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Original Article

Selection of the optimal dosage of tranexamic acid to reduce blood loss during pediatric cleft palate surgery

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Abstract

Objective: The aim of the present study was to evaluate and select the optimal dosage of tranexamic acid (TXA) to reduce blood loss during cleft palate surgery in children. **Materials and Methods:** This randomized double-blind clinical trial was performed on 80 children under 3 years of age that were candidates for cleft palate surgery. These children were divided into four groups as follows: the first, second, and third groups received 5, 7.5, and 10 mg/kg of TXA, respectively. Moreover, the fourth group was considered as the control group. Before induction of anesthesia and then every 15 min during the surgery, some parameters such as mean arterial pressure, heart rate, SpO_2, and $ETCO_2$ were recorded. Moreover, the amount of blood loss during the surgery, the level of surgeon's satisfaction, and incidence rate of complications were assessed and recorded. **Results:** The amount of blood loss during the surgery in TXA groups receiving dosages of 5, 7.5, and 10 mg/kg with the means of 63.75 ± 10.62, 61.25 ± 15.03, and 61.00 ± 14.29, respectively, was significantly lower than that of the control group with the mean of 92.25 ± 19.83 ($P < 0.001$). Moreover, no significant difference was found between the three groups receiving TXA dosages in terms of the amount of blood loss, the level of surgeon's satisfaction ($P > 0.05$). **Conclusion:** According to the results of the present study, all three dosages of TXA had a significant role in reducing blood loss in cleft palate surgery. Given the potential for increased risk of side effects from the drug, it seems safe to use the minimal dosage of this drug to control and reduce blood loss during cleft palate surgery in children <3 years of age.

Keywords: *Blood loss, Children, Cleft palate surgery, Tranexamic acid*

Introduction

Cleft palate is one of the most common congenital anomalies of the face, is characterized by an open communication between oral and nasal cavity, and can include all or part of the palate [1]. The treatment of this anomaly is performed at 9–18 months of age using different surgical techniques to separate oral and nasal cavities [2-4]. The risk of intraoperative blood loss is higher due to the long duration of its surgery. Furthermore, controlling and stabilizing the patient's hemodynamic parameters and reducing the blood loss during the surgery are of particular significance considering the age of children [2,3]. Various methods such as controlled hypotension with remifentanil, sevoflurane, or propofol-based anesthesia, and administration of antifibrinolytic drugs such as tranexamic acid (TXA) have been proposed to reduce the amount of blood loss and stabilize the hemodynamic status of the patient [5-7].

In addition, it should be taken into consideration that the antifibrinolytic activity of TXA is higher among the available antifibrinolytic drugs, while it has the least complications, as well [8].

This drug has been used for hemophilia, von Willebrand factor deficiency, primary menorrhagia, GI bleeding, thrombocytopenia and major orthopedic surgeries, spine surgery, cardiac surgery, tonsillectomy, endoscopic sinus surgery, rhinoplasty surgery, control of nosebleed, tooth extraction, and cleft lip and cleft palate [9,10].

According to TXA pharmacokinetics, preceding investigators have suggested a 10–30 mg/kg loading dose regimen for preoperative bleeding. Moreover, 5–10 mg/kg/h maintenance infusion rate has been recommended to follow the mentioned regimen in the

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case of pediatric trauma and surgery. However, an optimal dosage should be specified to obtain the minimum side-effects and the maximum efficacy in various surgeries [11-13], to determine what dosage of this drug in which types of surgeries can be considered as an optimal dosage, and to what extent this drug can reduce the amount of surgical blood loss.

Hence, the very aim of the present study was to evaluate the effect of three dosages of TXA on the amount of blood loss during cleft palate surgery in children under 3 years of age that were candidates for cleft palate surgery.

Materials and methods

Study design, participants

This study was a clinical trial (Randomized Clinical Trial code: IRCT20171030037093N26). The study population consisted of all children who were candidates for cleft palate surgery during 2020 in Imam Hossein Hospital, Isfahan, Iran. Considering a confidence interval of 95%, a test power of 80%, the blood loss amount of 12% based on previous studies [14], and the error level of 0.2, 20 patients were included in each group (four groups).

Convenience random sampling was used to select 80 patients under 3 years of age, with ASA grade I or II, with no history of systemic diseases, and satisfied to participate in this study (expressed by parents). In addition, the patients were excluded from the study in case of surgeries prolonging for more than 3 h, a history of allergies or other contraindications to administration of TXA, a history of coagulation disorders such as hemophilia, and a history of a previous surgery in the same area. Then the sample was randomly divided into four groups using random allocation software [Figure 1].

To meet the double-blindness conditions, 5, 7.5, and 10 mg/kg dosages of TXA as well as the placebo were prepared daily by the operating room nurse (without the knowledge of the researcher), put in separate bags, specified by A, B, C, and D labels daily, and were finally delivered to the researcher daily.

Moreover, all surgeries were performed by one qualified surgeon to control the surgeon's skill. The anesthesiologist and the operating surgeon were both blind regarding the administered study drug.

Before surgery, the patients' demographic data including age, sex, weight, and hemoglobin (Hb) level were recorded. Then selected patients underwent standard monitoring including electrocardiography, and the mean arterial pressure (MAP), heart rate (HR), SPO_2, and $ETCO_2$ were recorded.

Intervention

After premedication with Midazolam (0.1 mg/kg) and Ketamine (1 mg/kg), the patient was brought to the

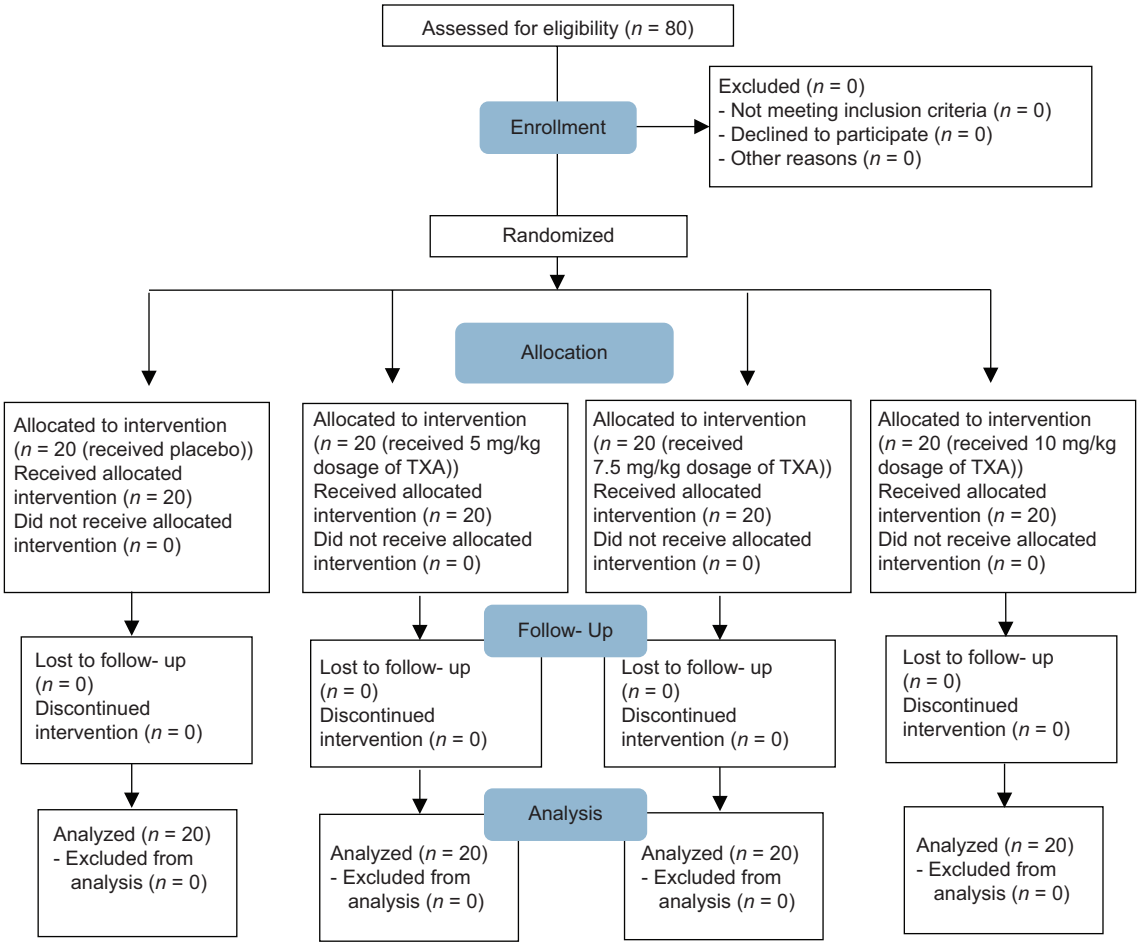

Figure 1: Consort chart

operating room and induction of anesthesia was performed by Atropine (0.02 mg/kg), fentanyl (2 μg/kg), propofol (2 mg/kg), and atracurium (0.05 mg/kg). Anesthesia was maintained by infusion of Propofol 200 g/kg/min, and atracurium and fentanyl with the above-mentioned dosages were repeated every 20 min during the surgery. Then, three pre-prepared and placebo dosages were intravenously injected slowly. All patients received Infiltration of adrenaline (1/400,000 with 0.5% lignocaine). It should be noted that the cleft palate repair surgery was performed using the Sommerlad's technique of cleft palate repair.

Outcome measures

Before the induction of anesthesia and then every 15 min during the surgery, parameters such as MAP, HR, SPO_2, and $ETCO_2$ were recorded.

The amount of blood loss during the surgery was also accurately recorded based on the amount of blood collected in the suction bottle and the number of blood-soaked gauzes (Each full gauze of 10 cm × 10 cm was considered equivalent to 15 and 30 cc of blood, respectively). Surgeon's satisfaction with the surgical field was scored and recorded on a Likert scale ranging from 1 (low satisfaction) to 5 (very high satisfaction).

The incidence of any intraoperative complications including hypotension (<20% of baseline), hypertension (more than 20% of baseline), bradycardia or tachycardia (all/rise of HR above 20% of baseline), and the incidence of the mentioned complications during the recovery were recorded for each group. In addition, complications such as nausea and vomiting, SPO_2 decline, laryngospasm, or bronchospasm were recorded in each group, as well.

Statistical analysis

Finally, the collected data were entered into SPSS software, version 23. The data were presented as mean ± standard deviation or frequency (percentage of frequency). According to the results of Kolmogorov–Smirnov test indicating the normal distribution of data, tests such as one-way ANOVA and Tukey *post hoc* test, repeated measures ANOVA, paired sample *t*-test, and Chi-square test were used. A $P < 0.05$ was considered in all analyses.

Ethical approval

Ethical approval for this study (IR. MUI. MED. REC.1398.057) was provided by the Ethical Committee of Isfahan University of Medical Sciences, Isfahan, Iran, on July 29, 2019. Informed written consent was obtained from all patients' parents prior to their enrollment in this study.

Results

Eighty children in four groups of 20 were recruited for the study. There was no statistically significant difference among the four groups in terms of age, sex, and weight ($P > 0.05$) [Table 1].

In addition, the mean of parameters including MAP, HR, SPO_2, and $ETCO_2$ before induction of anesthesia and up to 120 min during the surgery in the four groups indicated that none of the mentioned parameters were significantly different among the groups [Table 2]. However, there was a significant decrease in the mentioned parameter in each of the four groups 6 h after the surgery ($P < 0.001$). The mean of Hb in the control group was lower than that of the intervention groups receiving three dosages of TXA. Moreover, the TXA group receiving the highest dosage (10 mg/kg) had the highest Hb level ($P < 0.001$) [Table 2].

Furthermore, the evaluation of the amount of blood loss during the surgery revealed that the amount of blood loss in TXA groups with dosages of 5, 7.5, and 10 mg/kg with the means of 63.75 ± 10.62, 61.25 ± 15.03, and 61.00 61 14.29, respectively were significantly less than that of the control group with the mean of 92.25 ± 19.83 ($P < 0.001$). No significant difference was found among the three dosages of TXA ($P > 0.05$) [Figure 2].

Surgeon's satisfaction with the surgical field (based on the Likert scale) in the three TXA groups with dosages of 5, 7.5, and 10 mg/kg were 4.60 ± 0.50, 4.61 ± 0.50, and 4.75 ± 0.44, respectively, which were significantly higher than surgeon's satisfaction in the control group with the mean of 4.15 ± 0.49 ($P = 0.001$) [Table 3].

Finally, the findings regarding the complications during and after the surgery (in the postanesthesia care unit) indicated that no complications occurred during the surgery. Moreover, there was no significant difference among the four groups in terms of the frequency of complications during recovery ($P = 0.498$) [Table 4].

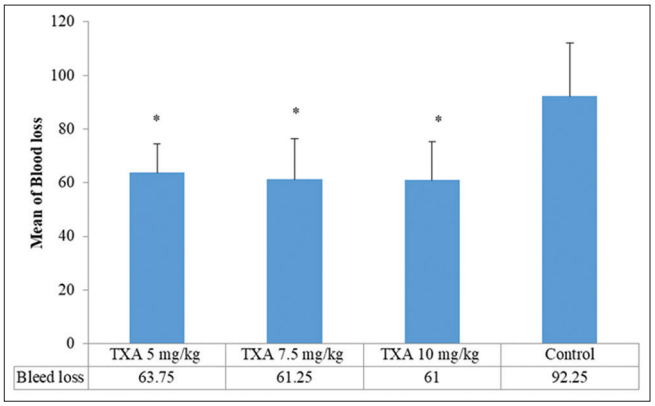

Figure 2: Determination and comparison of the mean of blood loss during the surgery in the four groups. *Significant difference with control group at significance level of <0.001 using Tukey *post hoc* test

Table 1: Demographic characteristics of patients in the four groups

Characteristics	TXA 5 mg/kg (*n*=20)	TXA 7.5 mg/kg (*n*=20)	TXA 10 mg/kg (*n*=20)	Control (*n*=20)	*P*
Sex, *n* (%)					
Boy	10 (50)	10 (50)	14 (70)	11 (55)	0.535
Girl	10 (50)	10 (50)	6 (30)	9 (45)	
Age (months)	10.55±1.54	10.45±1.57	10.55±1.28	10.85±1.35	0.833
Weight (kg)	9.00±1.05	8.75±0.91	8.65±0.75	8.80±0.89	0.675

TXA: Tranexamic acid

Table 2: Determination and comparison of the mean of patients' hemodynamic parameters and hemoglobin level in the four groups

Variables	TXA 5 mg/kg (*n*=20)	TXA 7.5 mg/kg (*n*=20)	TXA 10 mg/kg (*n*=20)	Control (*n*=20)	*P*[a]
MAP					
Baseline	65.19±6.49	63.35±6.98	65.30±6.72	63.15±6.63	0.696
15 min after	64.35±6.43	63.75±7.17	64.60±6.55	63.10±6.93	0.899
30 min after	64.50±6.64	63.65±7.47	64.60±6.80	63.05±6.85	0.879
45 min after	64.35±6.70	63.75±7.53	64.45±6.68	62.75±6.98	0.861
60 min after	65.65±8.06	63.35±7.49	64.30±6.81	62.65±7.12	0.605
75 min after	63.90±6.66	62.80±7.35	63.70±4.06	62.45±6.70	0.895
90 min after	63.95±6.70	62.70±7.34	63.50±7.04	62.35±6.71	0.882
105 min after	64.00±6.68	62.45±7.23	63.50±6.81	62.45±6.77	0.857
120 min after	63.25±6.13	62.27±7.67	62.18±7.30	62.82±6.97	0.597
P[b]	0.322	0.020	<0.001	0.075	
HR					
Baseline	120.60±8.05	120.00±9.53	119.90±9.72	118.30±10.53	0.428
15 min after	118.65±9.03	120.55±8.36	117.60±8.57	118.50±10.67	0.780
30 min after	119.30±9.34	120.35±7.84	117.10±8.73	118.35±10.01	0.703
45 min after	120.20±8.91	119.55±8.06	116.70±8.59	116.85±9.17	0.462
60 min after	120.60±9.38	119.05±8.22	115.15±9.11	116.35±9.26	0.215
75 min after	120.15±9.62	118.35±8.53	114.60±8.61	115.85±8.76	0.204
90 min after	119.95±9.95	118.25±8.57	114.10±8.50	115.30±8.28	0.149
105 min after	119.80±9.52	117.80±8.64	113.85±9.01	114.70±8.57	0.136
120 min after	119.56±9.63	116.87±7.93	114.35±9.94	113.18±8.67	0.201
P[b]	0.005	0.045	<0.001	0.008	
SpO_2					
Baseline	97.90±1.89	97.55±1.60	97.30±1.59	97.40±1.60	0.690
15 min after	98.55±1.23	98.55±1.15	99.00±0.97	98.65±1.04	0.526
30 min after	98.85±1.08	98.80±1.15	99.15±0.93	98.85±1.09	0.719
45 min after	99.10±1.07	99.00±0.97	99.35±0.81	99.30±0.73	0.577
60 min after	99.10±1.07	99.15±0.93	99.30±0.80	99.25±0.72	0.889
75 min after	99.10±1.02	99.30±0.86	99.40±0.75	99.20±0.77	0.716
90 min after	99.25±0.85	99.35±0.81	99.45±0.69	99.25±0.79	0.828
105 min after	99.45±0.76	99.50±0.61	99.50±0.61	99.35±0.67	0.877
120 min after	99.50±0.73	99.60±0.63	99.59±0.71	99.47±0.62	0.932
P[b]	<0.001	<0.001	<0.001	<0.001	
$ETCO_2$					
Baseline	37.65±3.16	37.68±4.23	37.88±3.93	37.99±4.00	0.981
15 min after	37.55±3.76	37.60±4.26	37.80±4.01	37.95±3.86	0.988
30 min after	37.40±3.82	37.70±3.89	38.05±3.69	37.80±3.36	0.956
45 min after	37.45±3.68	37.60±3.84	38.05±3.80	37.70±3.55	0.963
60 min after	37.70±3.63	37.65±4.11	38.00±3.77	37.65±3.76	0.990
75 min after	37.75±3.51	37.55±3.89	38.25±3.88	37.95±3.68	0.944
90 min after	37.70±3.58	37.50±3.89	38.25±3.89	37.60±3.79	0.925
105 min after	37.60±3.44	37.45±3.93	38.00±3.89	37.45±3.91	0.963
120 min after	37.81±4.04	36.93±4.08	38.24±3.99	37.18±4.02	0.785
P[b]	0.587	0.635	0.251	0.068	
Hb					
Preoperative	11.89±1.18	11.66±1.15	11.64±1.11	11.84±1.09	0.866
6 h after operative	10.10±0.87	10.24±0.91	10.44±0.92	9.28±0.64	<0.001
P[c]	<0.001	<0.001	<0.001	<0.001	

[a]*P* value of the ANOVA analysis, [b]*P* value of the repeated measurements ANOVA, [c]*P* value of the paired sample *t*-test. MAP: Mean arterial pressure, Hb: Hemoglobin, HR: Heart rate, TXA: Tranexamic acid

Discussion

According to the results of the present study, TXA administration may have an effective role in reducing the amount of blood loss. Moreover, its administration cannot significantly change the levels of MAP, HR, SPO_2, and $ETCO_2$. In fact, the administration of TXA (at each of the three dosages) as compared with the control group significantly reduced the amount of blood loss and consequently prevented the reduction of Hb level 6 h after the surgery. It is noteworthy that there was no significant difference among the three dosages in terms of the amount of blood loss. In other words, the effect of the lowest dosage (5 mg/kg), the middle dosage (7.5 mg/kg),

Table 3: Determination and comparison of the mean level of surgeon's satisfaction in the four groups

Surgeons' satisfaction	TXA 5 mg/kg (*n*=20), *n* (%)	TXA 7.5 mg/kg (*n*=20), *n* (%)	TXA 10 mg/kg (*n*=20), *n* (%)	Control (*n*=20), *n* (%)	*P*
Score satisfaction	4.60±0.50	4.61±0.50	4.75±0.44	4.15±0.49	0.001†
Grade of satisfaction					
3	0	0	0	1 (5)	0.019††
4	8 (40)	8 (40)	5 (25)	15 (75)	
5	12 (60)	12 (60)	15 (75)	4 (20)	

†Results of ANOVA, ††Results of Chi-square test. 1: Very low satisfaction, 2: Low satisfaction, 3: Moderate satisfaction, 4: High satisfaction, 5: Very high satisfaction, TXA: Tranexamic acid

Table 4: Determination and comparison of the frequency of complications during and after the surgery in the postanesthesia care unit in the four groups

Complications	TXA 5 mg/kg (*n*=20), *n* (%)	TXA 7.5 mg/kg (*n*=20), *n* (%)	TXA 10 mg/kg (*n*=20), *n* (%)	Control (*n*=20), *n* (%)	*P*
During surgery	0	0	0	0	-
During recovery					
SpO_2 decline	0	0	1 (5)	1 (5)	0.498†
Blood loss	0	0	0	1 (5)	
Respiratory distress	0	0	1 (5)	0 (0)	

†Results of Chi-square test. TXA: Tranexamic acid

and the highest dosage (10 mg/kg) was not significantly different. In fact, the administration of the lowest dosage of TXA can have the same effect as that of the highest dosage.

Reduced blood loss [15] without any adverse effects [16,17] has been revealed in studies reviewing the administration of TXA in children. TXA administered intraoperatively was observed to have a positive effect on blood conservation in both minor and major surgeries including craniosynostosis surgery [18], pediatric cardiac surgery [19], traumatic mandibular surgeries [20], scoliosis surgery [21], endoscopic sinus surgery [22,23], and pediatric neurosurgery (seizure surgery including hemispherectomy and tumor surgery) [24,25]. However, it must be mentioned that the role of TXA in surgical procedures that leads to less bleeding is indistinguishable. A single study reported that the incidence rate of primary hemorrhage after pediatric tonsillectomy was reduced following the administration of perioperative TXA in a single parenteral dose [26]; however, no difference was reported regarding the number of patients with bleeding in other studies [27,28]. In addition, following the administration of TXA, bleeding was not reduced in children during adenotonsillectomy [29].

Although the mentioned studies had a different surgery from that of the present study, other studies have revealed the efficacy of this drug in cleft palate surgery. Hence, considering that blood loss is usually minimal during this surgery that is mostly performed on pediatrics, it seems that paying due attention to the optimal dosage as a safe and effective dosage with the least side-effects is of particular significance.

In line with the present study, Durga *et al*., for instance, have pointed to the effect of 10 mg/kg of TXA on reducing the amount of blood loss in primary pediatric cleft palate surgery as compared to that of the control group [30].

In addition, Arantes *et al*. showed that reduction of the amount of intraoperative blood loss occurred in 11.9% of patients undergoing cleft lip and palate surgery although the mentioned finding was not statistically significant [14]. The nonsignificance of a decrease in the amount of blood loss in the mentioned study was inconsistent with the findings of the present study. This finding may be attributed to ignoring the amount of blood loss as the mentioned study has just pointed to the reduction of blood loss.

As the available evidence indicates therapeutic or prophylactic administration of TXA is an effective and well-tolerated strategy to decrease the need for allogeneic blood product transfusion, decrease bleeding, and improve patient outcome. At present, all recent guidelines regarding critical bleeding recommend TXA, which is considered as a significant part of pediatric patient blood management protocols [13]. Based on preceding studies, addressing TXA as well as pharmacokinetic modeling and simulation, a dosage regimen within the range of 10–30 mg/kg loading dose (2 g maximum) followed by a 5–10 mg/kg/h maintenance infusion rate can maintain the TAX plasma concentrations within the range of 20–70 mg/ml, respectively. Hence, the mentioned dosage can be regarded as a target for pediatric surgery and trauma [11-13].

For example, consistent with the findings of the present study, a study showed that HR and MAP of patients during endoscopic sinus surgery did not differ significantly between the two groups receiving two dosages of 5 mg/kg and 10 mg/kg TXA. Moreover, systemic administration of TXA had no effect on Hb level; however, the amount of blood loss was significantly reduced at both dosages of the drug [31].

In contrast with the findings of the present study, Abbasi *et al*. compared two dosages of 5 and 15 mg/kg of TXA and revealed that although there was no significant difference between the two dosages in terms of the mean of MAP, DBP, SBP, and HR during the endoscopic sinus surgery, the mean of blood loss at the dosage of 15 mg/kg TXA was significantly lower than that of the dosage of 5 mg/kg TXA [32].

Hence, according to previous studies, it can be conjectured that the effect of TXA dosage on different surgeries and different age groups may be different.

The results of our study revealed that a 5 mg/kg dosage of TXA can be considered as a safe and effective dosage in this surgery although further studies regarding this surgery with a larger sample size are also recommended.

Furthermore, the findings of the present study indicated that surgeon's satisfaction with the control of blood loss and the quality of surgery using three dosages of TXA were at the same level and were significantly higher than those of the control group. In line with the findings of the present study, another study indicated the surgeon's higher level of satisfaction with surgical field of the group receiving TXA 15 mg/kg with the mean scores of 4 (3–5) as compared with the group receiving TXA5 mg/kg mean scores of 3 (1–5) $P < 0.005$). In addition, TXA 15 mg/kg group, as compared with the control group, had shorter period of surgery and required fewer supplement drugs to control the amount of blood loss ($P < 0.05$) [32].

Durga *et al*. revealed a significant improvement in the surgeon's satisfaction and the surgical field in terms of reducing the amount of blood loss in the TXA 10 mg/kg group as compared with the control group [30]. These studies have evaluated the surgeon's satisfaction based on Boezaart criteria, whereas the Likert scale was used in the current study and asked open-ended question about the surgeon's perspective in this regard. However, it can be concluded that surgeon's satisfaction was generally high in TXA groups.

Regarding the observed complications, the findings revealed one case (5%) of SPO_2 decline and one case (5%) of respiratory distress in the TXA 7.5 mg/kg group. Moreover, one case (5%) of SPO_2 decline and one case (5%) of blood loss were recorded in the control group. In line with the mentioned findings, Abbasi *et al*.'s study revealed the low incidence rate of complications, as well [32]. The mentioned findings were consistent with findings presented in other studies [33-35]. Complications of systemic antifibrinolytics are usually associated with gastrointestinal system.

Although the findings of previous studies have generally indicated that TXA was safe even at high dosages, it is worth noting that the present study indicated that increased dosages of TXA did not differ from the lower dosages in terms of the efficacy of this drug in controlling and reducing the amount of blood loss. Moreover, the patient had experienced a complication although the incidence of the complications was very low and nonsignificant. Therefore, it seems safe to use lower dosages for children and conduct further studies in this respect.

Although the small sample size may be regarded as a drawback of the present study, one of the strengths of this study was evaluation and determination of the optimal dosage of TXA to reduce the amount of blood loss in one of the long-term surgeries, i.e., cleft palate surgery. It seems that further studies are required in this stratum of patients to select the optimal TXA dosage to reach a more definitive and generalizable conclusion to the target population.

Conclusion

According to the results of the present study, although in general this surgery is not associated with much bleeding, but TXA (all three dosages of TXA, i.e., 10, 7.5, and 5 mg/kg), had a significant role in reducing the amount of blood loss, and no significant differences can be found among the mentioned dosages. Surgeon's satisfaction level was similar in all three TXA groups and was significantly higher than that of the control group. Given the potential for increased risk of side effects from the drug, it seems safe to use a minimal dosage of TXA to control and reduce the amount of blood loss in children undergoing cleft palate surgery.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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