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Effectiveness of hemocoagulase, tranexamic acid, and their combination for reducing blood loss in bimaxillary orthognathic surgery: a retrospective study

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Abstract (J Korean Assoc Oral Maxillofac Surg 2023;49:208-213)

Objectives: Orthognathic surgery is a corrective intervention for maxillofacial deformities. Bleeding is a major concern for oral and maxillofacial surgeons. Various agents, such as hemocoagulase, tranexamic acid, and aprotinin have been developed to reduce intraoperative bleeding and transfusion requirements. Therefore, in this study we aimed to investigate the effects of hemocoagulase and tranexamic acid, as well as their simultaneous use, to reduce bleeding during orthognathic surgery.

Patients and Methods: This retrospective study included patients who had undergone simultaneous orthognathic surgery of the maxilla and mandible between January 2013 and September 2022 and were classified into three groups based on drugs administered: hemocoagulase (Botropase), tranexamic acid, and a combination of both drugs. We recorded patient age, sex, weight, blood loss, and duration of surgery. Red blood cell (RBC), hemoglobin, hematocrit, and platelet levels were measured before, immediately after, and one day after surgery.

Results: No statistically significant differences were found in blood loss, RBC, hemoglobin, hematocrit, or platelet levels between any of the groups. There were no differences in the drug effects between Le Fort I and bilateral mandibular sagittal split osteotomies, with or without double genioplasty. However, there were significant reductions in RBC, hemoglobin, hematocrit, and platelet levels during genioplasty.

Conclusion: Tranexamic acid, hemocoagulase, and their combination had similar efficacy in patients who underwent Le Fort I and bilateral mandibular sagittal split osteotomies with and without genioplasty.

Key words: Orthognathic surgery, Tranexamic acid, Hemocoagulase

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I. Introduction

Orthognathic surgery is a corrective intervention for various types of maxillofacial deformities and aims to readjust the anatomical and functional relationships through surgical manipulation of facial skeletal components[1].

Bleeding during orthognathic surgery is one of the main concerns of oral and maxillofacial surgeons[2]. Owing to the high vascularity of the maxilla and mandible, significant bleeding may occur during orthognathic surgery[3]. In some patients, bleeding may necessitate blood transfusions during or after orthognathic surgery[4].

Various agents have been developed to reduce intraoperative bleeding and transfusion, including hemocoagulase, tranexamic acid, and aprotinin[5]. Tranexamic acid inhibits the plasminogen activator, whereas hemocoagulase has a different mechanism that controls the conversion of fibrinogen to fibrin. Considering the different sites of action of the two drugs in the coagulation cascade, they have been reported to significantly reduce bleeding by complementing each other[6]. However, there are few studies of the effect of hemocoagulase or the combination of hemocoagulase and tranexamic acid on bleeding in orthognathic surgery. We investigated the effects of hemocoagulase, tranexamic acid, and their simultaneous use for reducing bleeding during orthognathic surgery.

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II. Patients and Methods

1. Study participants

The study was approved by the Institutional Review Board of Dankook University Dental Hospital (DKUDH IRB 2022-11-014). Patients who underwent orthognathic surgery of the maxilla and mandible including conventional Le Fort I and bilateral sagittal split ramus osteotomies (BSSRO) at Dankook University Hospital between January 2013 and September 2022 were enrolled. We excluded 9 patients who underwent intraoral vertical ramus osteotomy, 5 patients who underwent coronoidectomy, and 5 patients who underwent anterior segmental osteotomy of the maxilla. None of the patients' medications included antithrombotic agents.

2. Research methods

The following drugs were administered to all patients: hemocoagulase (Botropase; Hanlim Pharm.) 1 mL every 12 hours, and tranexamic acid (Shin Poong Pharm.) 500 mg every 24 hours. Patients were divided into three groups according to drugs received: Group T (tranexamic acid), Group B (Botropase), and Group BT (Botropase and tranexamic acid). According to each patient's diagnosis, the maxilla and mandible were adjusted to the planned positions by the same surgeon. The mean arterial pressure during surgery was maintained at 90-100 mmHg. Age, sex, weight, blood loss, and duration of surgery were recorded in the surgical and anesthetic records, and red blood cells (RBC), hemoglobin (Hb), hematocrit (Hct), and platelet levels were measured before, immediately after, and one day after surgery. Total blood loss was calculated using the following formula:

Total amount of blood loss={amount of fluid collected in suction apparatus (mL)–amount of saline wash given (mL)}+amount of blood content in weighed swabs (mL).

where, 1 g of blood=1 mL of blood.

3. Statistical methods

Statistical analysis was performed using IBM SPSS software (ver. 28; IBM). ANOVA and repeated measures ANOVA were used as statistical methods. $P<0.05$ was considered statistically significant.

III. Results

1. Characteristics of study participants

There were 26 patients in the tranexamic acid group (Group T; mean age, 24.65 years), 84 patients in the Botropase group (Group B; mean age, 23.73 years), and 72 patients in the Botropase+tranexamic acid combination group (Group BT; mean age, 22.69 years). The sex ratios (female:male) in Groups T, B, and BT were 14:12, 42:42, and 35:37, respectively. The mean weight of Groups T, B, and BT were 70.32 kg, 64.39 kg, and 64.25 kg, respectively. The mean operating time of Groups T, B, and BT were 208.23 minutes, 217.10 minutes, and 229.29 minutes, respectively. There was no significant differences between groups ($P>0.05$).(Table 1)

When preoperative RBC, Hb, Hct, and platelet levels were compared between the T, B, and BT groups, the *P*-values were 0.318, 0.234, 0.333, and 0.482, respectively, with no significant differences.(Table 2)

2. Bleeding volume, RBC, Hb, and Hct results

Intraoperative blood loss in T, B, and BT groups averaged 440.38 mL, 426.79 mL, and 450.69 mL, respectively. There were no significant differences between groups ($P=0.649$). (Table 3)

When RBC, Hb, and Hct levels were compared between the B, T, and BT groups before surgery, on the day of surgery,

Table 1. Demographic parameters and duration of surgery among study groups

Parameter	Tranexamic acid (T)	Botropase (B)	Botropase+tranexamic acid (BT)	*P*-value
No. of patients	26	84	72	-
Age (yr)	24.65±7.20	23.73±5.08	22.69±4.45	0.210
Sex, F:M	14:12	42:42	35:37	0.902
Weight (kg)	70.32±14.13	64.39±13.33	64.25±13.15	0.110
Duration of surgery (min)	208.23±66.70	217.10±42.08	229.29±48.77	0.115

(F: female, M: male)
Values are presented as number only or mean±standard deviation.
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Table 2. Comparison of blood parameters among study groups

Preop variable	Tranexamic acid (T)	Botropase (B)	Botropase+ tranexamic acid (BT)	*P*-value			
				Overall	T-B	T-BT	B-BT
RBC	4.92±0.44	4.77±0.43	4.76±0.51	0.318	0.348	0.320	0.993
Hb	14.86±1.41	14.25±1.47	14.36±1.77	0.234	0.206	0.306	0.901
Hct	43.87±3.54	42.63±3.74	42.60±4.39	0.333	0.348	0.347	0.999
Platelet	259.65±42.90	259.85±44.88	268.40±50.35	0.482	>0.999	0.694	0.493

(Preop: preoperative, RBC: red blood cell, Hb: hemoglobin, Hct: hematocrit)
Values are presented as mean±standard deviation.
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Table 3. Comparison of intraoperative blood loss between study groups

Intraop variable	Tranexamic acid (T)	Botropase (B)	Botropase+ tranexamic acid (BT)	*P*-value			
				Overall	T-B	T-BT	B-BT
Blood loss (mL)	440.38±139.30	426.79±171.89	450.69±153.48	0.649	0.924	0.957	0.624

(Intraop: intraoperative)
Values are presented as mean±standard deviation.
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Table 4. Comparison of red blood cell (RBC), hemoglobin (Hb), and hematocrit (Hct) values among study groups

	Tranexamic acid (T)	Botropase (B)	Botropase+ tranexamic acid (BT)	*P*-value			
				Overall	T-B	T-BT	B-BT
RBC ($\times 10^6/\mu L$)				0.596	0.574	0.667	0.982
Preop	4.915±0.44	4.77±0.43	4.76±0.51				
POD-0	4.012±0.58	3.90±0.52	3.84±0.47				
POD-1	3.66±0.60	3.62±0.51	3.73±0.51				
Hb (g/dL)				0.468	0.435	0.609	0.928
Preop	14.86±1.41	14.25±1.47	14.36±1.77				
POD-0	12.14±1.73	11.80±1.49	11.59±1.41				
POD-1	11.07±1.76	10.91±1.48	11.25±1.56				
Hct (%)				0.466	0.466	0.495	0.999
Preop	43.87±3.54	42.63±3.74	42.60±4.39				
POD-0	35.68±4.94	34.53±4.25	33.85±4.10				
POD-1	32.51±4.97	32.03±4.26	32.80±4.53				

(Preop: preoperative, POD: postoperative day)
Values are presented as mean±standard deviation.
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and the day after surgery, the *P*-values were 0.596, 0.468, and 0.466, respectively, with no significant differences.(Table 4)

3. Blood loss volume, RBC, Hb, and Hct results based on surgical methods

When comparing RBC, Hb, and Hct levels between the three groups, before and on the day of surgery, as well as one day after surgery for the patient group who underwent only Le Fort I and BSSRO, the *P*-values were 0.284, 0.508, and 0.357, respectively.(Table 5)

For the group that underwent Le Fort I and BSSRO, along with genioplasty, when the RBC, Hb, and Hct values were compared between the B, T, and BT groups before surgery, on the day of surgery, and the day after surgery, the *P*-values were 0.623, 0.897, and 0.833, respectively.(Table 6)

For the RBC, Hb, and Hct levels the day before, on the day, and the day after the surgery in the groups that underwent Le Fort I and BSSRO with and without genioplasty, the *P*-value was <0.01 in all groups, with a significantly greater reduction in the group that underwent Le Fort I and BSSRO with genioplasty.(Table 7)

IV. Discussion

Orthognathic surgery can necessitate blood transfusion due

Table 5. Comparison of red blood cell (RBC), hemoglobin (Hb), and hematocrit (Hct) values among Le Fort I osteotomy and BSSRO study groups

	Tranexamic acid (T)	Botropase (B)	Botropase+ tranexamic acid (BT)	*P*-value			
				Overall	T-B	T-BT	B-BT
RBC ($\times10^6$/μL)				0.284	0.255	0.641	0.739
Preop	5.13±0.39	4.80±0.43	4.80±0.52				
POD-0	4.32±0.52	4.04±0.53	4.07±0.46				
POD-1	3.93±0.59	3.79±0.54	4.06±0.50				
Hb (g/dL)				0.508	0.475	0.746	0.890
Preop	15.43±1.34	14.63±1.20	14.59±1.58				
POD-0	12.98±1.62	12.42±1.39	12.36±1.32				
POD-1	11.49±1.74	11.62±1.41	12.25±1.50				
Hct (%)				0.357	0.329	0.547	0.924
Preop	45.40±3.06	43.37±3.33	42.82±4.00				
POD-0	38.40±4.41	36.07±4.09	36.00±3.67				
POD-1	34.85±4.69	33.95±4.32	35.79±4.34				

(Preop: preoperative, POD: postoperative day, BSSRO: bilateral sagittal split ramus osteotomies)
Values are presented as mean±standard deviation.
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Table 6. Comparison of red blood cell (RBC), hemoglobin (Hb), and hematocrit (Hct) values among Le Fort I osteotomy, BSSRO, and genioplasty study groups

	Tranexamic acid (T)	Botropase (B)	Botropase+ tranexamic acid (BT)	*P*-value			
				Overall	T-B	T-BT	B-BT
RBC ($\times10^6$/μL)				0.623	0.597	0.679	0.979
Preop	4.70±0.38	4.76±0.43	4.75±0.51				
POD-0	3.71±0.48	3.85±0.51	3.75±0.45				
POD-1	3.39±0.50	3.54±0.47	3.61±0.46				
Hb (g/dL)				0.897	0.973	0.907	0.943
Preop	14.28±1.28	14.08±1.56	14.27±1.85				
POD-0	11.30±1.43	11.52±1.47	11.30±1.35				
POD-1	10.35±1.52	10.60±1.41	10.86±1.41				
Hct (%)				0.833	0.824	0.847	0.998
Preop	42.35±3.43	42.30±3.89	42.52±4.56				
POD-0	32.96±3.93	33.83±4.17	33.02±3.98				
POD-1	30.18±4.20	31.17±3.97	31.65±4.09				

(Preop: preoperative, POD: postoperative day, BSSRO: bilateral sagittal split ramus osteotomies)
Values are presented as mean±standard deviation.
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to significant intraoperative bleeding, which can lead to the development of blood-borne infections, allergic reactions, and other complications[7]. Various methods have been proposed to reduce surgical bleeding and need for blood transfusions[8].

Hemocoagulase (Botropase), a substance extracted from snake venom, promotes blood coagulation following a principle similar to thrombin[9]. Unlike thrombin, hemocoagulase affects only the fibrinogen conversion process and does not affect other factors. Therefore, the hemostatic effect appears only in the damaged area and does not cause coagulation in a wide range of blood vessels[6]. However, few studies have examined the effects of hemocoagulase on bleeding reduction in orthognathic surgery[10].

Tranexamic acid is a synthetic analogue of lysine with an antifibrinolytic effect caused by reversibly inhibiting the binding of plasminogen and lysine on the plasmin molecule[11]. Previous studies have reported that intraoperative administration of tranexamic acid can reduce intraoperative and postoperative bleeding and transfusion requirements in various surgeries[12].

A previous study showed that the two drugs act on different sites of the coagulation process and can reduce the need for blood transfusion by significantly reducing bleeding with complementary effects. However, no previous study has been conducted examining the use of this drug combination for reducing bleeding during orthognathic surgery[13]. Limited studies have been conducted to compare bleeding reduction in orthognathic surgery using hemocoagulase, tranexamic acid, and their simultaneous use.

Table 7. Comparison of red blood cell (RBC), hemoglobin (Hb), and hematocrit (Hct) values between Le Fort I osteotomy, BSSRO study group, and Le Fort I osteotomy, BSSRO, genioplasty study group

	Le Fort I osteotomy, BSSRO	Le Fort I osteotomy, BSSRO, genioplasty	*P*-value
RBC ($\times 10^6/\mu L$)			<0.01
Preop	4.87±0.47	4.75±0.46	
POD-0	4.11±0.51	3.79±0.48	
POD-1	3.91±0.54	3.55±0.47	
Hb (g/dL)			<0.01
Preop	14.79±1.39	14.18±1.65	
POD-0	12.52±1.42	11.40±1.41	
POD-1	11.87±1.52	10.68±1.41	
Hct (%)			<0.01
Preop	43.63±3.59	42.40±4.12	
POD-0	36.56±4.08	33.40±4.06	
POD-1	34.77±4.41	31.27±4.04	

(Preop: preoperative, POD: postoperative day, BSSRO: bilateral sagittal split ramus osteotomies)
Values are presented as mean±standard deviation.
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Shetty and Sriram[10] reported that hemocoagulase 1 mL was administered before orthognathic surgery to reduce blood loss. Christabel et al.[14] and Choi et al.[15] reported that administration of 10-20 mg/kg of tranexamic acid could reduce bleeding in orthognathic surgery. However, the appropriate dose for orthognathic surgery remains ambiguous, as the systemic use of this drug may increase the risk of thromboembolic complications. In the present study, a combination of 1 mL hemocoagulase and 500 mg tranexamic acid was administered in the simultaneous use patient group (Group BT). No drug side effects or thromboembolic complication occurred, consistent with the results of other surgical studies[6].

Meta-analyses by Mei and Qiu[5] and Song et al.[16] confirmed that tranexamic acid can effectively reduce intraoperative bleeding. However, it was recommended to conduct larger scale studies to ascertain changes in blood loss during orthognathic surgery employing different surgical methods. Therefore, we included patients who underwent Le Fort I and BSSRO with and without genioplasty. There was no significant difference between the surgical methods in the tranexamic acid and hemocoagulase combination group based on the drug effects. The RBC, Hb, and Hct levels were significantly lower in Le Fort I and BSSRO combined with genioplasty group compared with those in the group without genioplasty.

This study had several limitations. First, the volume of blood loss during surgery does not necessarily measure the exact amount of blood lost by the patient in total. Second, this was a retrospective study without a control group in which hemostatic agents were applied to patients to reduce bleeding in orthognathic surgery. More accurate results may be obtained by conducting a larger randomized control trial in the future.

V. Conclusion

The use of tranexamic acid coupled with hemocoagulase had similar efficacy in patients who underwent Le Fort I and BSSRO both with and without genioplasty. This knowledge can equip oral and maxillofacial surgeons with information necessary to provide better medical care and avoid bleeding complications in their planned surgeries.

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Authors' Contributions

M.S.K. participated in data collection, study design, performed the statistical analysis and wrote the manuscript. S.J.H. participated in the study design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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Ethics Approval and Consent to Participate

Ethical approval was provided by the Institutional Review Board of Dankook University Dental Hospital (DKUDH IRB 2022-11-014). The written informed consent was waived by the IRB due to the retrospective nature of the study.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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