Main Article

Preoperative Systemic Tranexamic Acid in Tonsillectomy and Adeno-tonsillectomy: A Relevant Underrated Outcome

https://doi.org/10.47210/bjohns.2021.v29i3.560

Rajarajeswari Nalamate,[1] Jishana J,[1] Mary Kurien,[1] Mamie Zachariah,[2] Sajeiv Koshy[1]

ABSTRACT

Introduction

Tranexamic acid, a synthetic anti-fibrinolytic plasminogen inhibitor, a relatively safe drug, is reported to reduce bleeding in various surgical procedures. Our study was to identify the efficacy of tranexamic acid in reducing intraoperative bleeding during tonsillectomy and adeno-tonsillectomy, a common paediatric ENT surgery done as day care procedure.

Materials and Methods

A randomised, placebo controlled, double blinded trial was undertaken with consecutive patients undergoing above procedures, sample size being 100, with 50 patients in each arm. Post induction, injection tranexamic acid 15mg /kg body weight and saline was given to the test and control group respectively. Intraoperative bleeding was measured and operating time was also noted.

Results

There were 80 participants, with 41 and 39 patients in treatment and placebo group respectively ranging from 4 to 32 years age. There was no significant difference in the amount of blood loss between the two groups. However, the duration of surgery was significantly lowered in tranexamic acid as compared to placebo group ($p = 0.008$).

Conclusions

Preoperative use of tranexamic acid in tonsillectomy or adeno-tonsillectomy, significantly reduced operating time though no significant reduction of intra or postoperative bleeding was noted. This previously unreported outcome has surgical implication, especially in children, for possible use of this widely accepted safe drug during these procedures..

Keywords

Adenoidectomy; Tonsillectomy; Haemorrhage; Operative Time; Tranexamic Acid

Tonsillectomy and adeno-tonsillectomy are common major surgeries in ENT practice, especially in paediatric ENT. Primary, reactionary and secondary bleeding related to surgery is a major issue. About 50% of the patients are managed as day care. Since blood volume in children is low, blood loss measurement in paediatric surgery is also important. The average amount of blood loss in cold knife dissection tonsillectomy is about 100 ml.[1] Blood loss also depends on various factors like age, sex, type of tonsillectomy, method of dissection, haemoglobin concentration, clotting time and the use of antibiotics.

Tranexamic acid has been used for many years to minimise blood loss during surgery. Tranexamic acid (TXA) is a synthetic amino acid lysine, antifibrinolytic–plasminogen inhibitor, trans-4-aminomethyl-cyclohexane carboxylic acid. It is a relatively safe drug with weak non-competitive inhibition of conversion

1 - Department of ENT, Pondicherry Institute of Medical Sciences, Pondicherry
2 - Department of Anaesthesia, Pondicherry Institute of Medical Sciences, Pondicherry
Corresponding author:
Dr Rajarajeswari Nalamate
email: rajisampathporal@gmail.com

of plasminogen to plasmin. It has been widely and successfully used to reduce bleeding in cardiac, orthopaedic, prostate and caesarean surgeries.[2]

Data available in the literature shows conflicting evidence regarding effect of tranexamic acid in reducing the amount of bleeding in tonsillectomy and adeno-tonsillectomy. Regarding intraoperative bleeding, two RCTs have reported preoperative use of Tranexamic acid to have insignificant reduction[3] or no reduction.[4] A meta-analysis,[5] another RCT[6] and most recent retrospective case control study[7] reported significant reduction. Regarding reactionary or secondary bleeding, two retrospective studies reported its use to reduce significantly.[7,8] Considering these conflicting reports and the most accepted study design for therapeutic outcome being randomized control trial (RCT) this study was initiated. The aim was to identify the efficacy of tranexamic acid in reducing bleeding during tonsillectomy and adeno-tonsillectomy.

Materials and Methods

Inclusion criteria: All patients posted for tonsillectomy or adeno-tonsillectomy between age of 3 and 40 years with recurrent or chronic tonsillitis, adeno-tonsillitis and obstructive symptoms secondary to hypertrophied tonsils.

Exclusion criteria: Patients with allergy to tranexamic acid, bleeding disorders, age <3 and >40 years and suspected cases of nasopharyngeal or tonsillar malignancy.

Method of randomization: Computer generated block randomization.

A randomised, placebo controlled, double blinded trial was undertaken in patients posted for tonsillectomy and adenotonsillectomy. Following clearances from Institutional Research and Ethics committee (IEC Ref No: IEC: RC/18/57) and Drug Controller of India, this study was registration in the Clinical Trials Registry of India (CTRI registration number: CTRI/2019/04/018352). Sample size was calculated based on the assumption that, to detect 50ml difference in volume of blood loss, when the average blood loss is 100ml/ patient, we need to study 50 patients per group. So, total of 100 patients with 95% confidence interval and 80% power was finalised. Informed consent / assent was obtained from the study participants / parent / legally authorized representative. The experimental group was given injection Tranexamic acid 15mg/kg body weight made up to 10ml and the control group was given 10ml saline. Both groups were given the injection, preoperatively over a period of 5 minutes, just after intubation prior to the start of the surgery. Surgery was done by cold steel method of tonsillectomy endoscopic assisted adenoidectomy, the operating surgeons were residents under faculty supervision, and all participants were given the same induction protocol. Both the operating surgeon and faculty supervisor were blinded.

The preoperative and postoperative measurement of blood loss was done by the operation theatre circulating nurse, who was also blinded. Amount of blood loss during surgery was measured by comparing the weight of the dry 4x4 gauze pads and cotton balls before surgery and at the end of the case, added to the amount of collected blood in the suction bottle9. Blood loss was assessed by finding out the difference in the weight of the gauze, cotton balls and the amount of saline used before and after surgery, adjusting to the specific gravity of blood (1.055). Any episodes of haemorrhage in immediate postoperative period and up to 10 days postop were noted. Any occurrence of adverse drug reactions was also noted.

Unfortunately, sample collection had to be terminated when it reached 80 due to abrupt, unprecedented suspension of elective surgeries due to the COVID pandemic. Following clearance from the Institutional Research and Ethics Committee, Interim analysis by Statistical Consultant was done. This showed no clinically significant difference in the blood loss between the two arms of the study. With 80% recruitment, there was only a 13ml blood loss difference with p value of 0.33. The result does not suggest that this would likely to show any statistical significance even if the study was prolonged and total 100 cases recruited.

Statistical Analysis:

The data was entered in MS excel and analysed using SPSS version 20.0. Qualitative data was represented frequency and percentage. Normality of the data

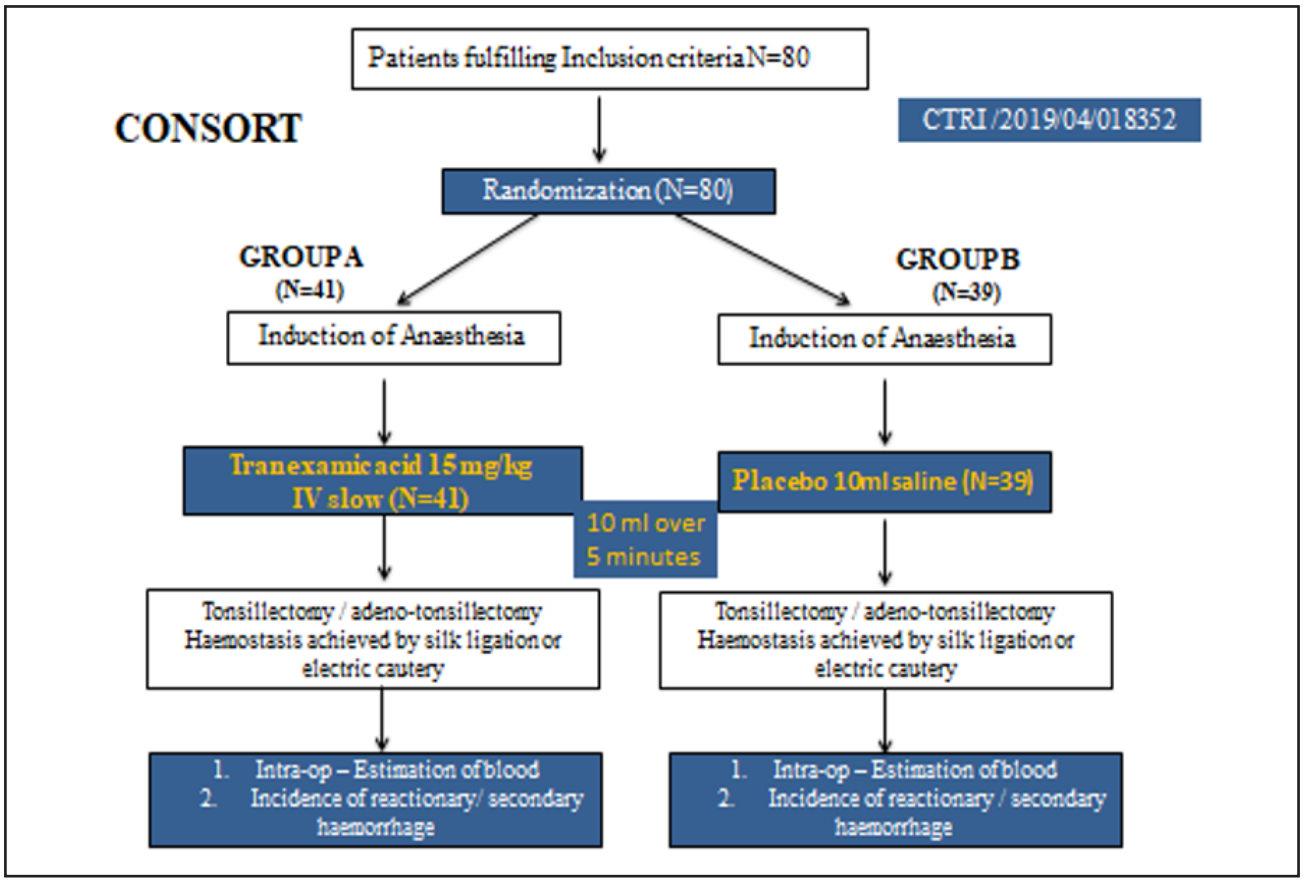

Fig.1. FlowChart

was assessed using Shapiro Wilk test. Since all the quantitative variables followed non normal distribution, median and inter-quartile range was used to represent the data. Mann Whitney U test was used to find the difference between quantitative variables. Qualitative variables were assessed using Chi- Square test and Fischer exact test wherever necessary. P value <0.05 was considered significant.

Results

There were eighty participants in this study with 39 in the experimental and 41 in the control group (Fig. 1)

The age ranged between 3 to 40 years. The median age was 11 years and 12 years in the Tranexamic acid (TXA) group and placebo group respectively. All the baseline characters were comparable in both the groups (Table I).

The average amount of blood loss was 119 (61) ml and 123 (114) ml in the Tranexamic acid group and placebo respectively. Though the amount of blood loss was higher in the placebo group compared to test group, there was no statistically significant difference in the amount of blood loss between them (p value was 0.573). Reactionary haemorrhage was seen only in one patient in placebo group, statistically not significant. Secondary haemorrhage was seen in one patient in the test group. The average duration of surgery in minutes was 75 (43) and 100 (35) in the test and placebo group respectively (p value of 0.008), indicating that duration of surgery was significantly lowered in group that received tranexamic acid (TXA) as compared to placebo group (Table II).

Comparative analysis of blood loss across the two age groups of above and below twelve years of age,

Table I: Baseline characters of the study participants

BASELINE CHARACTERS		TRANEXAMIC ACID	PLACEBO	P VALUE
Age (years) [median & IQR]		11.00 (7)	12.00 (6)	0.969*
Sex	F	21	17	0.495#
	M	20	22	
Indication	Chronic adenotonsillitis	27	30	0.489#
	Chronic tonsillitis	12	7	
	Hypertrophic tonsils	0	1	
	Obstructive hypertrophic tonsils	1	1	
	Tonsillar cyst	1	0	
Surgery done	Adenotonsillectomy	28	31	0.255#
	Tonsillectomy	13	8	
H/O allergy to Tranexamic acid		41	39	NA
Bleed/coagulation diseases		41	39	NA
H/O altered colour vision		41	39	NA
H/O renal diseases		41	39	NA
Grade of Tonsils	1+	0	1	0.335#
	2+	12	6	
	3+	25	29	
	4+	4	3	
Nasopharynx-Adenoids	0+	7	2	0.206#
	1+	8	7	
	2+	7	6	
	3+	16	15	
	4+	3	9	
Weight (kg) [median & IQR]		28.00 (17)	30.00 (14)	0.609*

*IQR: Inter quartile range; *Mann Whitney U test; #Chi-square test;*

Table II: Effect on duration of surgery, post operative bleeding episodes and side effects

CHARACTERS		TXA	PLACEBO	P VALUE
Duration of surgery (minutes) [median & IQR]		75.00 (43)	100.00 (35)	0.008*
Total blood loss (ml) [median & IQR]		119.00 (61)	123.00 (114)	0.573*
Reactionary haemorrhage (h'age)	Nil	41 (100.0%)	37 (94.9%)	0.340#
	Primary h'age	0 (0.0%)	1 (2.6%)	
	Reactionary h'age	0 (0.0%)	1 (2.6%)	
Secondary haemorrhage (h'age)	Nil	40 (97.6%)	39 (100.0%)	1.000$
	Secondary h'age 5th Post-operativeDay	1 (2.4%)	0 (0.0%)	
Final follow up	Fossa healthy	41 (100.0%)	39 (100.0%)	NA
Any A/E	Nil	41 (100.0%)	39 (100.0%)	NA

*IQR: Inter quartile range; *Mann Whitney U test; #Chi-square test; $Fisher's exact test; h'age – haemorrhage,*

percentage of body weight, and duration of time between tonsillectomy and adenotonsillectomy did not show any statistical significance. (Tables III and IV).

Discussion

Tranexamic acid (TXA) has been widely and successfully used to reduce bleeding in cardiac, orthopaedic, prostate and caesarean surgeries. It's preoperative use in reducing the amount of bleeding in tonsillectomy and adeno-tonsillectomy has had conflicting reports to date.[3,5-8]

TXA has been reported to be a statistically significant reduction in intraoperative blood loss was noted in two trials (n=180), when tranexamic acid was given as a single dose at induction (32.73ml, 95%CI -42.66, -22.78, P<0.001). This was reported in a systemic review and meta-analysis5 where most studies were done before 1980. Similarly, a retrospective review of clinical records between 2007 and 2013 showed perioperative tranexamic acid in a single, parenteral dose reduces the incidence of primary haemorrhage following paediatric tonsillectomy, facilitating discharge on the day of surgery.[8]

However, considering the study of effect of therapeutic intervention, an experimental study, being the best design previously published RCTs reported that preoperative use of TXA showed no statistical significant reduction in intraoperative bleeding volume.[5,7] One RCT has reported significant reduction in intraoperative bleeding though statistical analysis were not clarified6. The present double blinded RCT, like majority of the previous RCTs did not reveal significant reduction in intraoperative bleeding.

Considering post tonsillectomy reactionary and secondary bleeding, systemic and meta-analysis study[5] reported five studies (n=1,670) when compared the number of patients with post tonsillectomy haemorrhage between TXA and control groups, did not show significant reduction. Similarly, there was no significant decrease in secondary haemorrhage with the use of tranexamic acid in few reported RCTs. The present RCT too did not show significantly reduced postoperative haemorrhage. However, recent retrospective case-control study, reported a benefit in the acute management of paediatric secondary haemorrhage, reducing readmission to theatres for surgical re-intervention.[7]

The present study revealed significantly reduced operating time in the group that received TXA as compared to the placebo group. This is being reported

Table III: Blood loss and duration of surgery of participants above and below 12yrs of age.

AGE CATEGORY		DRUG USED	N	MEAN	STANDARD DEVIATION	P VALUE
</=12 yrs	Age	TXA	24	8.71	2.074	0.169
		Placebo	26	9.58	2.318	
	Estimated blood volume (ml)	TXA	24	1796.67	502.088	0.26
		Placebo	26	1960	510.623	
	total blood loss during surgery (ml)	TXA	24	134.33	61.451	0.595
		Placebo	26	144.58	73.87	
	% blood loss	TXA	24	8.046	4.1445	0.878
		Placebo	26	7.854	4.685	
	duration of surgery (minutes)	TXA	24	87.08	28.281	0.061
		Placebo	26	102.65	29.174	
>12 yrs	Age	TXA	17	19.29	5.924	0.149
		Placebo	13	16.85	2.853	
	Estimated blood volume (ml)	TXA	17	3115.29	834.971	0.87
		Placebo	13	3156.92	542.208	
	total blood loss during surgery (ml)	TXA	17	126.35	61.882	0.493
		Placebo	13	142	60.477	
	% blood loss	TXA	17	4.353	2.3423	0.792
		Placebo	13	4.569	2.0918	
	duration of surgery (minutes)	TXA	17	73.24	27.038	0.091
		Placebo	13	91.54	29.182	

*Student's t test - *Mann Whitney U test*

Among </=12 years, there was a statistically significant difference between the TXA & placebo groups with respect to duration of surgery.

Among >12 years, there was a statistically significant difference between the TXA & placebo groups with respect to duration of surgery.

for the first time. Even though, all surgeries were done by the residents under faculty supervision, the noticeable point was that, amount of blood loss among the groups was not significantly different, but the reduced operating time with tranexamic acid group was very much observable. There were no significant adverse side effects like vomiting, hypotension or change in colour vision noted in study participants.

Conclusion

Preoperative use of tranexamic acid in tonsillectomy and adenotonsillectomy, besides being safe, significantly reduced operative time though does not significantly

Table IV: Blood loss and duration of surgery based on percentage of body weight of participants.

WEIGHT CATEGORY		DRUG USED	N	MEAN	STANDARD DEVIATION	P VALUE
</=20kg	Age	TXA	9	6.89	2.028	
		Placebo	7	7	2.38	0.923
	Estimated blood volume (ml)	TXA	9	1324.44	174.865	
		Placebo	7	1325.71	200.571	0.99
	total blood loss during surgery (ml)	TXA	9	139.78	48.987	
		Placebo	7	154	92.416	0.721
	% blood loss	TXA	9	10.611	3.6498	
		Placebo	7	11.2	5.9961	0.824
	duration of surgery (minutes)	TXA	9	78.33	16.394	
		Placebo	7	103.57	26.412	0.052
>20kg	Age	TXA	32	14.84	6.471	
		Placebo	32	13.09	3.779	0.193
	Estimated blood volume (ml)	TXA	32	2630	843.158	
		Placebo	32	2585	650.38	0.812
	total blood loss during surgery (ml)	TXA	32	128.56	64.427	
		Placebo	32	141.47	64.313	0.426
	% blood loss	TXA	32	5.363	3.2052	
		Placebo	32	5.787	3.1661	0.596
	duration of surgery (minutes)	TXA	32	82.19	30.977	
		Placebo	32	97.94	30.161	0.044

reduce intraoperative and postoperative bleeding. This relevant former outcome which has not been previously reported has beneficial clinical implications, especially in children.

Acknowledgements

The authors thank the residents in department of ENT and department of Anaesthesia and Nursing for their efforts in preparing the medications and measurement of the blood loss during the study.

References

1. Prasad KC, Prasad SC. Assessment of Operative blood loss and the factors affecting it in Tonsillectomy and Adenotonsillectomy. Indian Journal of Otolaryngology, Head and Neck Surgery 2011; 63(4):343-8. doi 10.1007/s12070-011-0268-9
2. Weitz JI. Blood Coagulation and Anticoagulant, Fibrinolytic and Antiplatelet Drugs. In: Laurence LB, Bruce AC, Bjorn CK (eds). Goodman & Gilman's The Pharmacological basis of Therapeutics. 13th edition. New York: McGraw-Hill Education; 2017.p596.
3. Soliman R, Ali Alshehri A. Assessment of the effect of tranexamic acid on perioperative bleeding in paediatric patients undergoing tonsillectomy. Egyptian Journal of Anaesthesia

2015; 31:297-301. https://doi.org/10.1016/j.egja.2015.07.002

4. Brum MR, Miura MS, Castro SF, Machado GM, Lima LH, Lubianca Neto JF. Tranexamic acid in adenotonsillectomy in children: a double-blind randomised clinical trial. Int J Pediatr Otorhinolaryngol. 2012; 76(10):1401-5. doi: 10.1016/j.ijporl.2012.04.028
5. Chan CC, Chan YY, Tanweer F. Systematic review and meta-analysis of the use of tranexamic acid in tonsillectomy. Eur Arch Otorhinolaryngol. 2013; 270(2):735-48. doi:10.1007/s00405-012-2184-3
6. George A, Kumar R, Kumar S, Shetty S. A randomised control trial to verify the efficacy of pre-operative intra venous tranexamic acid in the control of tonsillectomy bleeding. Indian Journal of Otolaryngology Head and Neck Surgery 2011; 63(1):20-26.2. doi: 10.1007/s12070-010-0095-4
7. Alessandra LS, Hannah LC, Emily Z, Anton HB, Hayley H, Shyan V. The therapeutic use of tranexamic acid reduces reintervention in paediatric secondary post-tonsillectomy bleeding. Australian Journal of Otolaryngology doi: 10.21037/ajo.2020.04.02.https://www.researchgate.net/publication/340591997.
8. Robb PJ, Thorning G. Perioperative tranexamic acid in day-case paediatric tonsillectomy. Annals Royal College of Surgeons England 2014; 96(2):127-9. doi: 10.1308/003588414X13814021676477
9. Manikandan D, Musarrat F, Preetham AP, Anjali R. Measurement of blood loss during adenotonsillectomy in children and factors affecting it. Case Reports in Clinical medicine 2015; 04(05):151-6. doi: 10.4236/crcm.2015.45032.