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Efficacy of Tranexamic Acid in Reducing Blood Loss in Cleft Palate Surgeries - A Systematic Review

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Background: Cleft lip and palate is the most common congenital Craniofacial malformation, occurring in 1:700 births. The clinical manifestations involve upper lip, alveolar process, and the palate, in different extensions. Cleft palate treatment of this anomaly is performed at 9–18 months of age using different surgical techniques to separate oral and nasal cavities. The risk of intra operative blood loss is higher due to the long duration of its surgery. Controlling and stabilising the patient's hemodynamic parameters and reducing the blood loss during the surgery are of particular significance considering the age of children.Tranexamic acid is an anti-fibrinolytic agent. It acts by binding to lysine receptors on plasmin and blocks the binding of plasmin to fibrin, thereby fibrinolysis is inhibited. Materials and Methodology: The search was performed in pubmed, electronic databases using the search items alone and in combination by means of PUBMED search builder. Only Randomized Control Trials were included. The search results were screened for eligibility according to inclusion criteria by two independent reviewers by reading title, abstract, fulltext. Data for amount of blood loss and surgeon comfort during surgery was pooled and analysed. Studies were assessed for risk of bias and level of evidence. Results: A total of 137 articles were assessed and screened. And a total of 5 articles were selected according to the inclusion criteria . Risk of bias assessment concluded 2 were low risk studies, 2 had some concerns and 1 was low risk study. The studies indicate tranexamic acid significantly reduced the amount of bleeding and the duration of surgery in cleft palate surgery compared to the control group. Conclusion: Tranexamic acid can be recommended and routinely used without any fear of side effects in paediatric cleft palate surgeries for reduced blood loss. Which in turn decreases need for extra intra-operative Haemostatic measures and increases surgeons comfort and reduces need for post operative blood transfusion.

Keywords: Cleft palate, Palatoplasty, Blood loss, Tranexamic acid, Cleft lip and palate.

1. Introduction

Clefts of the lip and/or palate are one of the most common craniofacial malformations characterised by complete or partial cleft of the lip and/or palate, with severity ranging from notching of lip to a complete nonfusion of lip, primary cleft palate or secondary cleft palate (1,2). Prevalence also has a racial variation with Asiatic races exhibiting higher rates of cleft palate (3; 4).

Palatoplasty is usually performed when the child is between 6 months to 1 year of age. Repair of the hard palate is performed using a bi-layer closure with a bi-pedicled or posteriorly based mucoperiosteal flap and nasal mucosal flaps sutured in the midline. These flaps are based on the palatine vessels (5,6,7).

Controlling and stabilising the patient's hemodynamic parameters and reducing the blood loss during the surgery are of particular significance considering the age of children.

The mouth and face are vascular areas that can bleed profusely during surgery and subsequently create the need for blood transfusions. Although these hemorrhages are often manageable, they can lead to the presence of blood and degraded field quality during surgery. The various amount of bleeding during surgery can cause impaired surgeon vision and prolonged surgery and sometimes requires blood transfusions. Various methods are used to reduce bleeding in the surgical field, including head posture, controlled breathing, and medication to control hypotension, such as beta-blockers, nitro glycerol, and calcium channel blockers.

Tranexamic acid is an anti-fibrinolytic agent. It acts by binding to lysine receptors on plasmin and blocks the binding of plasmin to fibrin, thereby fibrinolysis is inhibited.

Tranexamic acid is indicated for the treatment of bleeding disorders like haemophilia, von Willebrand factor deficiency and in various surgical procedures like orthopaedics, cardiac, gynaecological, maxillofacial surgeries, where it has shown reduced peri operative blood loss which in turn reduces postoperative bleeding complications.(9,10)

Based on studies the peri operative administration of Tranexamic acid has not been shown to increase the occurrence of adverse events, including thromboembolic events, In addition to being safe and effective.

AIM

The aim of this systematic review was to analyze the existing literature on effectiveness of Tranexamic acid in reducing blood loss in patients undergoing cleft palate surgery.

STRUCTURED QUESTION

Is Tranexamic acid effective in reducing blood loss in patients undergoing cleft Palate surgery?

PICOS analysis

POPULATION - Children undergoing cleft palate surgery

INTERVENTION - Tranexamic acid infusion

COMPARISON – No other haemostatic agent used

OUTCOME - Blood loss and bleeding

STUDY DESIGN - Randomized Control Trials

NULL HYPOTHESIS

There is no difference in Efficacy of Tranexamic acid in reducing blood loss in cleft palate surgeries.

Methodology: The current review protocol was registered in PROSPERO (CRD42023450525)

SEARCH STRATEGY

The search was performed up to February 2023 in electronic databases (i.e., PUBMED Central, COCHRANE, Google Search, Web of Science, and Medline) using the search items alone and in combination by means of the PUBMED search builder

((Cleft palate) AND (tranexamic cid)) AND (blood loss) ("cleft palate"[MeSH Terms] OR ("cleft"[All Fields] AND "palate"[All Fields]) OR "cleft palate"[All Fields]) AND (("tranexam"[All Fields] OR "tranexamic"[All Fields]) AND "cid"[All Fields]) AND ("hemorrhage"[MeSH Terms] OR "hemorrhage"[All Fields] OR ("blood"[All Fields] AND "loss"[All Fields]) OR "blood loss"[All Fields])

2. SELECTION CRITERIA:

SCREENING AND SELECTION

Two reviewers independently screened the gathered papers, and their level of agreement in terms of making decisions was assessed with a value of 0.81, demonstrating improved agreement between the two reviews. After gathering all the information from the computer search, a screening was conducted, and articles that did not fit our inclusion and exclusion criteria as outlined in the four phases below were deleted. Step 1 involved eliminating publications and citations that were not relevant. One reviewer completed stage 2 by reading the titles and abstracts of all the acquired studies and selecting only those that were pertinent. Every story that lacked statistics and facts was instantly disqualified from our examination. The complete article was received and cross-checked with the second examiner for its consideration in the event that there was any remaining uncertainty.

In order to determine if the articles that were first reviewed in Stage 1 indeed contained information relevant to our review, both examiners double-checked them in Stage 3. Care was made to weed out any unfinished or publications with scant data during this phase. The uncited articles were also taken out.

The publications gathered in Stage 3 were carefully examined, and Stage 4 focused on the research that matched our PICOS data. In our review, certain articles were eliminated.

ELIGIBILITY CRITERIA

Inclusion Criteria: Articles describing Randomized Control Trials (RCTs), in vivo studies , and in vitro studies on patients undergoing primary palatoplasty with or without the use of tranexamic acid as an intervention were included in the review. Only studies with calibration

of the blood loss volume as primary outcome measure were included.studies with proper scale to assess operators comfort.

Exclusion Criteria: Studies with inadequate data with regards to the method of assessment of blood loss, studies with no defined method for assessment of operator comfort, Studies with only pre and post operative hemoglobin levels or Hematocrit values as indirect assessment of blood loss were excluded, systematic / narrative reviews, animal studies, and studies published in languages other than English were excluded from this systematic review. The studies were assessed for eligibility according to inclusion criteria by two independent reviewers.

DATA EXTRACTION

The required data for our review were obtained from the final articles by the first reviewer which was then reevaluated by the second reviewer. They were tabulated and the data were collected according to the headings as characteristics table and summation table.

- Author,
- year of publication,
- place of study,
- study design,
- Age
- total sample size,
- intervention group,
- control group,
- type of outcome,
- method of outcome assessment,
- Bleeding (in ml)
- Dose of tranexamic acid
- author conclusions.
- author conclusions.

RISK OF BIAS

Risk of Bias was assessed using the RoB 2.0 tool

The risk of bias parameters for each included study were evaluated by two authors. The risk of bias in was assessed according to the description given for the following parameters: random sequence generation; single-operator protocol implementation; the presence of a control group; blinding of the testing machine operator; standardization of the sample preparation; failure mode evaluation; use of the materials following manufacturer's instructions; clarification of the sample size calculation. If the examined parameter was reported by the author, the study received a "YES". On the other hand, if the information was missing, the parameter received a "NO." Risk of bias from each study was classified according

to the sum of the "YES" answers received: 1 to 3 corresponded to a high, 4 to 6 medium, and 7 to 8 to a low risk of bias. The quality of the articles selected were reviewed by two authors and the assessment was in accordance with CONSORT guidelines.

VARIABLE OF INTEREST

Bleeding: Gauze count and Suction count

A gauze of 10cm*10cm, fully soaked will have 12ml of blood and total suction count minus the saline used is used to total the blood loss.

Surgeon Comfort:

Table 1. FROMME'S ORDINAL SCALE OF ASSESSMENT OF SURGICAL FIELD AND FROMME'S MODIFIED SCALE

Level	Aspect of Surgical Field
Ordinal scale	
5	Massive uncontrollable bleeding
4	Bleeding heavy but controllable that significantly interferes with dissection
3	Reasonable bleeding that moderately compromises surgical dissection
2	Moderate bleeding that does not interfere with accurate dissection
1	Bleeding so mild it is not even a surgical nuisance
0	No bleeding, virtually bloodless field

SUMMARY SYNTHESIS

Consequently, we provided a narrative synthesis of the findings, summarizing the key results of each study and identifying any patterns or trends that emerged. Although we were not able to perform a meta-analysis, our narrative synthesis provided a qualitative summary of the available evidence, allowing us to draw meaningful conclusions and inform clinical practice.

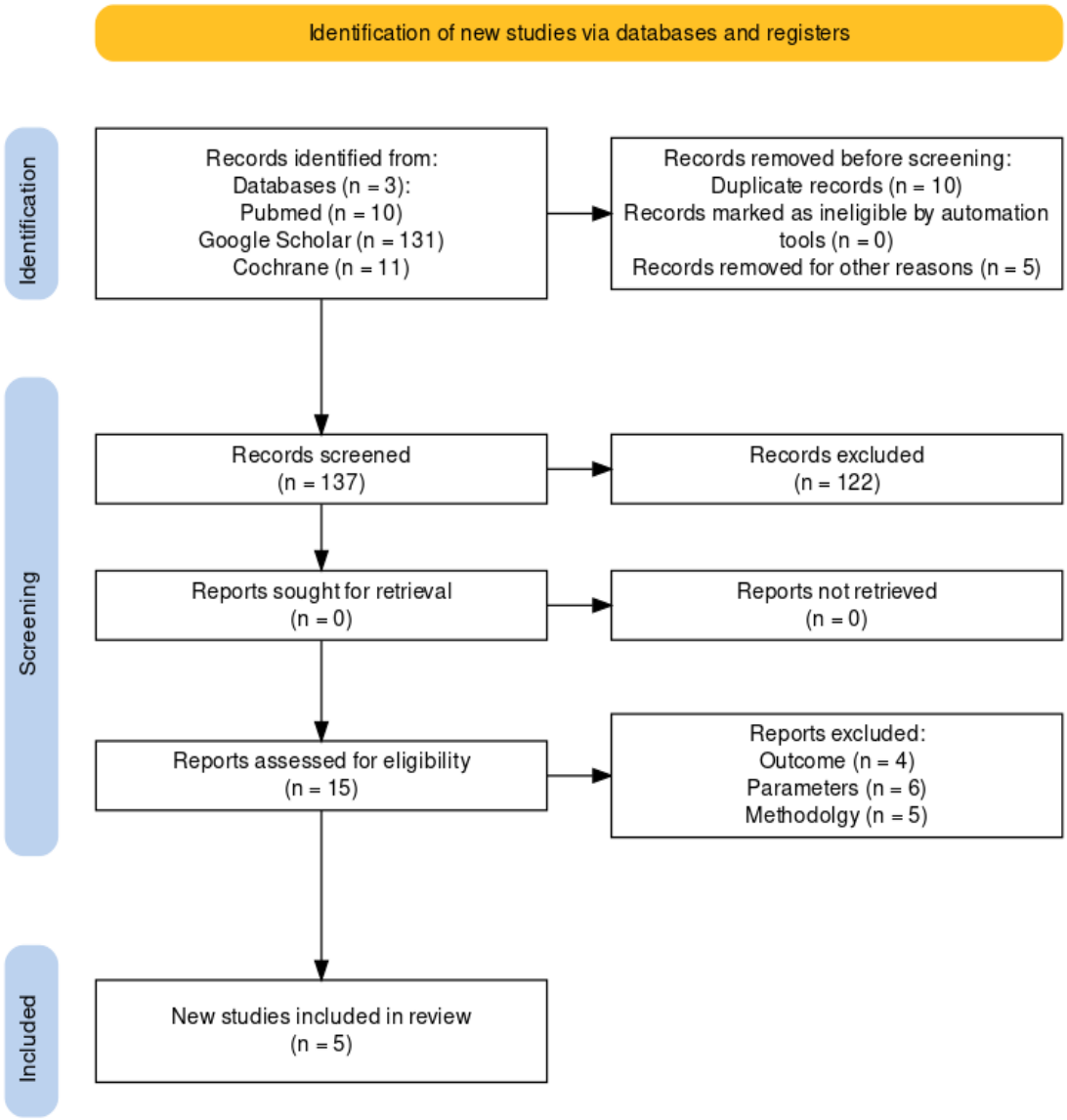
3. RESULTS:

A total of 137 articles were obtained from electronic databases and manual search. Out of which 15 studies qualified for full-text screening after review by 2 independent reviewers. and 10 articles were excluded because of difference inadequate data on the method of blood loss assessment studies were excluded due to lack of definitive scale for assessment of operator comfort.

CHARACTERISTICS TABLE

A total of 5 randomised controlled trials were included in the study. All included patients undergoing primary palatoplasty and used tranexamic acid as an intervention. In all the studies average blood loss was less in patients in tranexamic acid group than control group. Also the surgeons comfort and field of operation was more clearer in tranexamic acid group.

PRISMA FLOW CHART:



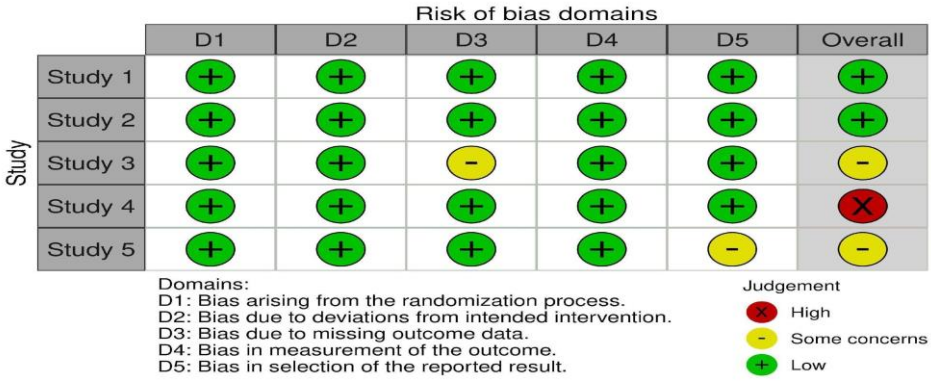
No	Author & Year	Study design & Sample Size	Method of Evaluation	Mean value	Outcomes
l	Dashti Khavidaki et al, 2022 (10)	Randomized clinical trial N=30	Effect of preoperative intravenous tranexamic acid on the amount of bleeding was assessed using the	Mean bleeding was 1 1.73 ± 4.42 mi llilitres in the TXA receiving group and 17.36 ± 4.99 mi llilitres in the control group, which was	TXA significantly reduced the amount of bleeding and the duration of surgery in cleft palate surgery compared to control group

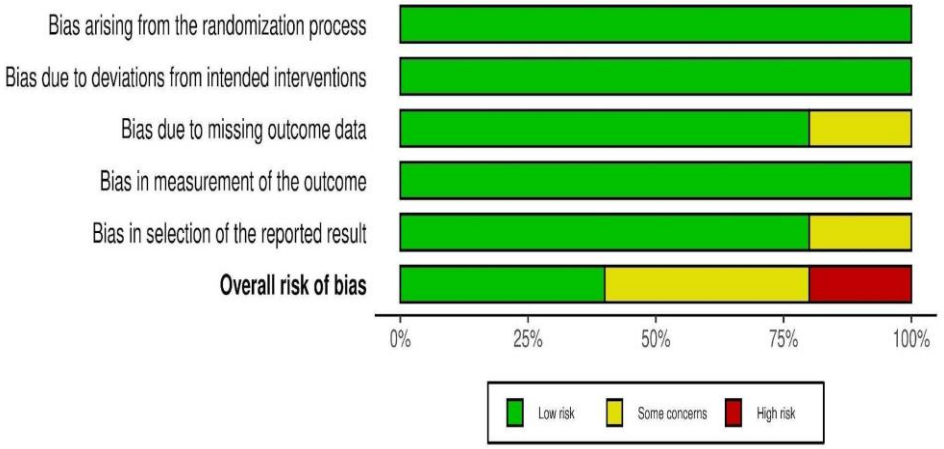
			number of blood-stained gases and the volume of the suctioned blood	significantly different (P-value = 0.00 I)	
2	Am ir Shafa et al, 2020 (11)	Random ized clinical trial N=80	Effect of preoperative dosage of tranexam ic acid to reduce blood loss was recorded based on the amount of blood collected in the suction bott le and the number of blood-soaked gauzes. Surgeon's satisfaction with the surgical fi ld was scored and recorded on a Likert scale ranging from I (low satisfaction) to 5 (very high satisfaction).	TXA groups with dosages of 5, 7.5, and 10 mg/kg with the means of 63.75 ± I 0.62, 61.25 ± 15.03, and 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)	All three dosages of TXA, 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 significantly higher than that of the control group. It seems safe to use a minimal dosage of TXA to control and reduce the amount of blood loss in ch ildren undergoing cleft palate surgery
3.	Mufassar N ishat et al, 2021 (12)	Prospective randomized clinical study N=82	Effect of preoperative tranexam ic acid on quality of surgery was assessed using grading of field of surgical n scale of I 0- points , gratification level (good, average, or poor) Time taken for Surgery, quality of surgical field, transfusions of blood, and problems related to blood loss were all recorded.	The median grading of the surgical operation was 4 in case of control individual group and 3 in case of individuals belonging to test group. The operating surgeons documented level of satisfaction as satisfactory with the surgical field in 11 of 31 in cases related to control group, whi le operating surgeon satisfaction was ranked as good in case of 24 to 34 sites in case of test group members	A bolus of tranexamic acid in dosage of 0.0 I g/kg was given prior to surgical incision showed noteworthy results with respect to improvement in case of surgery by surgeons
4	Amir Shafa et al, 2018(13)	Randomized clinical trial N=74	Effect of tranexamic acid and controlled hypotension with remifentanil on intraoperative blood loss was accurately recorded based on the amount of blood collected in the	The mean blood loss was 76.46± 14.7 and 57.76± 14.16 ml in the remifentanil and tranexamic acid groups, respectively (P< 0.001). The mean PACU stay times were 64.5± 5.3 and	Tranexamic acid is more effective than remifentanil in decreasing intraoperative blood loss and PACU stay.

			suction bottle and the number of bloodsoaked gauzes. Surgeon 's satisfaction was measured on a Likert scale at the end of each surgery. The patients' duration of PACU stay was also recorded based on the modified Aldrete scores and the data collected from the two groups were compared.	46.35 ± 4.4 min in the rem ifentani l and tranexamic acid groups, respectively (P< 0.00 1)	
5	Padmaja Durga et al, 2015 (14)	Prospect ive randomized clinical study N=70	Efficacy of tranexamic acid on surgical field was evaluated using grading of Sw-gical Field on a l 0-poi nt scale and surgeon 's satisfaction with field was graded as good, average or poor	The median grades of assessment of the surgical field were 4 in the control group and 3 in the test group (P=0.003) The surgeon reported good satisfaction with the field in l 0 of 32 (31.3%) cases in the control group, whereas surgeon satisfaction was graded as good in 23 of 33 (69.7%) sites in the test group (P=0.008)	This study showed a modest improvement in the sw-gical field, but the consequent satisfaction of the surgeon with the surgical field increased significantly

RISK OF BIAS ASSESSMENT

Risk of bias assessment concluded 2 were low risk studies, 2 had some concerns and 1 was high risk study.





Blood loss and Surgeons Comfort in Cleft palate Surgery:

According to the study conducted by Khavidaki et al in 2022, tranexamic acid significantly reduced the amount of bleeding and the duration of surgery in cleft palate surgery compared to control group (P value = 0.001)

Similar results were also found in a study conducted by Nishat et al in 2021 where a bolus of tranexamic acid in dosage of 0.01 g/kg was given prior to surgical incision, showing noteworthy results with respect to improvement in case of surgery.

Shafa et al in 2021 assessed three doses of TXA (5, 7.5, and 10 mg/kg) and concluded that all the three dosages of TXA had a significant role in reducing the amount of blood loss when compared to control group ($P < 0.001$) and no significant differences was found among the mentioned dosages ($P > 0.05$).

In the study conducted by Shafa et al in 2019, a significant decrease in intraoperative blood loss and PACU stay was found in Tranexamic acid group compared to remifentanil group ($P< 0.001$)

Efficacy of tranexamic acid on surgical field was evaluated by Durga et al in 2015 and concluded that median grades of assessment of the surgical field were 4 in the control group and 3 in the test group ($P=0.003$). The surgeon reported good satisfaction with the field in 10 of 32 (31.3%) cases in the control group, whereas surgeon satisfaction was graded as good in 23 of 33 (69.7%) sites in the test group ($P=0.008$).

4. DISCUSSION

Blood loss is one of the important parameters that needs to be given high priority in Paediatric surgeries. Low circulatory volume that is seen in this patients restricts that allowable loss that can have detrimental effects on the overall surgical outcome.

In Pediatric patients undergoing cleft palate surgeries with average body weight of 10 kgs, the overall circulatory volume remains 800 ml with maximum allowable loss being restricted to

80 to 100 ml. (15)

The average blood loss that has been reported for a palatal repair includes 50 to 60 ml. (16) Though this range appears to be within the physiological acceptable limits, this may be of greater cardiovascular burden in patients with low body weight or borderline anaemic patients. This minimising the blood loss not only aids to circumvent these problems but also facilitates overall better healing of the surgical sites with better outcomes.

Various measures have been described in the literature so far to reduce the intra operative volume loss. These strategies range from use of hypotensive agents including clonidine, NTG infusion, Dexmedetomidine infusion, Intravenous Beta blocker administration. These agents have been reported to minimise blood loss and improve the operator comfort by providing blood less field, their use is often restricted to use in adult patients. (17)

Inhalational agents including enflurane and isoflurane can be used to however these all the foresaid IV/ Inhalational agents facilitate hypotension by reducing * the systemic vascular resistance that can be fatal In a year old infants who are predisposed to have a high Vagal tone predisposing them to cardiogenic shock.(18)

Tranexemic acid is one of the safest antifibrinolytic ageing that inhibits fibrinolysis. TXA has been found to have a great role in reducing the intra operative blood loss when administered an hour prior to surgery. (19) TXA also has found a major role in hemostatic resuscitation in acute trauma life support. The drug is administered as an intravenous infusion and is metabolised and excreted through the renal system. This has been found to be safe in Pediatric and renal compromised patients.

Hence its has found greater application for haemorrhage control in this age group (20)

From the current review it is certain that use of TXA for cleft palate repair reduces the intra operative loss to 20 to 30 ml which is half the volume loss when it is not used. The operator comfort also has been found to be significantly better in groups with the use of TXA.(11)

Intraoperative bleeding is a serious challenge in various surgical procedures. It is associated with relatively high mortality and morbidity, especially in pediatric procedures, such as cleft palate repair. The primary treatment for cleft lip and cleft palate disorders is surgery. One of the main complications of this surgery is bleeding.

At present, all recent guidelines regarding critical bleeding recommend TXA, which is considered as a significant part of pediatric patient blood management protocols. The mean bleeding rate was significantly lower in the TXA receiving group than in the control group or remifentanil. Also decreased PACU stay was found in TXA group when compared to remifentanil. The mean values of PT, PTT, and Hb were not significantly different between the TXA receiving and control groups before and after surgery.

5. CONCLUSION

- Surgeon's satisfaction with the surgical field in the TXA groups were significantly higher than surgeon's satisfaction in the control group. Tranexamic acid can be recommended and routinely used without any fear of side effects in paediatric cleft palate surgeries for

reduced blood loss. Which in turn decreases need for extra intra-operative Haemostatic measures and increases surgeons comfort and reduces need for post operative blood transfusion.

References

1. Mossey, P. A. et al. (2003) Global Registry and Database on Craniofacial Anomalies: Report of a WHO Registry Meeting on Craniofacial Anomalies : Baurú, Brazil, 4-6 December 2001
2. Spritz, R. A. (2001) 'The genetics and epigenetics of orofacial clefts', Current opinion in pediatrics, 13(6), pp. 556–560 :
3. Sadove AM, van Aalst JA, Culp JA. Cleft palate repair: art and issues. Clin Plast Surg. 2004;31(2):231-241. doi:10.1016/S0094-1298(03)00136-6
4. Liau JY, Sadove AM, van Aalst JA. An evidence-based approach to cleft palate repair. Plast Reconstr Surg. 2010;126(6):2216-2221. doi:10.1097/PRS.0b013e3181f830eb
5. Jonnavithula N, Durga P, Madduri V, et al. Efficacy of palatal block for analgesia following palatoplasty in children with cleft palate. Paediatr Anaesth. 2010;20(8):727-733. doi:10.1111/j.1460-9592.2010.03347.x
6. Vyas T, Gupta P, Kumar S, Gupta R, Gupta T, Singh HP. Cleft of lip and palate: A review. J Family Med Prim Care. 2020;9(6):2621–5. doi: 10.4103/jfmpc.jfmpc_472_20. [PubMed: 32984097]. [PubMed Central: PMC7491837].
7. Rossell-Perry P, Schneider WJ, Gavino-Gutierrez AM. A comparative study to evaluate a simple method for the management of postoperative bleeding following palatoplasty. Arch Plast Surg. 2013;40(3):263– 6. doi: 10.5999/aps.2013.40.3.263. [PubMed: 23730606]. [PubMed Central: PMC3665874].
8. Haddadi S, Parvizi A, Fadaee Naiini AR, Atkar Roshan Z, Arghand S, Naderi Nabi B. [Efficacy of the prophylactic dose of tranexamic acid in the amount of blood during mandibular surgeries]. Anesthesiol Pain. 2015;6(1):16–24. Persian
9. Arantes GC, Pereira RMR, de Melo DB, Alonso N, Duarte M. Effectiveness of tranexamic acid for reducing intraoperative bleeding palatoplasties: A randomized clinical trial. J Craniomaxillofac Surg. 2017;45(5):642–8. doi: 10.1016/j.jcms.2016.12.021. [PubMed: 28318926].
10. Dashti Khavidaki G, Yaghoubi S , Naderi M, Malek F. The Effect of Preoperative Intravenous Tranexamic Acid on the Amount of Bleeding in Patients Undergoing Cleft Palate Reconstruction Surgery. Iran J Pediatr. 2022;32(5):e118170. https://doi.org/10.5812/ijp-118170.
11. Shafa A, Shetabi H, Adineh-Mehr L, Bahrami K. Selection of the optimal dosage of tranexamic acid to reduce blood loss during pediatric cleft palate surgery. Tzu Chi Med J 2021; 33(2): 181-7.
12. Nishat, M., Iqbal, S., Ahmed, A., Younas, S., Deokah, L.A., & Rashid, Z. (2021). Clinical study of Evaluation of the Effect of Tranexamic Acid in Primary Cleft Palate Surgery in Children. Pakistan Journal of Medical and Health Sciences.
13. Amir Shafa ,Azade Bahadori, Abdolfatah Mamipour. (2019) A Comparative Study on The Effects of Tranexamic Acid and Controlled Hypotension with Remifentanil on Blood Loss During Cleft Palate Repair. Archives of Anesthesiology and Critical Care
14. Durga, P., Raavula, P., Gurajala, I., Gunnam, P., Veerabathula, P., Reddy, M., Upputuri, O., & Ramachandran, G. (2015). Evaluation of the Efficacy of Tranexamic Acid on the Surgical Field in Primary Cleft Palate Surgery on Children-A Prospective, Randomized Clinical Study. The Cleft palate-craniofacial journal : official publication of the American Cleft Palate-

Craniofacial Association, 52(5), e183–e187. https://doi.org/10.1597/14-263
15. Kim BJ, Choi TH, Kim S. Prospective Study on the Intraoperative Blood Loss in Patients with Cleft Palate Undergoing Furlow's Double Opposing Z-Palatoplasty. Cleft Palate Craniofac J. 2018;55(7):954-958. doi:10.1597/15-278
16. Adeyemo WL, Ogunlewe MO, Desalu I, et al. Frequency of homologous blood transfusion in patients undergoing cleft lip and palate surgery. Indian J Plast Surg. 2010;43(1):54-59. doi:10.4103/0970-0358.63967
17. Shah A, Palmer AJR, Klein AA. Strategies to minimize intraoperative blood loss during major surgery. Br J Surg. 2020;107(2):e26-e38. doi:10.1002/bjs.11393
18. Miller AL, Theodore D, Widrich J. Inhalational Anesthetic. [Updated 2023 May 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554540/
19. UK Royal Colleges Tranexamic Acid in Surgery Implementation Group, Grocott MPW, Murphy M, Roberts I, Sayers R, Toh CH. Tranexamic acid for safer surgery: the time is now. Br J Surg. 2022;109(12):1182-1183. doi:10.1093/bjs/znac252
20. Urban D, Dehaeck R, Lorenzetti D, et al. Safety and efficacy of tranexamic acid in bleeding paediatric trauma patients: a systematic review protocol. BMJ Open. 2016;6(9):e012947. Published 2016 Sep 22. doi:10.1136/bmjopen-2016-012947