% lower systemic absorption and may decrease the risk of thromboembolic complications compared with intravenous administration[41]. All included RCTs reported no adverse events or complications associated with the application of tranexamic acid for orthognathic surgery.

This meta-analysis has several potential limitations that should be taken into account. Firstly, our analysis is based on only six RCTs and all of them had a relatively small sample size ($n < 100$). Overestimation of the treatment effect is more likely in smaller trials compared with larger samples. Next, there is significant heterogeneity when performing sensitivity analysis, possibly owing to the approaches of taking tranexamic acid, operation time, detailed surgical procedures, and serum concentrations of drug, etc. Finally, postoperative bleeding is not available based on current included RCTs.

In conclusion, tranexamic acid can have significantly reduce blood loss, and improve postoperative haemoglobin in patients undergoing orthognathic surgery.

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Competing interests

None.

Ethical approval

Not applicable.

Patient consent

Not required.

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