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Review

Comprehensive assessment of tranexamic acid during orthognathic surgery: A systematic review and meta-analysis of randomized, controlled trials

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A B S T R A C T

The objective of this study was to comprehensively assess the use of tranexamic acid (TXA) during orthognathic surgery. A systematic review and meta-analysis of randomized controlled trials addressing these issues were carried out. Three electronic databases, included PubMed, Web of Science, and Cochrane Library, were searched until April 30, 2018. Eligible studies were restricted to randomized, controlled trials (RCTs). Weighted mean differences (WMD) for blood loss, operation time, haematocrit, quality of surgical field, and odds ratio (OR) for transfusion rates were pooled for the included studies. Eight randomized, controlled trials were included for analysis. Compared with the control group, the TXA group showed a reduction in intraoperative blood loss of 165.03 ml ($p < 0.00001$; 95% CI, −200.93 to −129.13 ml), a reduction in the drop of haematocrit of 2.32 g/dl ($p < 0.00001$; 95% CI, −3.38 to −1.26 g/dl), and an improved quality of surgical field ($p < 0.00001$; MD, −1.01; 95% CI, −1.23 to −0.80). Tranexamic acid has a limited effect on reducing operative time ($p < 0.00001$; MD, −16.18 min; 95% CI, −19.60 to −12.75 min) and on decreasing the transfusion rates ($p = 0.02$; OR = 0.33; 95% CI, 0.13 to 0.83).

1. Introduction

With the development of contemporary orthodontics and cranio-maxillofacial surgery, increasing numbers of patients with dentomaxillofacial deformities have chosen orthodontic surgery for correction (Huang et al., 2014). As a type of plastic surgery, orthognathic surgery is also recognized for its long operating times and high degree of complexity. Maxillofacial blood supply is very abundant. Too much blood loss can easily result in reduced clinical effects. Avoiding life-threatening events due to excessive bleeding has always been a difficult problem for surgeons and anaesthesiologists. There are many techniques for reducing intraoperative bleeding, including antifibrinolytic agents (Apipan et al., 2018; Choi et al., 2009; Christabel et al., 2014; Eftekharian et al., 2015), hypotensive anaesthesia (Lin et al., 2017), desmopressin (Stewart et al., 2001), and aprotinin (Kaewpradub et al., 2011).

Tranexamic acid (TXA) exerts its antifibrinolytic effect by reversibly blocking the lysine binding site on the plasminogen molecule that is a synthetic derivative of the amino acid lysine. It competitively inhibits the activation of plasminogen; that is, it reduces the conversion of plasminogen to plasmin. Plasmin is an enzyme that degrades fibrin clots, fibrinogen, and other plasma proteins, including procoagulant factors V and VIII. TXA is 5–10 times more potent than ε-aminocaproic acid (McCormack, 2012) and therefore theoretically reduces bleeding. It has been reported that TXA has a positive effect on intraoperative bleeding, operation time, and hospital stay. In orthognathic surgery, reducing intraoperative bleeding can create a higher-quality surgical field (Apipan et al., 2018; Choi et al., 2009; Sankar et al., 2012).

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2. Materials and methods

2.1. Search strategy

Two authors (H.Z. and S.L.) searched the Web of Science, PubMed, and Cochrane Library databases to identify randomized, controlled trials (RCTs) up to April 30, 2018. The key search items were bleeding, haemorrhage, blood loss, intraoperative blood loss, maxillofacial osteotomy surgery, orthognathic surgery, bimaxillary osteotomy, oral surgery, maxillary osteotomy, mandibular osteotomy, Lefort I osteotomy, tranexamic acid, antifibrinolytic agents. The search strategy is presented in Table 1.

2.2. Criteria for eligibility

Only RCTs that met the following inclusion criteria were included in the meta-analysis: 1) the studies enrolled patients undergoing orthognathic surgery for correction of dentofacial deformities, or patients who were scheduled for bimaxillary osteotomy surgery or Lefort I osteotomy surgery; 2) patients were randomly allocated to the tranexamic acid group (experimental group) and the control group; 3) intraoperative blood loss and other relative indicators were reported as outcomes; 4) the full-text article was available; 5) a minimum of 10 participants were included in each study group. The exclusion criteria were: 1) animal studies; 2) studies published in languages other than English with no English translation available.

2.3. Study quality assessment

The quality assessment of the included studies was determined according to the Cochrane Collaboration tool (Higgins et al., 2011), which includes the following seven criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

2.4. Extraction of data

Each retrieved citation was reviewed independently by the two aforementioned authors (H.Z. and S.L.). Most citations could be excluded based on information provided by their titles or abstracts. 49 full-text articles were obtained and carefully reviewed by the two authors. Any disagreement between them was resolved by consensus. The following relevant information was recorded: author's name, publication year, patient demographic data, number of participants in each group, and types of osteotomy performed. The primary predictor variable was defined as intravenous or irrigated tranexamic acid during orthognathic surgery. The main outcome variable was intraoperative blood loss. The secondary outcome variables were operation time, preoperative and postoperative changes in blood indicators, and surgical transfusion rates. The mean, standard deviation, and number of participants for each group were identified throughout the study for the purpose of performing a meta-analysis.

2.5. Statistical analysis

Statistical analyses were conducted using Review Manager 5.3 (Cochrane Community; http://community.cochrane.org/tools/review-productiontools/revman-5/revman-5-download). Weighted mean differences (WMD) and corresponding 95% confidence intervals (CIs) were used to evaluate the effects of intraoperative blood loss, operation time, drop in haematocrit, and surgical field assessment after intravenous or irrigated tranexamic acid administration during orthognathic surgery (Higgins, 2011). Statistical heterogeneity was measured using the I^2 statistic. According to the I^2 value, a fixed effects model with lower power was used for studies with no obvious heterogeneity ($I^2 \leq 50\%$); otherwise, a random-effects model was applied ($I^2 \geq 50\%$) (DerSimonian and Laird, 2015). The level of statistical significance was set at a *p*-value of less than 0.05.

Because patient characteristics, osteotomy type, dosage of tranexamic acid, and other factors were not consistent among the included studies, a sensitivity analysis was performed to explore possible explanations for heterogeneity by omitting the studies sequentially. By comparing the patients, settings, and intervention characteristics of the studies, clinical heterogeneity was assessed qualitatively. The Cochrane risk-of-bias tool was used to assess methodological heterogeneity (Higgins et al., 2011). Funnel plot graphics were used to evaluate publication bias. Symmetric funnel plot graphics indicated minimal publication bias.

3. Results

3.1. Eligible studies

The initial search resulted in 392 titles from the Web of Science, 314 titles from PubMed, and 100 titles from the Cochrane Library. The study selection procedure, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Shamseer et al., 2015; Moher et al., 2015),

Table 1
Search strategies.

Database		Keywords	Search results
Pubmed	1#	(((((((orthognathic surgery) OR bimaxillary osteotom*) OR oral surgery) OR maxillary osteotom*) OR mandibular osteotom*) OR Lefort I osteotom*) OR maxillofacial osteotomy surgery) OR maxillofacial surgery	193599
	2#	(((bleeding) OR hemorrhage) OR blood loss) OR intraoperative blood loss	636461
	3#	tranexamic acid OR antifibrinolytic agents	10022
	4#	(((((((((orthognathic surgery) OR bimaxillary osteotom*) OR oral surgery) OR maxillary osteotom*) OR mandibular osteotom*) OR Lefort I osteotom*) OR maxillofacial osteotomy surgery) OR maxillofacial surgery)) AND ((((bleeding) OR hemorrhage) OR blood loss) OR intraoperative blood loss)) AND (tranexamic acid OR antifibrinolytic agents)	314
Web of Science		(((((((((orthognathic surgery) OR bimaxillary osteotom*) OR oral surgery) OR maxillary osteotom*) OR mandibular osteotom*) OR Lefort I osteotom*) OR maxillofacial osteotomy surgery) OR maxillofacial surgery)) AND ((((bleeding) OR hemorrhage) OR blood loss) OR intraoperative blood loss)) AND (tranexamic acid OR antifibrinolytic agents)	392
Cochrane Library	1#	orthognathic surgery:ti,ab,kw or bimaxillary osteotomy:ti,ab,kw or oral surgery:ti,ab,kw or maxillary osteotomy:ti,ab,kw or mandibular osteotomy:ti,ab,kw or Lefort I osteotomy	14212
	2#	bleeding:ti,ab,kw or hemorrhage:ti,ab,kw or blood loss:ti,ab,kw or intraoperative blood loss:ti,ab,kw	45012
	3#	tranexamic acid:ti,ab,kw or antifibrinolytic agents	1792
	4#	((((((bleeding) OR hemorrhage) OR blood loss) OR intraoperative blood loss)) AND ((((((orthognathic surgery) OR bimaxillary osteotom*) OR oral surgery) OR maxillary osteotom*) OR mandibular osteotom*) OR Lefort I osteotom*)) AND ((tranexamic acid) OR antifibrinolytic agents)	100

is illustrated in Fig. 1. 287 articles were rejected because of repetition. 519 studies were selected for reviewing the abstracts. 463 articles were excluded because they were reviews, editorial letters, single case reports, or were not controlled clinical trials. The titles and abstracts retrieved through this search were screened by two of the authors. The titles and abstracts screening process identified 56 articles that met the inclusion criteria. After the full-text articles ($n = 12$) were assessed, four were excluded because they were review articles (two articles) and meta-analyses (two articles). Basic demographic data and study characteristics of the eight relevant RCTs included in the meta-analysis are presented in Table 2. 575 patients were included in the studies: 292 participants underwent orthognathic surgery with intravenous or irrigated tranexamic acid, and 283 were control patients.

3.2. Study quality assessment

The methodological quality of each RCT included in the meta-analysis was assessed by the Cochrane Collaboration tool. It addressed the seven specific domains discussed in Sections 8.9 to 8.15: namely, sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and ‘other issues’ (Higgins, 2011). Each domain in the RCTs includes one or more specific entries in a ‘risk of bias’ table. This is achieved by assigning a judgement of ‘low risk’ of bias, ‘high risk’ of bias, or ‘unclear risk’ of bias. The quality assessment of the included studies is illustrated in Fig. 2.

3.3. Subgroup analysis

Subgroup analysis was carried out for the primary outcomes studied — intraoperative blood loss, haematocrit, and operation time. Subgroups were based on the types of osteotomy performed and on dosages of intravenous or irrigated tranexamic acid. Six subgroups were created based on dosages of intravenous or irrigated tranexamic acid: 10 mg/kg, 15 mg/kg, 20 mg/kg, 500 mg, 1000 mg of intravenous injection, and 1000 mg of irrigated tranexamic acid. Four RCTs used dosages of 10 mg/kg of intravenous tranexamic acid, one RCT used a dosage of 15 mg/kg of intravenous tranexamic acid, and three RCTs reported dosages of 20 mg/kg of intravenous tranexamic acid. Two RCTs used fixed dosages of intravenous tranexamic acid. One RCT used fixed dosages of irrigated tranexamic acid. Seven RCTs considered bimaxillary osteotomy surgery and one RCT considered single maxillary osteotomy surgery.

3.4. Intraoperative blood loss

All eight RCTs provided relevant data on intraoperative blood loss, with 332 enrolled in the tranexamic acid group and 323 in the control group. The unit of intraoperative blood loss in all RCTs was millilitres. The detailed method for measuring haemorrhage volume in each RCT is shown in Table 2. Blood loss in seven RCTs was calculated from the difference between the fluid in the suction canisters and the irrigation fluid used plus the amount of blood in the surgical gauze estimated by weight; the MD was applied. In only one RCT was the calculation based on return of scavenged blood, suction canisters, and sponges. The resulting forest plot is presented in Fig. 3. The pooled estimate of effect size for total blood loss indicated that tranexamic acid significantly reduced intraoperative blood loss compared with the control group (mean difference, −153.97 ml; $p < 0.00001$; 95% CI, −166.52 to −141.41 ml), in the presence of moderate heterogeneity ($p = 0.001$; $I^2 = 65\%$).

290 participants were included in the 10 mg/kg subgroup, with 145 in the TXA group and 145 in the control group. The TXA group

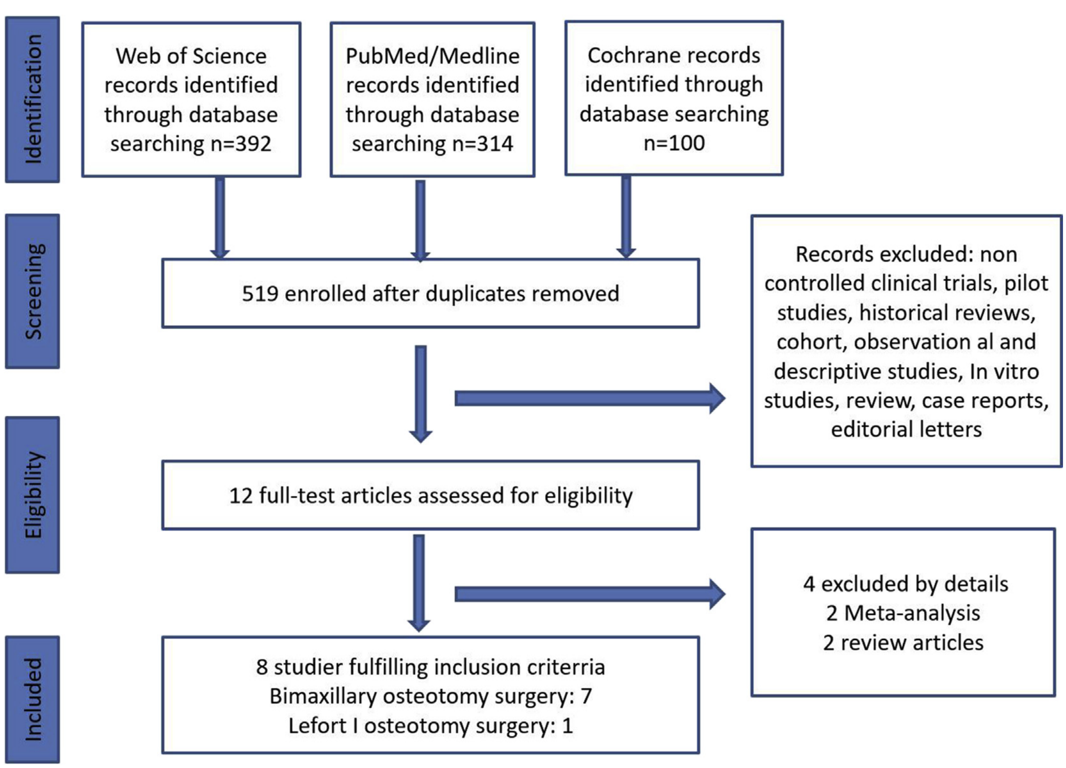

Fig. 1. Flowchart of study selection process.

Table 2
Study Characteristics of Random Control trails in META-analysis.

Reference	Year	Study design	Patient groups	Type of osteotomy	Method of measuring blood loss	Evaluation indicators	Transfusion rate reported
Apipan et al.	2017	RCT (parallel)	Group control: 20 Group 10 mg/kg: 20 Group 15 mg/kg: 20 Group 20 mg/kg: 20	Bimaxillary osteotomy	Suction canisters + surgical gauze − irrigation fluid = total blood loss	Blood loss Transfusion Baseline hct Drop in hct Vacuum drainage Operative time Hospital stay	Yes
Choi et al.	2009	RCT (parallel)	Group control: 29 Group TXA: 32	Bimaxillary osteotomy	Suction canisters + surgical gauze − irrigation fluid = total blood loss	Blood loss; Transfusion; APTT, PT; Hb, Hct; Operative time; Hospital stay	Yes
Christabel et al.	2016	RCT (parallel)	Group saline + dysjunc: 50 Group saline + tuberosity: 50 Group TXA + dysjunc: 50 Group TXA + tuberosity: 50	Le Fort I osteotomy	Suction canisters + surgical gauze − irrigation fluid = total blood loss	Blood loss Operating time Drop in Hb Drop in PCV Surgical field assessment Transfusion	Yes
Eftekharian et al.	2015	RCT (parallel)	Group control: 28 Group TXA: 28	Bimaxillary osteotomy	Suction canisters + surgical gauze − irrigation fluid = total blood loss	Blood loss Operating time Baseline Hb Baseline Hb	No
Kaewpradub et al.	2011	RCT (parallel)	Group control: 20 Group TXA: 20	Bimaxillary osteotomy	Calculated from the return of scavenged blood, suction canisters, and sponges	Blood loss Operating time Preoperative Hct Postoperative Hct	No
Karimi et al.	2012	RCT (parallel)	Group control: 16 Group TXA: 16	Bimaxillary osteotomy	Suction canisters + surgical gauze − irrigation fluid = total blood loss	Blood loss Operating time Transfusion Hospital stay	Yes
Sankar et al.	2012	RCT (parallel)	Group control: 25 Group TXA: 25	Bimaxillary osteotomy	Suction canisters − irrigation fluid + blood-soaked gauze − dry gauze = total blood loss	Blood loss Operating time Surgical field assessment Operative MAP	Yes
Secher et al.	2017	RCT (parallel)	Group control: 45 Group TXA: 51	Bimaxillary osteotomy	Suction canisters + surgical gauze − irrigation fluid = total blood loss	Blood loss Operative time	No

RCT: randomized controlled trial; TXA: tranexamic acid; Hct: hematocrit; Hb: hemoglobin; APTT: activated partial thromboplastin time; PT: prothrombin time; PCV: packed cell volume; MAP: mean arterial pressure.

showed significantly less intraoperative blood loss (TXA group vs control group: MD, −151.67 ml; 95% CI, −164.40 to −138.73 ml; $p < 0.00001$), with high heterogeneity ($p = 0.006$; $I^2 = 76\%$). For the subgroup in which a dosage of 20 mg/kg TXA was reported, three studies provided relevant data. The 133 participants were allocated as follows: 68 in the TXA group and 65 in the control group. Intravenous TXA significantly reduced intraoperative blood loss by 288.90 ml (95% CI, −400.86 to −176.94 ml; $p = 0.0004$), with moderate heterogeneity ($p = 0.14$; $I^2 = 49\%$).

3.5. Drop in haematocrit

This meta-analysis included four RCTs that examined haematocrit preoperatively and postoperatively. The mean difference between preoperative haematocrit and 24-h postoperative haematocrit was the drop in haematocrit. The resulting forest plot is presented in Fig. 4. There was a significant difference between the TXA group and the control group (MD, −2.32 g/dl; 95% CI, −3.38 to −1.26 g/dl; $p < 0.00001$), with moderate heterogeneity ($p = 0.007$; $I^2 = 66\%$).

There was a certain amount of blood loss in both the Lefort I osteotomy group and the bimaxillary osteotomy group; therefore, the haematocrit assessment was also performed in a subgroup analysis. Three studies reported haematocrit drops in bimaxillary surgery. Compared with the control group, the TXA group showed an average 3.17 g/dl decrease in haematocrit (MD, −3.21 g/dl; 95% CI, −4.92 to −1.51 dl; $p = 0.0002$), with moderate heterogeneity ($p = 0.06$; $I^2 = 56\%$). Only one study evaluated Lefort I osteotomy surgery in terms of haematocrit drop after the operation. The TXA group showed an average 1.32 g/dl decrease compared with the control group (MD, −1.32 g/dl; 95% CI, −1.87 to −0.78 g/dl; $p < 0.00001$), with low heterogeneity ($p = 0.82$; $I^2 = 0\%$) (Fig. 4).

3.6. Operation time

All RCTs provided relevant data on operation time. Patients were treated with bimaxillary osteotomy in seven studies and with single maxillary osteotomy in one study; a subgroup analysis was applied. Heterogeneity was not observed among eight studies, so a fixed effects model was used. The corresponding forest plot is presented in Fig. 5. There was limited difference in operation time after merging all studies for analysis (MD, −16.18 min; 95% CI, −19.60 to −12.75 min; $p < 0.00001$), with moderate heterogeneity ($p = 0.03$; $I^2 = 49\%$).

Two subgroups were created, based on single maxillary osteotomy and bimaxillary osteotomy. In the single maxillary

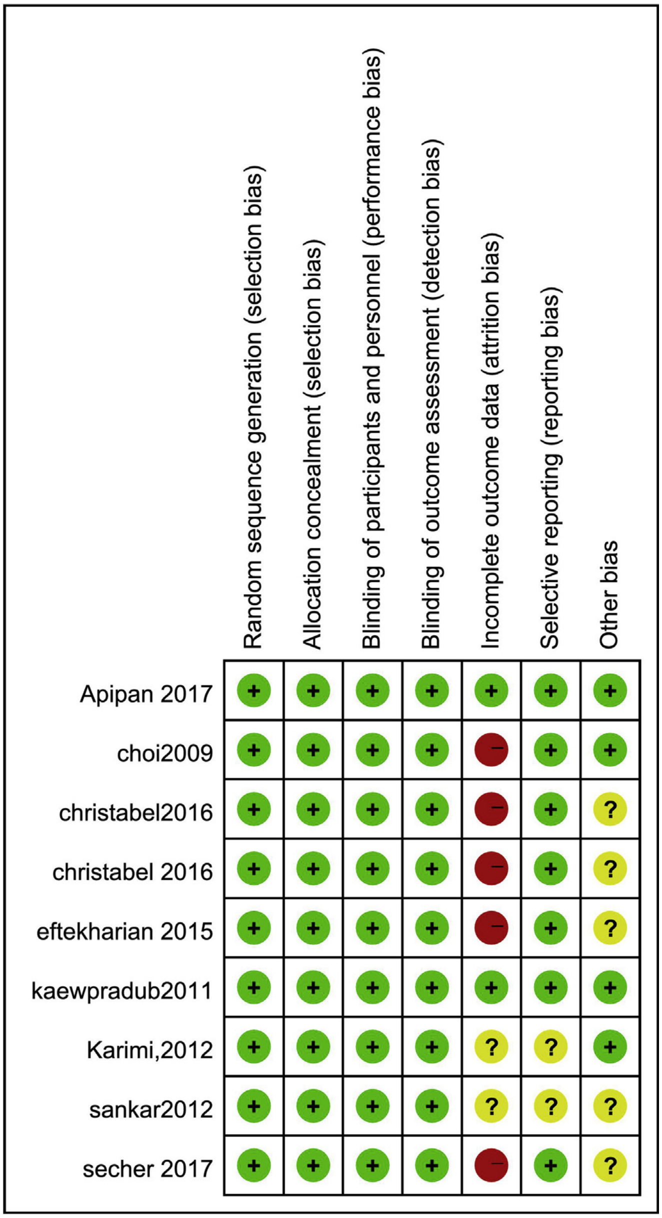

Fig. 2. Quality assessment of included studies.

osteotomy subgroup, results for the TXA group showed a significantly decreased operation time (TXA group vs control group: MD, −17.91 min; 95% CI, −21.72 to −14.10 min; $p < 0.00001$), with high heterogeneity ($p = 0.03$; $I^2 = 78\%$). However, in the of bimaxillary osteotomy subgroup, there was a limited difference between the TXA group and the control group (MD, −8.88 min; 95% CI, −16.69 to −1.07; $p = 0.03$), with low heterogeneity ($p = 0.20$; $I^2 = 27\%$).

3.7. Quality of surgical field

Only two RCTs provided relevant data on quality of the surgical field using the scale devised by Fromme et al. (1986), from 0 (best) to 5 (worst) (Table 3). The 250 participants were allocated as follows: 125 in the hypotensive group and 125 in the control group. Standardized mean difference was used as a summary statistic to account for differences in the surgical field assessment scales used. Pooling of data showed statistically significant improvement in quality of the surgical field compared with the control group (MD, −1.01; 95% CI, −1.23 to −0.80; $p < 0.00001$), in the presence of moderate heterogeneity ($p = 0.02$; $I^2 = 74\%$) (Fig. 6).

3.8. Transfusion rates

The data from four RCTs were collated to compare the rates of surgical transfusion. Allocation of the 463 participants was as follows: 233 in the TXA group and 230 in the control group. A fixed-effect model test showed a significant difference (OR = 0.33; 95% CI, 0.13 to 0.83; $p = 0.02$), with low heterogeneity ($p = 0.89$; $I^2 = 0\%$) (Fig. 7).

3.9. Publication bias

The primary outcome of the study (intraoperative blood loss) generated a funnel plot to assess publication bias. Funnel plot graphics were asymmetrical when blood loss was compared between TXA groups and control groups, indicating an underlying publication bias. Therefore, the funnel plot excluded two RCTs, including Apipan et al. (2018) in the TXA 20 mg/kg injection group and Sankar et al. (2012) in the TXA 10 mg/kg injection group. The distribution of remaining RCTs is plotted on the graph, and the distribution of data points is relatively symmetrical around the estimated difference in blood loss estimates (Fig. 8).

4. Discussion

4.1. Type of osteotomy

This study evaluated both single maxillary and bimaxillary surgery. Because bimaxillary surgery involves BSSRO and genioplasty, the complexity of the osteotomy surgery cannot be ignored. In single maxillary surgery, especially Lefort I osteotomy, intraoperative tranexamic acid significantly reduces operation time. Many RCT cases concerned segmental osteotomies in both the maxilla and mandible, involving multiple bone cuts with additional cancellous bone and intraosseous capillary exposure.

4.2. Main finding

The number of studies included in this study was more than twice the number reported in previous studies, and the number of patients admitted was also double. The evaluation indicators were therefore more comprehensive, and the conclusions obtained more reliable and stable. From the results of the assessment of study quality, the eight RCTs included in this meta-analysis had high quality and strong evidence (Fig. 2). In the evaluation of blood loss, seven RCTs adopted a uniform measurement method: the fluid in the suction canisters plus the amount of blood in the surgical gauze minus the irrigation fluid. Only one RCT was different from other studies (Kaewpradub et al., 2011). In the analysis of blood loss subgroup, two RCTs (Apipan et al., 2018; Sankar et al., 2012) were excluded due to excessive heterogeneity. The reasons may be differences in ethnicity or operative time.

The data demonstrated that tranexamic acid use resulted in a sparing of approximately 158.88 ml ($p < 0.00001$; 95% CI, −172.56 to −145.21 ml) of blood in orthognathic surgery compared with the control groups. The study demonstrated that of the five doses of tranexamic acid studied and two interoperative application methods. Apipan et al. (2018) reported three dosages of intravenous tranexamic acid during bimaxillary surgery, and the most efficacious and cost-effective dose to reduce bleeding during orthognathic surgery was an intravenous dosage of 10 mg/kg.

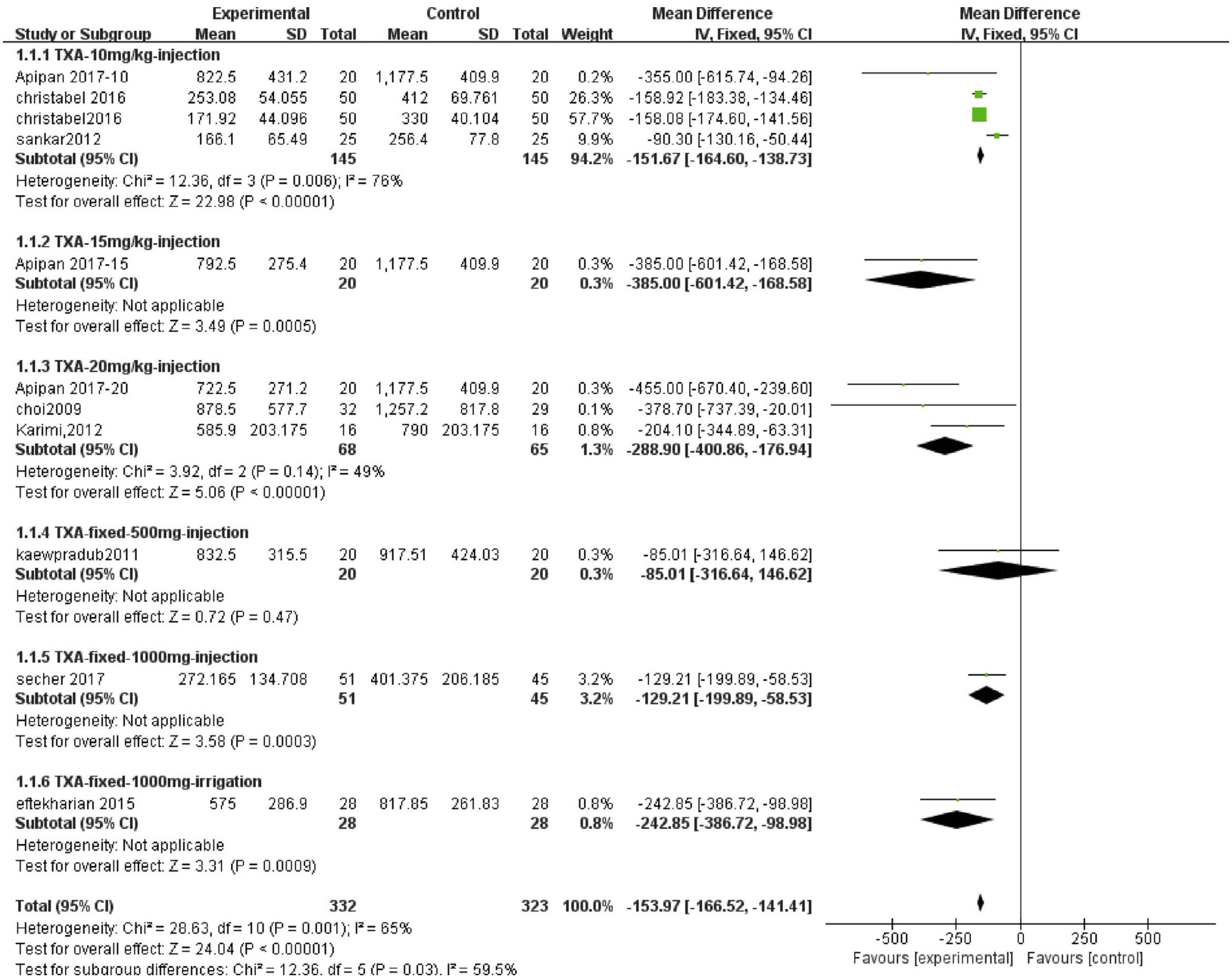

Fig. 3. Forest plots comparing TXA groups and control groups for the outcome intraoperative blood loss. CI, confidence interval; SD, standard deviation.

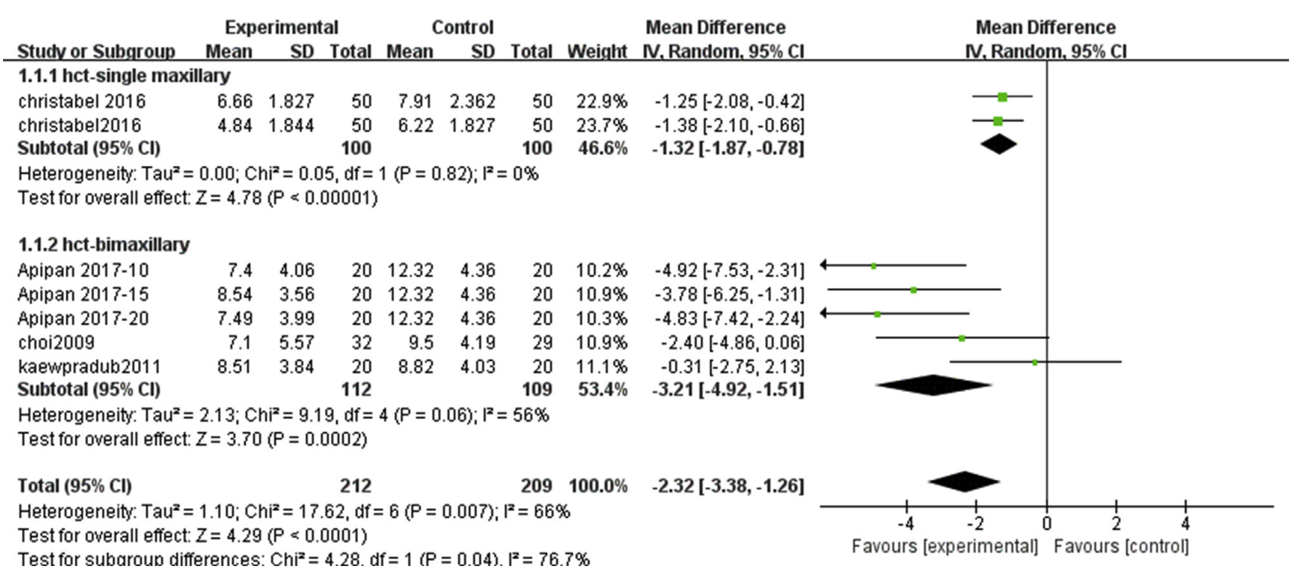

Fig. 4. Forest plots comparing TXA groups and control groups for the outcome drop in hematocrit.

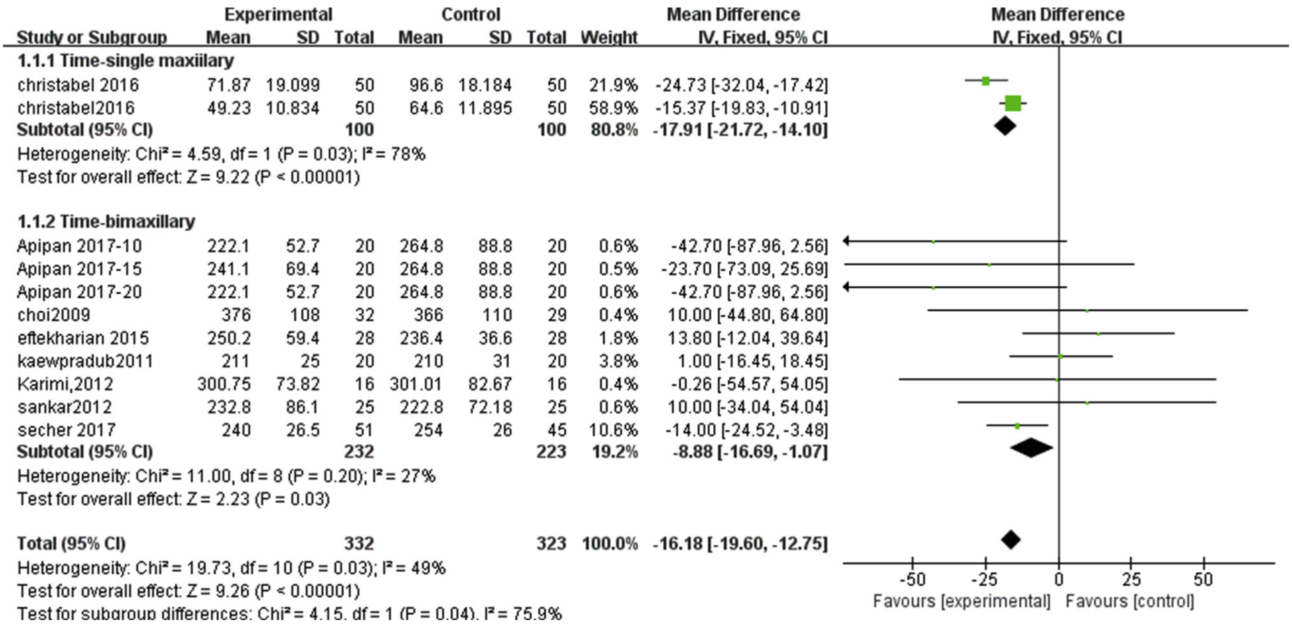

Fig. 5. Forest plots comparing TXA groups and control groups on the outcome operation time.

Table 3
Fromme's ordinal scale for assessing quality of surgical field.

No bleeding, virtually bloodless field	0
Minimal bleeding; not a surgical nuisance	1
Mild bleeding; a nuisance,but does not compromise dissection	2
Moderate bleeding; slightly compromises dissection	3
Severe bleeding; significantly compromises dissection	4
Massive bleeding; cannot carry out dissection	5

However, the blood loss analysis subgroup did not confirm this result: 10 mg/kg vs 20 mg/kg; −158.88 ml vs −227.41 ml (95% CI, −172.56 to −145.21 ml vs −358.47 to −96.35 ml). In terms of reduced haematocrit, there was a statistical significance between the two groups (TXA group vs control group; MD, −2.32 g/dl; 95% CI, −3.38 to −1.26; $p < 0.00001$). These results are inconsistent with previous studies. This may be because more studies were included. Whether in single maxillary surgery or bimaxillary surgery, our findings show reductions in the drop in haematocrit, which may represent shorter postoperative recovery time.

Our study indicates that tranexamic acid improves the quality of the surgical field in orthognathic surgery (MD, −1.01; 95% CI, −1.23 to −0.80; $p < 0.00001$). Based on this, we believe that tranexamic acid can reduce bleeding and improve the visibility of the surgical field, thereby reducing operation time. However, our study only showed a limited reduction in operation time in orthognathic surgery (MD, −16.18 min; 95% CI, −19.60 to −12.75 min; $p < 0.00001$). One likely explanation for this finding is that the operation time for orthognathic surgery is not solely dependent on the quality of the surgical field, but rather on several other important factors, including the complexity of the osteotomy design and the surgical skill of the operating surgeon.

4.3. Clinical application

Tranexamic acid is effective in preventing excessive postoperative bleeding in patients undergoing third molar extraction while under the long-term influence of warfarin (Soares et al., 2015; Carter et al., 2003). There also have been reports on the effect of tranexamic acid on reducing blood loss during orthognathic surgery, and related meta-analyses (Song et al., 2013; Murphy et al., 2016). However, recent RCTs (Apipan et al., 2018; Christabel et al., 2014; Eftekharian et al., 2015; Secher et al., 2018) have emphasised the shortcomings of previous meta-analyses, which are shown not to be comprehensive — few articles were included and the results were not persuasive. Our meta-analysis assessed more comprehensive indicators by including more RCTs to indicate that tranexamic acid has an optimizing effect on orthognathic surgery. This conclusion is more convincing than those of previous studies. The purpose of our study was to comprehensively evaluate the effect of TXA on bleeding, surgical time, and transfusion rates during orthodontic and bimaxillary osteotomy. Simultaneously, relevant auxiliary indicators, including haematocrit, were evaluated. By assessing the quality of the surgical field from the point of view of the surgeon, tranexamic acid was judged to have an optimizing effect in terms of

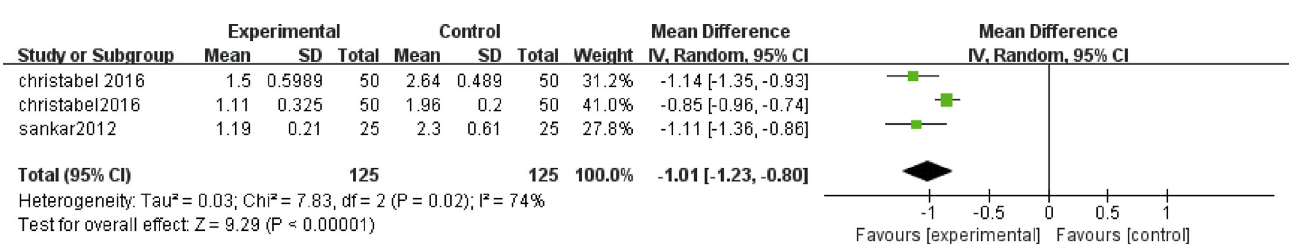

Fig. 6. Forest plots comparing TXA groups and control groups on the outcome of quality of surgical field.

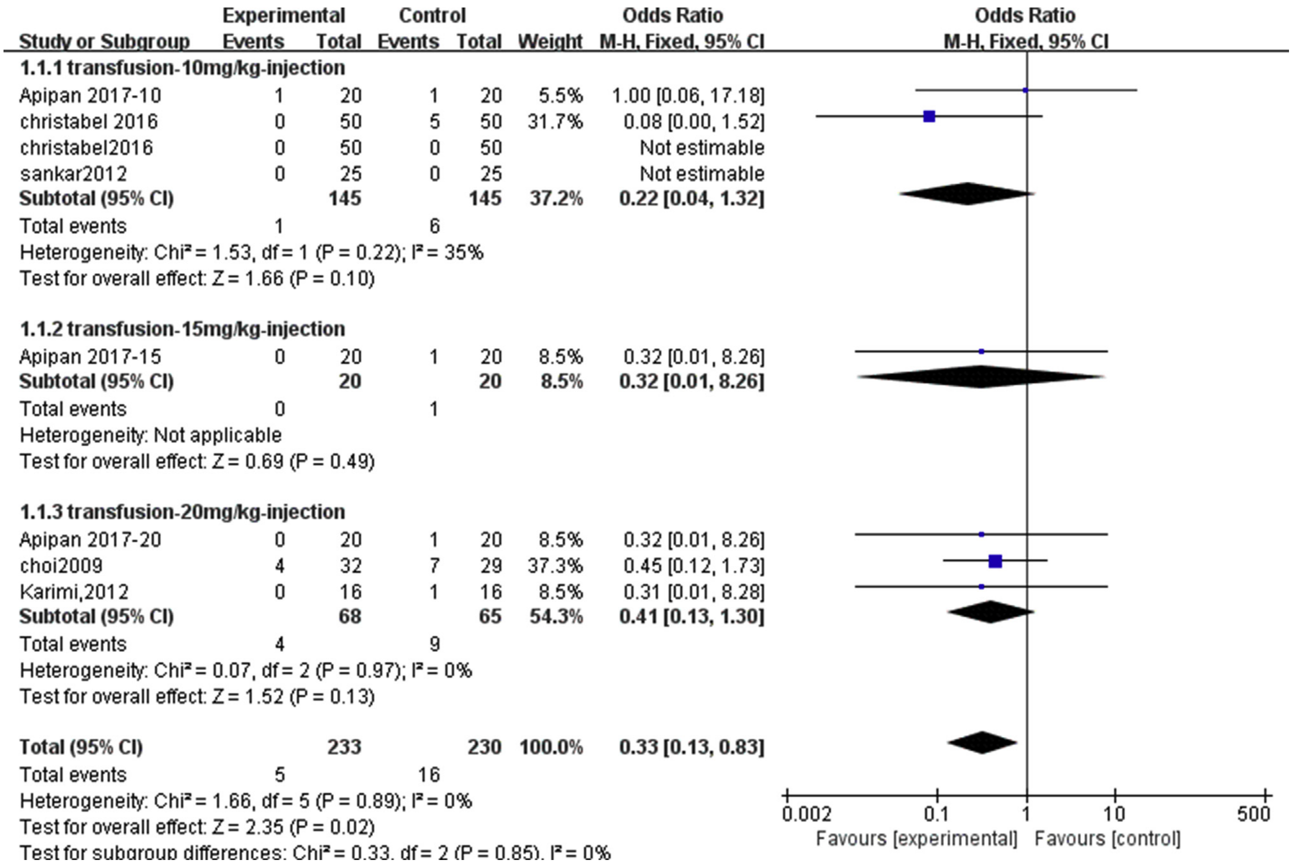

Fig. 7. Forest plots comparing TXA groups and control groups on the outcome transfusion rates.

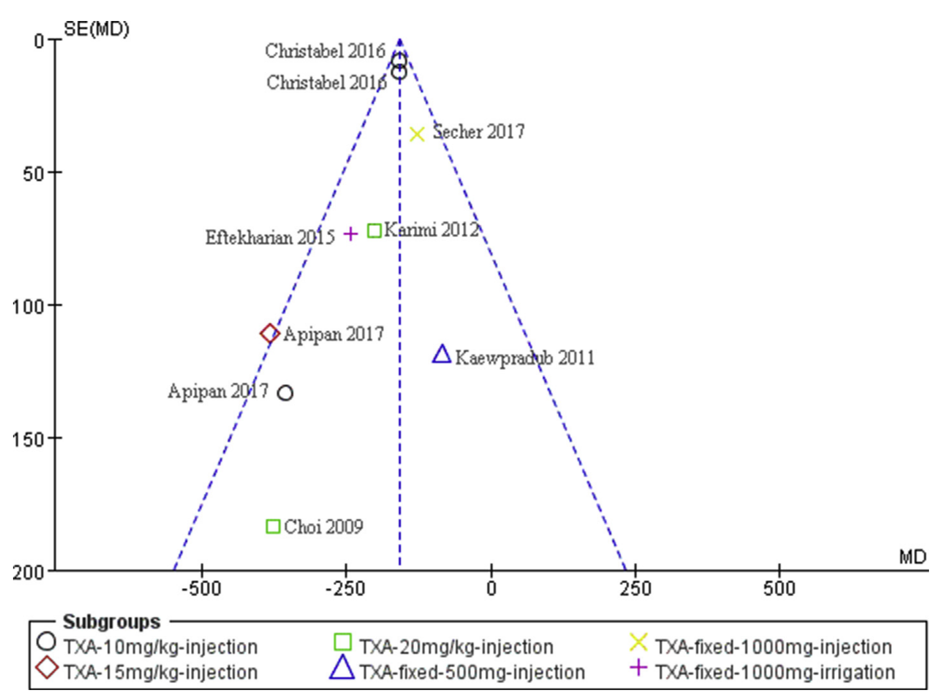

Fig. 8. Funnel plot for studies reporting on the outcome late trismus. MD, mean difference; SE, standard error.

reduction of intraoperative bleeding. Reducing the amount of bleeding can be key in reducing operating time.

Orthognathic surgery can lead to significant intraoperative blood loss. The purpose of any intervention in orthognathic surgery should be to minimize the risk of blood loss and the need for blood transfusions. Numerous approaches have been advocated to achieve this. Blood transfusion is associated with an increased risk of transmission of blood-borne pathogens, possible allergic reactions, and other such complications. TXA, which is a powerful coagulant, exerts its antifibrinolytic effect by reversibly inhibiting the lysine-binding sites on plasminogen and plasmin molecules, preventing degradation of the fibrin that forms the framework of blood clots.

Intraoperative administration of TXA in a variety of surgical procedures has been found to significantly decrease intraoperative and postoperative blood loss, and the need for blood transfusion; these procedures include total hip and knee arthroplasty (Hynes et al., 2003; Ho and Ismail, 2003; Poeran et al., 2014), cardiac surgery (Sigaut et al., 2014), spinal surgery (Yang et al., 2013), and even third molar extraction (Senghore and Harris, 1999). It has also been used in dentistry and oral surgery as a mouthwash for patients with anticoagulation or haemorrhagic problems (Carter et al., 2003). Nonetheless, concerns persist regarding the risk of thromboembolic complications after systemic administration of this medication (Konig et al., 2013). No adverse reactions or complications associated with the use of tranexamic acid were observed in all RCTs. Theoretically, tranexamic acid does not alter blood clotting. It is a clot stabilizer that slows down the dissolution of the blood clots, and does not initiate blood clot formation spontaneously.

There is no strong evidence available showing a definite risk of thromboembolism associated with the use of tranexamic acid. Nevertheless, it should be used with caution and should be avoided in patients with a high risk of thrombosis, including those with history of a thromboembolic event, or a family history of thromboembolic disease. Because tranexamic acid is excreted in the urine, dose reduction may also be required in patients with renal insufficiency.

4.4. Limitations

Although we included more high-quality studies, our study was nevertheless limited by the following defects.

First, the leading discrepancy among examined indicators may be related to the complexity of the operation, for example in one-piece osteotomy versus segmental osteotomy. This can influence the amount of blood loss intraoperatively. In segmental osteotomies, not only is the operation time increased but also there are greater surface areas where bleeding can occur. The duration of the operation and the experience level of the surgeon can greatly influence the amount of blood loss in orthognathic surgery (Rummasak et al., 2011). With improvement in surgical skills and meticulous soft tissue handling, blood loss can be minimized.

The second limitation was the relatively low number of studies available on this topic. From the beginning, we set strict inclusion criteria to include only RCTs, to minimize heterogeneity, and to ensure high levels of evidence.

Third, because of the nature of the operations, the selected RCTs had relatively small numbers of participants in the hypotensive and normotensive groups; only 358 pooled participants were included in the study.

Finally, the variability in the types of orthognathic surgery included in the RCTs presented another limitation of this study. Ideally, we would have liked to perform subgroup analysis on each of the common orthognathic procedures, including Le Fort I osteotomy, bilateral sagittal split osteotomy, intraoral vertical ramus osteotomy, anterior maxillary osteotomy, and double-jaw surgery. Because a minimum of two studies is required to conduct a meta-analysis, we were only able to perform subgroup analysis for bimaxillary surgery and anterior maxillary osteotomy. This meta-analysis showed a statistically significant reduction in blood loss and improvement in the quality of the surgical field (Zellin et al., 2004) when using tranexamic acid in orthognathic surgery. Hypotensive anaesthesia was not shown to reduce operation time in orthognathic surgery. Findings from subgroup analysis suggested that when hypotensive anaesthesia was used in conjunction with local anaesthesia for nerve blocks, the reduction in intraoperative blood loss was enhanced.

The use of tranexamic acid has a substantially positive effect on the reduction in blood loss and improvement in the quality of the surgical field. This meta-analysis showed a statistically significant avoidance of blood transfusion in orthognathic surgery. Tranexamic acid was also shown to reduce operation time, a finding that was different from those of previous studies.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcms.2019.01.021.

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