Original Article

The therapeutic use of tranexamic acid reduces reintervention in paediatric secondary post-tonsillectomy bleeding

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Background: Secondary haemorrhage is an uncommon but potentially fatal complication affecting 0.2–7.5% of patients after tonsillectomy. Tranexamic acid (TXA) is widely used to reduce intraoperative and traumatic blood loss in both paediatric and adult populations, however there are sparse data assessing the use of TXA in the acute management of paediatric secondary post-tonsillectomy bleeding (PTB).

Methods: Retrospective case-control study using records generated contemporaneously to assess the effect of TXA on reintervention rates in theatre and need for blood transfusion in children presenting with a secondary PTB. Within 24 h remaining stable, patients were discharged with 5 days on oral TXA; 165 patients received TXA; 65 patients did not.

Results: Twenty-six (13%) patients in the TXA group and 15 (23%) patients in the control group returned to theatre for management of PTB. Difference between groups (P=0.042) with OR 0.51 (95% CI, 0.252–0.983). No difference was observed in the incidence of blood transfusion, however the study was underpowered with regards to this outcome. Surgical expertise and surgical technique did not seem to affect the rate of return to theatre in this population.

Conclusions: Intravenous TXA may be of benefit in the acute management of paediatric secondary PTB, reducing readmission to theatres for surgical reintervention. Large multi-centre randomised controlled trials are required to convincingly demonstrate causation and to evaluate the effect of TXA on rates of blood transfusion).

Keywords: Tonsillectomy; haemorrhage; secondary bleeding, paediatric; tranexamic acid (TXA)

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Introduction

Secondary post-tonsillectomy bleeding (PTB) is defined as bleeding occurring greater than 24 hours postoperatively (1). PTB remains a significant and dangerous complication of tonsillectomy affecting between 0.2% and 7.5% of patients, with a mortality rate of approximately 1 in 500,000 (2).

Tranexamic acid (TXA), acts to increase the coagulation cascade by competitively inhibiting plasminogen activation, decreasing fibrin degradation products and increasing blood clot stability (3). In use for over 40 years, TXA has been widely reported to significantly reduce blood loss

and need for blood transfusion during surgery (4), and it is routinely used in a broad range of adult and paediatric emergent and elective surgery (5). Mild side effects such as nausea, headaches and diarrhea have been described on the literature (3). And whether TXA is thrombogenic still not a consensus, however ongoing acute venous or arterial thrombosis are established contraindications, as so allergy and known hypersensitivity to that drug. Moreover, precautions should be taken among patients with increased risk for thrombosis or thromboembolism (3).

The efficacy of TXA in reducing PTB is unclear. Prophylactic TXA appears ineffective in reducing secondary PTB (6). When given intraoperatively, TXA reduced intraoperative blood loss but had no significative effect on PTB rate or reintervention in theatres (6,7). Post-operative topical application of TXA did not affect incidence of PTB (8). A recent Cochrane systematic review protocol to assess TXA for the prevention and treatment of tonsillectomy-related haemorrhage in adults was published but subsequently withdrawn (9).

TXA also remains of uncertain benefit in the therapeutic management of paediatric PTB. Previous studies (10-12) have reported small sample sizes and were underpowered with respect to this outcome. In light of this uncertainty, the aim of this study was to assess the effect of TXA on secondary PTB management at a large paediatric tertiary referral hospital. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/ajo.2020.04.02).

Methods

Retrospective case-control study comparing contemporary medical records of secondary post tonsillectomy bleeding in a paediatric population to a previously published historical cohort. The study aims to assess the effect of TXA on reducing operative reintervention in secondary PTB at a major metropolitan tertiary paediatric hospital.

Case inclusion criteria encompassed children younger than 16 years old who were admitted at Perth Children's Hospital with secondary PTB between September 2017 and December 2018. Patients underwent tonsillectomy or adenotonsillectomy due to sleep breathing disorder or recurrent tonsillitis by trainee surgeons and consultant surgeons at PCH or privately by PCH surgical consultants. Children who underwent Intracapsular tonsillectomy, or had tonsillectomy in a presence of a quinsy, base of tongue procedure at same operation, or malignancy suspected were excluded.

The control group was extracted from a published historical cohort (13), similarly defined as patients aged 16 or below who presented between December 2010 and August 2011 to the Princess Margaret Hospital for Children in Perth (PMH), with a secondary bleeding after tonsillectomy or adenotonsillectomy also performed by a consultant or registrar at PMH, or privately by the consultants who also worked at PMH at that time.

All paediatric otolaryngology services were transferred from Princess Margaret Hospital for Children to Perth Children's Hospital following completion of construction of the latter in May 2018. The planned closure of Princess Margaret Hospital for Children was completed in June 2018. Incidences of PTB were recorded contemporaneously in the medical records at both hospitals. Our historical cohort was selected as the most appropriate control group due to its similarity in patient composition, catchment area, and surgical practices.

The current protocol dictates that all children presenting at the Perth Children's Hospital Emergency Department with secondary PTB are admitted and tested for Hb levels and coagulation profile. Once admitted, every patient receives routinely in the Emergency Department TXA IV 10 mg/kg, 8-hourly + amoxycillin 25 mg/kg, IV, 8-hourly and then reviewed by the ENT team. In the event of ongoing or recurrent bleeding, patients may undergo operative intervention under a general anaesthetic. Patients are discharged after 24 h of observation if there is no further bleeding and the follow-up is completed in the outpatient setting. This is our intervention/study group. The control group protocol omitted the use of TXA, but was otherwise identical.

Based on above, the aim was to analyse the rate of return to theatre for surgical management of paediatric secondary PTB, and the rate of blood transfusion among children with secondary PTB. The Pearson's χ^2 test and Fisher's exact test were used to assess differences in rates, which are reported as odds ratios and 95% confidence intervals. Patient demographics, PTB rate for each cohort, and relevant clinical variables including surgical technique and surgeon expertise were collected and differences assessed using one-way ANOVA (*Table 1*). Statistical data analysis was completed using SPSS version 23.0 (IBM Corp., NY, USA). We considered P values smaller than 0.05 statistically significant.

Results

Between 2017 and 2018, 3,054 children underwent

Table 1 Distribution of children with respect to cohort size (n), reported PTB rate (%, total n tonsillectomies at hospital in period), sex, indication for surgery, surgical technique (n, %), age and post-operative days at readmission for PTB (mean, SD), stratified by cohort

Variable	TXA group	Control	P value
Cohort size	195	65	
PTB rate*	6.3 (N=3,054)	4.6 (N=1,396)	
Sex			
Male	90 (46.1)	28 (43.6)	
Female	105 (53.8)	37 (56.4)	0.718
Age	6.6 (3.6)	6.8 (4.2)	0.745
Post-operative days at readmission	7.3 (3.1)	7.8 (3.9)	0.208

TXA, tranexamic acid; PTB, post-tonsillectomy bleeding. *, PTB—considering all tonsillectomies performed in each group.

Table 2 Incidence and rate of return to theatre and blood transfusion (n, %), stratified by cohort

Outcome	TXA group	Control	OR	95% CI	P value
Return to theatre	26 (13.3)	15 (23.1)	0.513	0.252–0.983	0.042
Blood transfusion	1 (0.5)	2 (3.1)	0.162	0.014–1.821	0.155

TXA, tranexamic acid; OR, odds ratio; CI, confidence interval.

tonsillectomy, compared to 1,396 in the previous audit.

After medical record review of all PTBs, we had 195 patients in the TXA group and 65 patients in the control group. Twenty-six (13%) patients in the TXA group and 15 (23%) patients in the control group returned to theatre for surgical management of PTB. This difference was statistically significant (P=0.042) with odds ratio 0.51 (95% CI, 0.252–0.983).

Only three incidences of blood transfusion occurred: one in the TXA group (0.5%) and two in the control group (3.1%). There was no statistically significant difference in rate of blood transfusion (P=0.155) (*Table 2*).

In the TXA group, 179 had no haematological disorder, 7 children had a known haematological disorder, and 7 were not investigated for haematological disorders. There was no significant difference in rate of readmission to theatre (P=0.489) or blood transfusion (P=0.961) between these subgroups.

There was no difference in rate of return to theatre when stratified by surgeon expertise or surgical technique (*Table 3*).

Discussion

The current use of TXA for secondary PTB on readmission reduced the risk of return to theatre by 49% in our paediatric cohort. It was not possible to conclude whether TXA affected the incidence of blood transfusion due to the small number of patients receiving this intervention. We believe that this is the first large observational study to assess the therapeutic effect of TXA in the acute management of paediatric PTB.

Brum *et al.* (10) assessed the effect of perioperative TXA with a final dose 16 hours postoperatively on intraoperative bleeding volume and postoperative bleeding rates in children undergoing adenotonsillectomy. Compared to placebo, Brum *et al.* observed no difference in intraoperative bleeding volume or rate of primary and secondary PTB. However, the study was underpowered with respect to the latter outcome, with none cases reporting significant PTB. Fewer children who received TXA observed streaks of blood in saliva, though this difference was not statistically significant (26.1% *vs.* 41.7%, P=0.08).

Pittore *et al.* (11) similarly found no effect of a 10-day course of postoperative oral TXA on the incidence of PTB in children undergoing adenotonsillectomy. However, as above, this study was underpowered, with only 3 children reporting PTB in each group (2.01% with TXA *vs.* 3.44% no TXA) and no measure of PTB severity. Neither study observed any adverse events attributable to TXA. As yet, there is insufficient evidence to confirm or refute any

Table 3 Distribution of children in the TXA group with respect to surgeon expertise and surgical technique (n, %), stratified by need for surgical management (return to theatre)

Variable	Returned to theatre	Did not return to theatre	P value
Surgeon expertise			0.889
Registrar	9 (15.0)	51 (85.0)	
Consultant	4 (11.8)	30 (88.2)	
Fellow	13 (12.9)	88 (87.1)	
Surgical technique			0.53
Cold steel	0	1 (100.0)	
Bipolar	9 (13.8)	56 (86.2)	
Monopolar + bipolar	1 (12.5)	7 (87.5)	
Coblation	16 (15.4)	88 (84.6)	
Bizact	0	17 (100.0)	

TXA, tranexamic acid.

benefit of TXA in the prevention of PTB.

Schwarz *et al.* (12) reported the successful therapeutic use of nebulised TXA to halt post-tonsillectomy haemorrhage in a 3-year-old child post nebulised epinephrine. Consistent with the above, we propose that TXA has a role in the safe and effective management of PTB.

Side effects related to TXA were not actively measured in this study, and common mild side effects such as headaches and nausea are known complications to tonsillectomies and post general anaesthesia period regardless of TXA. Respecting established contraindications for TXA, the drug was not administered in patients with increased risk for thrombosis or thromboembolism or known hypersensitivity that medication. Thrombogenic events were not seen during the post-operative period among patients who received TXA.

The level of surgical expertise and surgical technique did not significantly affect the incidence of surgical reintervention in paediatric secondary PTB. This is not consistent with the earlier results of Hinton-Bayre *et al.* (13), who suggested that return to operating theatre was less frequent following tonsillectomy by a consultant (0.7%) than a surgical trainee (2.5%). However, as a proportion of all PTBs in the study group, returning to operating theatre was broadly similar in the two groups (*Table 3*). Thus, we determine that surgical expertise does not account for the reduction in theatre readmissions observed with the use of TXA in this study.

The reported relative risk of PTB associated with the various surgical techniques available is inconsistent in the literature, with some studies finding higher rates of PTB with 'hot' techniques (14,15), and others the inverse (16) or no difference (17,18). One Cochrane systematic review could not exclude a small increased risk of PTB with coblation (19). However, the randomised controlled trials available were of very low quality.

In our practice, parents and carers are instructed to return paediatric patients to hospital if they observe active bleeding or clots in the oral cavity, of any volume or severity. Whether all PTB requires admission for observation is a point of contention in the medical literature and this topic was not assessed in this study (1,20).

The retrospective nature of our analysis is a limitation of our study. Accurate estimations of patient blood loss in PTB were not available. However, as procedures and incidences of PTB presenting to our hospitals were documented contemporaneously in the medical records and they are the outcome of relevance for practicing otolaryngologists, being routinely assessed on audits, we believe that there is a very low probability of systematic bias in our reported results. Also, despite temporal differences between TXA and control groups, there was considerable homogeneity in patient demographics. A prospective, randomized controlled trial would be the gold standard in confirming the effect of TXA on secondary PTB.

Conclusions

In conclusion, we observed that the therapeutic use of

TXA in secondary PTB showed to significantly reduce the rate of return to theatre in our paediatric cohort. This promising result suggests that the addition of TXA to the current arsenal of PTB therapeutics should be considered. However, we believe that large randomized controlled trials should be conducted to conclusively confirm this effect.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/ajo.2020.04.02

Conflicts of Interest: SV serves as an unpaid editorial board member of *Australian Journal of Otolaryngology*. Dr. Cornwall reports grants awarded by The Royal College of Surgeons of Edinburgh/ Binks Trust, The Enid Linder Foundation, and Green Templeton College during the conduct of the study. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the relevant Hospital Quality Improvement Committee (No. 28324), and informed consent was waived due to its retrospective nature.

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