Preoperative Intravenous Tranexamic Acid in the Control of Bleeding in ENT Surgery, efficacy and side effects

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Abstract

Bleeding related to Ear, Nose and Throat surgery is a major problem in daily ENT surgical practice. This study is done to verify the efficacy of preoperative intravenous tranexamic acid in the control of tonsillectomy and inferior turbinectomy(IT) bleeding. Hundred cases undergoing tonsillectomyand ITwere randomized into two groups, one of which received pre-operatively intra venous tranexamicacid, 15 mg/kg. 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, IT and other surgeries with hemorrhagic conditions. Tranexamic acid in the dose of 15 mg /kg given intra venous pre-operatively is effective in the control of Ear, Nose and Throat bleeding.

The RCPCH and NPPG Medicines Committee recommend a pragmatic dosageschedule – 15mg/kg tranexamic acid loading dose (max 1g) over 10 minutes followedby 2mg/kg per hour.

Introduction

Even today in some patients haemorrhagefrom tonsillectomy and or IT will be the most feared complication and sometimes even life threatening. Post tonsillectomy haemorrhage becomes a risk due to airway obstruction, shock and ultimately death, if not diagnosed early or inappropriately treated[1]. Turbinectomy/Turbinoplasty and generally nasal surgery is one of the most basic and popular operations done in otolaryngology today. The most essential concern after removal of the tonsils and performing nasal surgery is complete control of haemorrhage. The instruments used for tonsillectomy and the use of endoscopy in nasal surgery have helped a lot in the control of the resultant bleeding. The complication rate for tonsillectomy has declined although the types of complications remain the same [2].

Trancxamic acid (mwis-4-aminomcthyl-cyclohexanc carboxylic acid) is a relatively safe antifibrinolytic drug with relatively weak non-competitive inhibition of plasmin at high concentrations. Native human plasminogen contains one lysine binding site with high affinity for tranexamic acid (Jt^i = I.I iimol I"[1]) and four or five with low affinity (&$_4$i = 750 fimol I"[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 scrine-histidinc enzyme site. Conversely, when the lysine binding sites of plasmin are blocked by tranexamic acid, inactivation by a2"antiplasmin is virtually impossible[3].

Tranexamic acid has been widely and successfully used to reduce bleeding in cardiac[4-6],orthopedic[7, 8]. Prostatic[9]and caesarean sections surgeries[10, 11]. In this study we plan to verify the efficacy of preoperative intravenous tranexamic acid in reducing Tonsillectomy and Turbinectomy bleedingtime as well as the time taken for surgery.

Materials and Methods

A total of 85 patients who underwent tonsillectomy and 15 patients to whom performed unilateral or bilateral IT and or septoplastyat Zawia Teaching Hospital from Mar 2009 to Jan 2011 were included in this study.

Exclusion Criteria

- Known allergy to tranexamic acid.
- Disturbances of colour vision.
- Preoperative use of anticoagulant therapy within 5 days of surgery.
- Fibrinolytic disorders requiring intra-operative antifi- brinolytic treatment.
- Haematological diseases (thromboembolic events, hae- moglobinopathy. 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 15 mg/ kg body weight. In the control group 5 cc of plain saline was injected intravenously 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. Thoughthe 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 intraoperative 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 with ISI mark was used. 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 I.

All observations were collected, tabulated and analyzed. Tests of statistical significance were applied and results were arrived at.

CONCLUSIONS

Tranexamic acid is useful in a wide range of haemorrhagic conditions. The drug reduces postoperative blood losses and transfusion requirements in a number of types of surgery, with potential cost and tolerability advantages, and appears to reduce rates of mortality and urgent surgery in patients with haemorrhage.

A total of 85 patients who underwent tonsillectomy and 15 patients to whom performed unilateral or bilateral ITat Zawia Teaching Hospital from Mar 2009 to Jan 2011 were included in this study. The age and sex distribution of these cases were as shown in Table 1. More number of patients was seen in the second and third decades of life. Fewer patients were seen between 0 and 15 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 adenoidcctomy is done.Tranexamic acid is well tolerated; nausea and diarrhoea are the most common adverse events. Increased risk of thrombosis with the drug has not been demonstrated in clinical trials.

Age and sex distribution

Table 1

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

The mean blood loss in the study group, as shown in Table 2.was 36.64 ml, while the mean blood loss in the 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.

Table 2

Operative blood loss

A. Study Group Blood Loss

S.N.	Case	Loss(ml)	S.N.	Case	Loss(ml)
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

Table 2

Operative blood loss

A. Control Group Blood Loss

S.N.	Case	Loss(ml)	S.N.	Case	Loss(ml)
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	49
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
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= 1832ml
Mean blood loss in study group=36.64ml
Total blood loss in control group=3316ml
Mean blood loss in control group=66.32ml
There is 44.75% lesser bleeding in study group
*t*value is 4.783 with 49 degree of freedom which is highly significant
There were five cases of reactionary bleeding in the control group four post-tonsillectomy and two post-turbinectomywhich 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 15 mg/kg body weight significantly reduces tonsillectomy and turbinectomybleeding and lead to reduction in time taken for surgery.

Discussion

Tonsillectomy and Turbinectomy have been done since antiquity and still continues to be part of the basic surgeries in otolaryngology. 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.

Tranexamic acid is a plasminogen inhibitor which has been successfully used to control bleeding in a variety of surgeries. The study of Castelli G andVogts 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 3. 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.

Table 3

Comparison with similar studies done for other surgeries,

Study Parameter	Schott U., Jacobs son A. et al[9]	MayurC.PuniP. et al[10]	Hiippala S.,Strid L. et al [7]	Aflatoon MA. et al[5]	Present study
Surgery	Prostatectomy	Cesarean section	Total knee arthroplasty	Coronary bypass	Tonsillectomy
N	40	100	28	66	100
Study/control	20/2	50/50	15/13	33/33	50/50
Reduction in bleeding	52.94%	34.09%45.32%	33.00%	44.75%	
P<0.01	<0.001	<0.001	< 0.01	<0.0005	
Side effects of tranexamic acid	0	0	0	0	0

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 4,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[17, 18]. In the study done by Biggs JC, Hugh TB et al.[16], 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.

Table 4.

Comparison with similar studies done for certain haemorrhagic conditions

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

Inspite of the overwhelming evidence in favour of the efficacy of tranexamic acid in the reduction of bleeding, there have been studies where tranexamic acid has not proven to be useful. The findings in these studies are summarized in Table 5. 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[19].

Table 5.

Studies showing doubtful efficacy of tranexamic acid.

Study	Erik L., Joanne G. et al.[8]		Senghore N., Harris M [18]	
Parameter				
Surgery	Total hip replacement		Third molar extraction	
N	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%
P	0.255	0.026	0.4	0.023
Side effects of tranexamic acid	Nil		Nil	

Conclusion

Tonsillectomy and Turbinedctomy are basic and common ENT surgical procedures. Inspite of advances in instruments and technique of tonsillectomy and endoscopy in nasal surgery, bleeding still remains the major cause of morbidity and mortality associated with these procedures. 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 and nasal surgery namely turbinectomybleeding with no recorded side effects.Pre-operative intravenous tranexamic acid in a dose of 15 mg /kg body weight achieves statistically highly significant control of tonsillectomy and turbinectomybleeding.

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

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