A Randomized Control Trial to Verify the Efficacy of Pre-Operative Intra Venous Tranexamic Acid in the Control of Tonsillectomy Bleeding

Ajay George · Ranjan Kumar ·
Sanjay Kumar · Sharankumar Shetty

Received: 18 April 2010 / Accepted: 7 June 2010 / Published online: 11 January 2011
© Association of Otolaryngologists of India 2011

Abstract Tonsillectomy is an age old surgery which is still very commonly done. Bleeding related to surgery is the major problem. This study is done to verify by randomized control trial the efficacy of preoperative intravenous tranexamic acid in the control of tonsillectomy bleeding. Hundred cases undergoing tonsillectomy were randomized into two groups, one of which received pre-operatively intra venous tranexamic acid, 10 mg kg^{-1} . The other group patients were given a placebo. Amount of bleeding was assessed in each case. The study group had statistically highly significant reduction in bleeding. There were no side effects of the drug. This finding is similar to that in other studies for tonsillectomy, other surgeries and other hemorrhagic conditions. Tranexamic acid in the dose of 10 mg kg^{-1} given intra venous pre-operatively is effective in the control of tonsillectomy bleeding.

Keywords Tonsillectomy · Bleeding · Tranexamic acid

Introduction

Removal of the tonsils (derived from tonsa, Latin for “oar”) has been practiced since antiquity. Tonsillectomy is one of the most basic and popular operations done in otorhinolaryngology today for a variety of reasons. The most essential part of tonsillectomy after removal of the tonsils is complete control of haemorrhage. Early methods for controlling bleedings included pressure and caustic

agents; later, catgut, silk, noose ties, and sutures became popular. The suture instruments designed by Negus allowed control of haemostasis during and after tonsillectomy. The instruments used for tonsillectomy have evolved to render it a precise operation. The complication rate for tonsillectomy has declined although the types of complications remain the same [1].

Even today in some patients haemorrhage will be the most feared complication and sometimes even life threatening. Post tonsillectomy too haemorrhage becomes a risk due to airway obstruction, shock and ultimately death, if not diagnosed early or inappropriately treated [2]. With the advent of newer and newer antibiotics tonsillectomy is most of the times avoidable. Hence any intervention which reduces the mortality and morbidity of an otherwise avoidable surgery is of lot of clinical importance.

Tranexamic acid (*trans*-4-aminomethyl-cyclohexane carboxylic acid) is a relatively safe antifibrinolytic drug with weak non competitive inhibition of plasmin at high concentrations. Native human plasminogen contains one lysine binding site with high affinity for tranexamic acid ($k_d = 1.1 \mu\text{mol l}^{-1}$) and four or five with low affinity ($k_d = 750 \mu\text{mol l}^{-1}$). The binding of plasminogen and of the heavy chain of plasmin to fibrin monomer is also mediated through the lysine binding sites of plasminogen to specific lysine residues of fibrin; this interaction is virtually completely blocked by the synthetic antifibrinolytic amino acids. It is primarily the high affinity lysine binding site of plasminogen which is involved in its binding to fibrin; saturation of this binding site with tranexamic acid displaces plasminogen from the fibrin surface. This results in retardation of fibrinolysis because no matter how rapidly plasmin is formed, it cannot bind to fibrinogen or fibrin monomers, thereby precluding the proteolytic action by serine–histidine enzyme site. Conversely, when the lysine

A. George (✉) · R. Kumar · S. Kumar · S. Shetty
Department of ENT, Kamineni Institute of Medical Sciences,
Sreepuram, Narketpally, Andhra Pradesh, India
e-mail: doc_ajay@yahoo.com

binding sites of plasmin are blocked by tranexamic acid, inactivation by α_2 -antiplasmin is virtually impossible [3].

Tranexamic acid has been widely and successfully used to reduce bleeding in cardiac [4–6], orthopaedic [7, 8], prostate [9] and caesarean sections surgeries [10, 11]. In this study we plan to verify the efficacy of tranexamic acid in reducing tonsillectomy bleeding.

Aims and Objectives

To verify by randomized controlled trial the efficacy of preoperative intravenous tranexamic acid in reducing tonsillectomy bleeding.

To measure effect on time taken for surgery.

Materials and Methods

A total of 100 patients who underwent tonsillectomy at Kamineni Institute of Medical Sciences Hospital, Narketpally from Oct 2007 to Sept 2009 were included in this study, after taking informed consent about the nature of the study, drug to be administered, its possible side effects and the option to refuse inclusion into the study.

Inclusion Criteria

All patients of chronic tonsillitis undergoing tonsillectomy at Kamineni Institute of Medical Sciences Hospital, Narketpally.

Exclusion Criteria

- Patients undergoing adenotonsillectomy.
- Participation in any other clinical trial.
- Known allergy to tranexamic acid.
- Disturbances of colour vision.
- Preoperative use of anticoagulant therapy within 5 days of surgery.
- Fibrinolytic disorders requiring intra-operative antifibrinolytic treatment.
- Haematological diseases (thromboembolic events, haemoglobinopathy, coagulopathy and haemolytic disease).
- Anaesthetic risk worse than ASA Grade 2.

All cases included in the study were randomized in equal proportions into a control group and a study group using random number chart [12]. In the study group, preoperative intravenous tranexamic acid was given in the dosage of 10 mg kg⁻¹ body weight. In the control group 5 cc of plain saline was injected intravenous before surgery. Blinding was achieved as the randomizer did not operate the case and left

the operation theatre after giving the protocol from an unlabelled syringe. The surgeon did not know about the protocol given in any patient. The patient also did not know the protocol under which he/she was operated. Comparability of surgical skill was achieved as all cases included in the study were operated by experienced surgeons. Other factors like anesthetic drugs used and intubation techniques were kept constant for every patient to ensure comparability.

Blood loss was calculated by gravimetric method and by measuring the blood collected in the suction jar. Though the colorimetric method is the more correct method of measuring blood content in used gauze pieces, it has been proved that the gravimetric method of estimation correlates well with the colorimetric method and hence is accurate enough to be used to evaluate intra-operative blood loss [13]. For measuring blood in the suction jar, the fluid in the suction jar was poured into a measuring cylinder and the quantity of fluid present before the surgery was subtracted. The lower edge of the fluid meniscus after the foam had settled was considered for the readings. An electronic weighing scale of HMT company with ISI mark was used for all weightings. It had a sensitivity of 2 g with a minimum and maximum capacity of 10 g and 6 kg respectively. Gauze pieces to be used for the surgery were weighed before keeping on the surgery tray. Post surgery all soiled gauze pieces and unused gauze pieces were weighed again and the difference was taken as the amount of bleeding with the conversion of 1 g = 1 ml of blood [14].

At the end of the study i.e. after 100 cases were operated, the randomization coding was revealed. This coding is shown in Table 1. All observations were collected, tabulated and analyzed. Tests of statistical significance were applied and results were arrived at.

Observation and Results

A total of 100 cases of chronic tonsillitis undergoing tonsillectomy in Kamineni Institute of Medical Sciences Hospital, Narketpally, during the period October, 2007 to September, 2009 were included in the study. The age and sex distribution of these cases were as shown in Table 2. More number of patients was seen in the second and third decades of life. Fewer patients were seen between 0 and 10 years age group, which is the traditional age group for chronic tonsillitis. This discrepancy is because most of the patients in this age group have adenoids with chronic tonsillitis and require adenotonsillectomy. Patients of adenotonsillectomy were excluded from the study as it is difficult to assess exact amount of bleeding when adenoidectomy is done.

The mean blood loss in the study group, as shown in Table 3 was 36.64 ml, while the mean blood loss in the

Table 1 Randomization coding

Case no.	Group
1	Control
2	Control
3	Study
4	Study
5	Control
6	Study
7	Study
8	Control
9	Control
10	Study
11	Study
12	Control
13	Control
14	Control
15	Study
16	Study
17	Control
18	Study
19	Control
20	Control
21	Study
22	Control
23	Control
24	Study
25	Study
26	Study
27	Study
28	Control
29	Study
30	Study
31	Control
32	Control
33	Control
34	Study
35	Study
36	Study
37	Study
38	Study
39	Control
40	Study
41	Control
42	Control
43	Control
44	Control
45	Study
46	Study
47	Study
48	Control

Table 1 continued

Case no.	Group
49	Control
50	Control
51	Study
52	Study
53	Study
54	Control
55	Study
56	Study
57	Control
58	Control
59	Study
60	Control
61	Control
62	Study
63	Study
64	Control
65	Study
66	Control
67	Control
68	Control
69	Control
70	Study
71	Study
72	Study
73	Control
74	Control
75	Control
76	Study
77	Study
78	Control
79	Study
80	Control
81	Study
82	Control
83	Study
84	Study
85	Study
86	Control
87	Study
88	Control
89	Control
90	Study
91	Control
92	Control
93	Control
94	Control
95	Study
96	Control

Table 1 continued

Case no.	Group
97	Study
98	Control
99	Study
100	Study

control group was 66.32 ml. There was 44.75% less bleeding in the study group. On applying the *t* test we got a value of 4.783 with 49 degrees of freedom suggesting a *P* value of less than 0.0005. Thus the reduction in bleeding due to the studied drug is statistically highly significant. There was 4.97% less time taken for surgery in the study group. On applying the *t* test we got a value of 0.328 with 49 degrees of freedom suggesting a *P* value of 0.7443. Thus the reduction in time taken for surgery due to the studied drug is statistically insignificant.

There were three cases of reactionary bleeding in the control group which however did not require any operative intervention. There were no complications in the study group.

There were no adverse effects of tranexamic acid in any of the cases in the study.

Thus it can be concluded that pre-operative intra venous tranexamic acid given in a dose of 10 mg kg⁻¹ body weight significantly reduces tonsillectomy bleeding. However it does not lead to any reduction in time taken for surgery.

Discussion

Tonsillectomy has been done seen antiquity and still continues to be one of the basic surgeries in otorhinolaryngology. However the issues encountered during the surgery have remained the same i.e. anesthesia, access and bleeding. Though the first two issues have largely been dealt with bleeding, still remains the major cause of morbidity

and mortality due to tonsillectomy. It is against this backdrop that we have done this study.

Tranexamic acid is a plasminogen inhibitor which has been successfully used to control bleeding in a variety of surgeries. However on searching the internet through the popular search engines using the terms, tonsillectomy, haemorrhage and tranexamic acid there is only one similar previous study. The study of Castelli G and Vogts E [15] included a total of 80 patients randomized equally into the study and control groups. They noted a reduction of bleeding of 28% as against 44.75% in our study. Though complication rate was high both in study and control group in their study as compared to ours what is notable is the reduction of complication rate in the study group.

Similar studies done for a variety of surgeries have shown the efficacy of tranexamic acid in the reduction of operative bleeding. The findings in these studies are shown in Table 4. The study done in prostatectomy showed a reduction of 52.94% with tranexamic acid. In caesarean section there was a reduction of 43.09%. In orthopedic and cardiac surgeries like total knee arthroplasty and coronary bypass also tranexamic acid caused a reduction of 45.32 and 39.81% respectively. All these figures well match up to the reduction of 44.75% achieved in our study. In none of the studies was any side effect of tranexamic acid reported.

Besides surgeries, tranexamic acid has also been used to reduce bleeding in certain non operative conditions with lot of success. Two such studies shown in Table 5, one done in upper gastro-intestinal bleeding and the other done in menorrhagia has shown statistically significant reduction in bleeding with the use of tranexamic acid. In the study done by Biggs JC, Hugh TB et al., effectiveness of tranexamic acid was proved using criteria like transfusion requirements, transfusion rates and surgical intervention rate as it is not possible to collect blood in upper gastro-intestinal bleeding accurately. Again there were no side effects of tranexamic acid reported in any of the studies.

Inspite of the overwhelming evidence in favour of the efficacy of tranexamic acid in the reduction of tonsillectomy bleeding, there have been studies where tranexamic

Table 2 Age and sex distribution

S. No.	Age group (in years)	Study group			Control group		
		Male (%)	Female (%)	Total (%)	Male (%)	Female (%)	Total (%)
1	0–10	8 (16.00)	9 (18.00)	17(34.00)	13 (26.00)	–	13 (26.00)
2	11–20	15 (30.00)	9 (18.00)	24(48.00)	13 (26.00)	10 (20.00)	23 (46.00)
3	21–30	–	9 (28.00)	9 (18.00)	3 (6.00)	9 (18.00)	12 (24.00)
4	31–40	–	–	–	–	2 (4.00)	2 (4.00)
Total (%)		23 (46.00)	27 (54.00)	50 (100%)	29 (58.00)	21 (42.00)	50 (100.00)

N = 100, Study—50, Control—50

Table 3 Operative blood loss

Sr.	Case	Loss (ml)	Sr.	Case	Loss (ml)
Study group blood loss					
1	3	58	26	51	59
2	4	78	27	52	80
3	6	26	28	53	29
4	7	30	29	55	34
5	10	102	30	56	10
6	11	44	31	59	50
7	15	62	32	62	69
8	16	12	33	63	20
9	18	26	34	65	35
10	21	10	35	70	20
11	24	28	36	71	39
12	25	34	37	72	48
13	26	26	38	76	24
14	27	60	39	77	48
15	29	40	40	79	29
16	30	84	41	81	10
17	34	68	42	83	58
18	35	16	43	84	8
19	36	26	44	85	19
20	37	12	45	87	6
21	38	18	46	90	13
22	40	10	47	95	6
23	45	20	48	97	17
24	46	18	49	99	16
25	47	8	50	100	7
Control group blood loss					
1	1	82	26	54	88
2	2	78	27	57	80
3	5	46	28	58	50
4	8	58	29	60	59
5	9	46	30	61	54
6	12	68	31	64	69
7	13	40	32	66	46
8	14	38	33	67	50
9	17	24	34	68	34
10	19	32	35	69	40
11	20	16	36	73	22
12	22	34	37	74	42
13	23	10	38	75	20
14	28	70	39	78	60
15	31	40	40	80	26
16	32	82	41	82	76
17	33	74	42	86	62
18	39	134	43	88	133
19	41	70	44	89	66

Table 3 continued

Sr.	Case	Loss (ml)	Sr.	Case	Loss (ml)
20	42	94	45	91	84
21	43	78	46	92	77
22	44	120	47	93	118
23	48	74	48	94	68
24	49	102	49	96	94
25	50	98	50	98	90

Total blood loss in study group—1832 ml

Mean blood loss in study group—36.64 ml

Total blood loss in control group—3316 ml

Mean blood loss in control group—66.32 ml

There is 44.75% lesser bleeding in study group

t value is 4.783 with 49 degree of freedom which is highly significant

acid has not proven to be useful. The findings in these studies are summarized in Table 6. As shown in the table there have been studies where tranexamic acid has not reduced operative bleeding. However even in these studies tranexamic acid has reduced post operative bleeding hence reducing morbidity. This could be because tranexamic acid may not be having effect on major vessel bleeding and is more effective in controlling capillary oozing. Here too no reports of side effects of tranexamic acid exist.

Conclusion

Tonsillectomy is a basic and common ENT surgical procedure. In spite of advances in instruments and technique, bleeding due to tonsillectomy still remains the major cause of morbidity and mortality associated with the procedure. Pro-coagulants like tranexamic acid have been used successfully in the control of bleeding in various other types of surgeries. In this study we have proved by randomized control trial the efficacy of pre-operative intra venous tranexamic acid in the control of tonsillectomy bleeding with no recorded side effects.

Key Message

Pre-operative intravenous tranexamic acid in a dose of 10 mg kg⁻¹ body weight achieves statistically highly significant control of tonsillectomy bleeding.

No side effects of tranexamic acid were noted during the study. So it is a safe drug to be used.

Table 4 Comparison with similar studies done for other surgeries

Study Parameter Surgery	Schott U., Jacobsson A. et al. [9] Prostatectomy	Mayur G., Purvi P. et al. [10] Cesarean section	Hiippala S., Strid L. et al. [7] Total knee arthroplasty	Aflatoon MA. et al. [5] Coronary bypass	Present study Tonsillectomy
<i>N</i>	40	100	28	66	100
Study/Control	20/20	50/50	15/13	33/33	50/50
Reduction in bleeding	52.94%	43.09%	45.32%	33.00%	44.75%
<i>P</i>	<0.01	<0.001	<0.001	0.01	<0.0005
Side effects of tranexamic acid	0	0	0	0	0

Table 5 Comparison with similar studies done for certain haemorrhagic conditions

Study Parameter	Biggs JC., Hugh TB. et al. [16]	Sheila T., Callender et al. [17]	Present study
Condition	Upper GI bleeding	Menorrhagia	Tonsillectomy
<i>N</i>	200	32	50
Study/Control	103/97	16/16	25/25
Reduction in bleeding	Bleeding reduction calculated by other criteria	34.05%	44.75%
<i>P</i>	<0.05	<0.05	<0.0005
Side effects of tranexamic acid	0	0	0

Table 6 Studies showing doubtful efficacy of tranexamic acid

Study parameter	Erik L., Joanne G. et al. [8]		Senghore N., Harris M [18]	
Surgery	Total hip replacement		Third molar extraction	
<i>N</i>	39		52	
Study/Control	20/19		26/26	
	Intra-op	Post-op	Intra-op	Post-op
Reduction in bleeding	10.96%	56.15%	15.93%	54.17%
<i>P</i>	0.255	0.026	0.4	0.023
Side effects of tranexamic acid	Nil		Nil	

References

- Ramzi TY, Rande HL (2002) History and current practice of tonsillectomy. *Laryngoscope* 112:3–5
- Macnamara M (2008) Acute and chronic pharyngeal infection. In: Michael G, George GB, Martin JB, Ray C, John H, Nicholas SJ et al. (eds) *Scott-Brown's otorhinolaryngology, head and neck surgery*, 7th edn. Edward Arnold (Publishers) Ltd, London, p 1991, 1994, 1995
- Colin D (1999) *Tranexamic acid* In: *Therapeutic Drugs*, 2nd edn. Churchill Livingstone, New York, p T150–T152
- Hekmat K, Zimmermann T, Kampe S, Kasper SM, Weber HJ, Geissler HJ et al (2004) Impact of tranexamic acid vs. aprotinin on blood loss and transfusion requirements after cardiopulmonary bypass: a prospective, randomised, double-blind trial. *Curr Med Res Opin* 20(1):121–126
- Mehr-Aein A, Sadeghi M, Madani-civi M (2007) Does tranexamic acid reduce blood loss in off-pump coronary artery bypass? *Asian Cardiovasc Thorac Ann* 15(4):285–289
- Alexander FL, Jacinta JM, Frank HM, Michel IM, Eline FB, Robert AE et al (2009) Tranexamic acid and aprotinin in low and intermediate risk cardiac surgery: a non-sponsored, double-blind, randomised, placebo-controlled trial. *Eur J Cardiothorac Surg* 36:322–329
- Hiippala S, Strid L, Wennerstrand M, Arvela V, Mnatyla S, Ylinen J et al (1995) Tranexamic acid (Cyklokapron) reduces perioperative blood loss associated with total knee arthroplasty. *Br J Anaesth* 74(5):534–537
- Erik L, Joanne G, Christiane C, Alain R (2004) Tranexamic acid reduces the need for allogenic red blood cell transfusions in patients undergoing total hip replacement. *Can J Anesth* 51(1):31–37
- Schott U, Jacobsson A, Ekstorm B, Annerstedt M (2005) Single postoperative dose of tranexamic acid reduces blood loss and heterologous blood transfusion in radical retropubic prostatectomy. *J Thromb Hemost* 3(1):Ab. No. P1375
- Gohel M, Patel P, Gupta A, Desai P (2007) Efficacy of tranexamic acid in decreasing blood loss during and after caesarean

- section: A randomized case controlled prospective study. *J Obstet Gynecol* 57(3):227–230
11. Yang H, Zheng S, Shi C et al (2004) Clinical study on the efficacy of tranexamic acid in reducing postpartum blood loss: a randomized comparative, multicenter trial. *Chin J Obstet Gynecol* 6:590–592
 12. Park K (2000) Health information and basic medical statistics. In: Park's textbook of preventive and social medicine, 16th edn. M/s Banarsidas Bhanot, Jabalpur, p 599
 13. Marcel HL, Britt TI, Jolle K, Asger L, Annemarie TK (2006) Quantification of surgical blood loss. *Vet Surg* 35(4):388–393
 14. Richard ML, Monty CM (2000) Critical care; fluid, electrolyte and acid-base balance; blood transfusion. In: Russell RCG, Norman SW, Christopher JKB (eds) Bailey & Love's short practice of surgery, 23rd edn. Arnold, London, p 46
 15. Castelli G, Vogts E (1977) Result of an antifibrinolytic treatment using tranexamic acid for the reduction of blood loss during and after tonsillectomy. *Schweiz Med Wochenschr* 107(22):780–784
 16. Biggs JC, Hugh TB, Dodds AJ (1976) Tranexamic acid and upper gastrointestinal haemorrhage—a double-blind trial. *Gut* 17: 729–734
 17. Sheila TC, Warner GT (1970) Treatment of menorrhagia with tranexamic acid. A double-blind trial. *Br Med J* 4:214–216
 18. Senghore N, Harris M (1999) The effect of tranexamic acid (cyclokapron) on blood loss after third molar extraction under a day case general anaesthetic. *Br Dent J* 156(12):634–636