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REVIEW ARTICLE

Tranexamic acid – a useful drug in ENT surgery?

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Abstract

Background: Tranexamic acid is a synthetic antifibrinolytic drug. It has been widely available for over 40 years, but only recently has it started to be used routinely in many surgical disciplines. For ENT surgeons, epistaxis and post-tonsillectomy bleeding contribute a significant proportion of the morbidity and emergency workload in a general ENT department. Published evidence indicates a potentially helpful role for tranexamic acid in managing epistaxis.

Results and conclusion: To date, the benefits of tranexamic acid as a prophylactic treatment to reduce the rate and severity of post-tonsillectomy bleeding are less certain. Two recently published pilot studies looking at primary haemorrhage in children and secondary haemorrhage in adults following tonsillectomy suggest that further large, randomised trials should explore the efficacy of tranexamic acid in routine ENT surgery. There are potential reductions in patient morbidity and cost savings if tranexamic acid is found to be efficacious in larger trials.

Key words: Tranexamic Acid; Tonsillectomy; Day Surgery; Hemorrhage; Complications

Introduction

Bleeding after ENT operations is a common and potentially serious complication, particularly in children because of the small total blood volume and physiological compensation for blood loss. In a large German audit of 720 hospitals, pre-operative routine coagulation estimation failed to identify children who subsequently bled after adenoidectomy or tonsillectomy.[1] These tests could not routinely identify von Willebrand's disorder. A detailed history to exclude abnormal bleeding or bruising in the patient, or any significant family history of these, is crucial in identifying such patients. This requires detailed pre-operative assessment of clotting and coagulation. In that study of children undergoing tonsillectomy and/or adenoidectomy, bleeding occurred most commonly within the first 24 hours.

Pre-operatively identified Willebrand's disorder has been treated with tranexamic acid and/or 1-desamino-8-D-arginine vasopressin (desmopressin) to reduce the risk of intra- and post-operative bleeding. An increasing body of evidence suggests that tranexamic acid might be a useful drug for preventing bleeding following adenotonsillectomy, managing bleeding during sinus surgery and managing epistaxis.

Tranexamic acid (trans-4 amino methyl-cyclohexane carboxylic acid) is a well-established drug that has been available for over 40 years. While commonly used as an adjunct to desmopressin in patients with von Willebrand's disorder,[2] tranexamic acid has more recently been widely proposed as an important pharmaceutical tool to reduce blood loss during surgery and following major trauma.[3,4] It is included in the current core World Health Organization List of Essential Medicines, which is defined as 'a list of minimum medicine needs for a basic healthcare system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment'.[5]

Tranexamic acid is a potentially useful drug for ENT surgeons in the prevention and reduction of both the frequency and severity of blood loss during and after tonsillectomy.[6] While the benefits of tranexamic acid seem potentially high, the risks of thromboembolic events and mortality are unclear. In a meta-analysis of tranexamic acid used to manage surgical bleeding, fewer deaths were reported in the tranexamic acid group, but there was uncertainty about serious adverse effects.[7]

Pharmacology and applications

Tranexamic acid is a synthetic lysine analogue that facilitates antifibrinolysis via a competitive reversible blockade of lysine-binding sites on plasminogen

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molecules and as a non-competitive inhibitor of plasmin. These actions inhibit the conversion of plasminogen to plasmin on the surface of the fibrin, producing stabilisation of fibrin clots.[8] Tranexamic acid might be particularly effective at reducing bleeding following ENT surgery as the oral mucosa (and salivary glands) are rich in plasminogen activators and have a low concentration of plasminogen inhibitors.[6]

Tranexamic acid has been widely used parenterally in elective cardiac, orthopaedic and urological surgery to reduce peri-operative blood loss.[9] In orthopaedic surgery, tranexamic acid has been shown to reduce the blood loss during knee arthroplasty by 50 per cent, mitigating the need for transfusion with no increase in the risk of thromboembolic complications.[10]

A Cochrane review of tranexamic acid for reducing mortality in urgent and emergency surgery concluded that the administration of tranexamic acid reduced the probability that a patient would receive a blood transfusion by around 30 per cent. However, it was noted that further, larger studies were needed to assess any adverse effects in this group of patients.[11]

Tranexamic acid has been used topically as a mouthwash following dental and oral surgery.[12] It has been recommended parenterally during cleft palate and lip surgery to help minimise blood loss at the time of operation, particularly following vomerine flap surgery.[13] Tranexamic acid mouthwashes used after oral surgery in patients taking anticoagulants (typically 1 g three times daily for 5 days) reduces the rate and volume of bleeding.[14] For patients undergoing dentoalveolar surgery, without a known clotting disorder, a single dose of peri-operative tranexamic acid administered at 25 mg/kg prevented excessive post-operative bleeding, thereby facilitating day-case discharge.[14]

A randomised, controlled trial of 73 patients undergoing elective bimaxillary osteotomy showed a significant reduction in blood loss in the treatment group following a single dose of tranexamic acid (20 mg/kg) just prior to surgery. The mean total blood loss was 422 ml greater in the placebo group than in the treatment group.[15]

Prescribed orally, tranexamic acid is part of the management of menorrhagia, and in the UK it can be purchased over the counter to self-manage heavy periods.[16,17]

As a topical preparation, tranexamic acid is also used as a skin whitener, and for managing skin hyperpigmentation and melasma. The action of tranexamic acid reducing epidermal pigmentation is not fully understood, but is likely to be due to the blocking of plasminogen to keratinocyte binding, with resultant decreased melanocyte tyrosine activity.[18–20]

In the UK, tranexamic acid is usually prescribed orally at 1 g three times daily, as a 10-day course, for therapeutic indications. In the USA, the tablets are produced in 650 mg strength with a higher recommended daily dose range of 3–6 g. The most common adverse effects of tranexamic acid are gastrointestinal side effects, including nausea, diarrhoea and abdominal cramping, which are generally mild, but uncommon. A current US patent describes a proposed modified release formulation, which could minimise these unwanted effects.[21]

Renal toxicity is a potential concern in those with reduced renal function. When tranexamic acid is used on a long-term basis in patients with angioneurotic oedema, regular liver function testing and assessment of vision is recommended. Caution is advised when administering tranexamic acid intravenously, as too rapid a bolus injection can produce significant hypotension.

In trauma patients, the benefit of tranexamic acid in reducing blood loss has been demonstrated without a clear increased risk of morbidity or mortality due to thromboembolic sequelae.[3,4] However, in 2011, a report described ischaemic stroke in two younger women receiving tranexamic acid over 3 days for gynaecological bleeding. Following genetic testing, both women were found to have a metabolic genetic abnormality that produced a synergetic effect on the plasminogen inhibitory action of tranexamic acid.[22] This genetic mutation of methylenetetrahydrofolate reductase is an independent risk factor for occlusive stroke, present in about 10 per cent of the US population, highest in the Hispanic ethnic group and lowest in the Afro-Caribbean group.[23]

In high-dose administration, tranexamic acid with a loading dose of 4 g over 1 hour, and then 1 g per hour for 6 hours, was shown to reduce blood loss and maternal morbidity in women who suffered a postpartum haemorrhage with blood loss of more than 800 ml. The side effects were mild and transient, but the authors acknowledge the study was not adequately powered to address safety issues.[24] In developing countries, tranexamic acid is likely to be the most cost-effective intervention for postpartum haemorrhage. Of the 500 000 maternal deaths worldwide each year, approximately 99 per cent occur in the Third World.[25] The lifetime risk of mortality from postpartum haemorrhage for a woman living in Northern Europe is 1:30 000, while in the poorest nations the risk is as high as 1:6.[26]

In ultra-high doses (equal to or greater than 100 mg/kg) administered during cardiopulmonary bypass, the risk of seizure within 24 hours of bypass was related to tranexamic acid administered in a dose-dependent fashion.[27]

Donor blood for transfusion is a scarce resource and the transfusion itself is not without risk. The authors of an authoritative meta-analysis comment that tranexamic acid reduces the need for blood transfusion.[7] In 2011, 1 unit of blood cost the National Health Service (NHS) £125. Worldwide, most do not have access to safe blood, with the inherent risk of transmission of syphilis, human immunodeficiency virus, hepatitis B and C, and variant Creutzfeldt–Jacob disease. In Sub-Saharan Africa, an average of 5 units of blood per 1000 population are donated annually, compared with 30–60 units

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per 1000 population in First World countries.[28] In those countries where there is a blood shortage and the risk of blood-borne infection is higher, it has been estimated that the cost per life saved using tranexamic acid is US$83–93.[28] The authors conclude that a modest increase in the risk of thromboembolic events could outweigh the benefits of reduced blood use. Nevertheless, the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage ('CRASH-2') study showed a significant reduction in mortality with no increase in such events, and a statistically significant reduction in the risk of myocardial infarction.[3]

While the published literature supports the use of tranexamic acid for tonsillectomy as a means of reducing blood loss during surgery, and in those with defects of clotting or coagulation, there is little evidence to date to indicate that tranexamic acid could be useful in reducing primary or secondary haemorrhage. In September 2013, the protocol for a Cochrane review of tranexamic acid for the prevention and treatment of tonsillectomy-related haemorrhage in adults was published.[29] This Cochrane review will investigate primary outcomes, including intra-operative blood loss, post-operative haemorrhage (primary and secondary), and re-admission and return to operating theatre rates. Secondary outcomes will include side effects of tranexamic acid (such as thromboembolic events) and length of hospital stay related to post-operative bleeding.

Tonsillectomy

A number of studies have published variable results on bleeding after tonsillectomy using different types of antifibrinolytics. One study showed no significant benefit from the routine use of tranexamic acid during tonsillectomy,[30] while others have confirmed a significant reduction in blood loss during surgery using conventional dissection techniques.[31,32] In a further randomised, controlled trial, a single dose of intravenous, peri-operative tranexamic acid at 10 mg/kg was associated with a mean blood loss of 36.64 ml, compared with 66.32 ml in the control group.[33] The authors reported no adverse effects from tranexamic acid. Three patients (3 per cent) developed primary haemorrhage, but none of those patients required operative intervention.

In a double-blind, randomised trial from Brazil, in which 95 children underwent adenotonsillectomy for hyperplasia (sic), the authors concluded that tranexamic acid administered at 10 mg/kg pre-operatively, and at 8 and 16 hours post-operatively, produced no significant reduction in blood loss at the time of surgery, nor any reduction in the rate of secondary bleeding at 10 days following the operation.[34] Eight surgeons operated on the 95 children, using cold dissection with absorbable sutures in the tonsillar fossae (sic) for haemostasis. Two surgeons did not complete their randomisation blocks. In different sections of the paper, the authors report either 7 or 12 patients not receiving the second and third doses of tranexamic acid. Seventeen patients outside of the sample calculation were included to complete an intention-to-treat analysis, possibly producing an underestimate of any benefit from tranexamic acid. Given the short half-life of tranexamic acid, it is surprising that the authors anticipated any effect of tranexamic acid administered only on the day of surgery in preventing bleeding 10 days later.

A systematic review and meta-analysis of the use of tranexamic acid in tonsillectomy confirmed that the use of tranexamic acid reduced blood loss during surgery, but failed to demonstrate any reduction in the rate of post-tonsillectomy haemorrhage.[35] The authors note that of 38 citations, an extensive literature search yielded only 7 that could be included in their final analysis. These studies varied enormously in terms of the age range of patients, the dosage of tranexamic acid, and the schedule and duration of treatment. One such paper reported the topical application of a tranexamic acid paste that resulted in a higher bleeding rate than the placebo group.[36] The small number of studies included in this meta-analysis were so heterogeneous that it is difficult to draw meaningful conclusions regarding the applicability of tranexamic acid in reducing post-operative bleeding after tonsillectomy. A helpful conclusion of this meta-analysis is the safety of tranexamic acid, with only 1 of the 7 studies reporting adverse effects, in 3 out of 40 patients. All the adverse effects were minor, including headache, dizziness and vomiting.

In one pilot study, 476 children aged between 3 and 16 years underwent elective day-case tonsillectomy for recurrent tonsillitis or sleep disordered breathing (within current guidance and commissioning restrictions[37,38]), with or without adenoidectomy and/or ventilation tube insertion. In that study, tranexamic acid was administered as a single, slow intravenous peri-operative dose of 10–15 mg/kg.[39] The same surgeon operated upon all the children, using Coblation™ dissection and haemostasis for the tonsillectomy, and suction diathermy for the adenoidectomy.[40] Operative blood loss was not measured in that study, but was clinically negligible, with swabs rarely required for haemostasis. The children were anaesthetised using an adapted version of a previously published day-case anaesthetic protocol.[41] The protocol was modified to substitute intravenous paracetamol at 15 mg/kg for rectal paracetamol. Following the publication of a recent Medicines and Healthcare Products Regulatory Agency drug safety update, post-operative codeine as a rescue analgesic has since been excluded from the protocol.[42] In that study, tranexamic acid appeared to reduce the risk of primary haemorrhage on the day of surgery to 0.4 per cent, facilitating same-day discharge. No bleeding was recorded during the first 24 hours following tonsillectomy. The rate of secondary haemorrhage was not observed. Tranexamic acid is routinely available only in tablet form, which is unsuitable for

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paediatric administration. The short half-life of tranexamic acid means that no effect on secondary haemorrhage would be expected from a single peri-operative dose.

In a further prospective, observational study of adults undergoing day-case Coblation tonsillectomy between 2007 and 2013, 111 adults were given 1 g of tranexamic acid by slow intravenous injection peri-operatively, and then 1 g 3 times per day orally for 10 days post-operatively.[43] None of these patients experienced post-operative nausea, vomiting or bleeding on the day of surgery or within the 24 hours following tonsillectomy. Two patients (1.8 per cent) given tranexamic acid post-operatively developed nausea, with one stopping the treatment after a few days. This latter patient had no bleeding. While there were no episodes of significant post-tonsillectomy haemorrhage, three patients (2.7 per cent) spat up some blood or had some blood-stained saliva during the two weeks after surgery; these were reported as minor episodes for which none of the patients sought medical advice. (On the 0–4 Windfuhr classification of post-tonsillectomy haemorrhage, 97.3 per cent of cases were category 0 and 2.7 per cent were category 1.[44])

Adenoidectomy

There is almost no literature on the use of tranexamic acid for adenoidectomy without tonsillectomy. A solitary double-blind, prospective, randomised, controlled study of 400 children compared the topical application of tranexamic acid with saline following curettage adenoidectomy. The tranexamic acid (at 1 g in 10 ml of normal saline) was irrigated through a catheter into the nasopharynx and left in situ for 5 minutes before suction clearance of the nose, nasopharynx and pharynx. The volume of blood loss at operation and frequency of primary haemorrhage, with or without post-nasal packing or transfusion, was significantly higher in the placebo group.[45] It is, however, likely that with the increasing use of direct vision techniques for adenoidectomy (suction diathermy or Coblation), post-adenoidectomy bleeding will become exceptional.

Epistaxis

The most common ENT emergencies are usually the result of bleeding from local trauma and/or infection arising from Kiesselbach's plexus on the antero-inferior part of the nasal septum or from the retro-columellar vein. A detailed history can, however, point to more serious generalised disorders such as leukaemia or bleeding diatheses, typically von Willebrand's disorder.[46] A Cochrane protocol looking at tranexamic acid for epistaxis, first published in 2003, was updated in 2010 with new authors redrafting the protocol; it remains in progress.[47]

In a randomised, controlled trial, a single intravenous injection of tranexamic acid (500 mg) was compared with anterior nasal packing using a tetracycline and vasoconstrictor solution. In the tranexamic acid group, the bleeding stopped within 10 minutes in 71 per cent of patients, with re-bleeding within 24 hours in 4.7 per cent. In the nasal packing group, the bleeding stopped within 10 minutes in only 31.2 per cent of patients and the re-bleed rate was 11.0 per cent. The authors also reported increased patient satisfaction in the tranexamic acid group and recommended this as an initial treatment for anterior epistaxis.[48]

Endoscopic sinus surgery

In a double-blind, randomised, controlled trial of 28 patients receiving either intravenous tranexamic acid or saline during endoscopic sinus surgery for chronic rhinosinusitis with or without polyposis, there was no measurable difference in intra-operative blood loss. The authors do not report whether the tranexamic acid group had a lower post-operative bleeding rate or less need of nasal packing.[49]

In a larger comparative analysis of 200 patients undergoing endoscopic sinus surgery, individuals were randomly assigned to a peri-operative intravenous tranexamic acid (500 mg) group or a non-treatment group. In the treatment group, blood loss was reduced by 72.48 per cent ($p < 0.05$).[50] The authors note that the antifibrinolytic effect of tranexamic acid remains in some tissues for about 17 hours and in serum for up to 7–8 hours, potentially reducing the risk of bleeding in the early post-operative period.

A literature review of measures to control bleeding in endonasal, endoscopic skull base surgery concluded that low-dose, topical tranexamic acid (100 mg peri-operatively) provided improved haemostasis and surgical field quality at 2, 4 and 6 minutes after application, with no adverse effects.[51]

Conclusion

Among routine ENT operations, tonsillectomy is an intervention where blood loss during and bleeding after operation are frequent and potentially serious; tranexamic acid could significantly reduce the incidence of haemorrhage. In addition to the medical and psychological morbidity associated with bleeding following tonsil surgery, there is a financial cost, currently excluded from the NHS tariff and borne by the provider organisation.

For a typical general hospital, the annual cost of managing post-tonsillectomy haemorrhage could reach nearly £40 000.[52] The number of hospitals carrying out tonsillectomy is difficult to confirm, but the best estimate for England is about 200.[53] This equates to a financial burden of £8 million annually to manage post-tonsillectomy bleeding. In contrast, tranexamic acid at 1 g three times daily for 10 days costs £2.60.[54] With approximately 450 tonsillectomies performed annually in a typical general hospital, the cost of tranexamic acid would be approximately £1170 per hospital per year, equalling £0.23 million nationally, with a potential saving of up to £7.77

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million each year from avoidable re-admissions to hospital for post-tonsillectomy bleeding.

There are, to date, no large, high quality prospective studies investigating the applications of tranexamic acid for routine ENT surgery. The few studies published indicate a potential benefit, both in terms of morbidity and cost efficiency. The Cochrane review, currently in progress, is likely to conclude that large multicentre, randomised, prospective trials are needed to determine the efficacy of tranexamic acid applied to ENT surgery. The circumstantial evidence to date is, however, encouraging.

References

1 Bidlingmaier C, Olivieri M, Stelter K, Eberl W, von Kries R, Kurnik K. Postoperative bleeding in paediatric ENT surgery. First results of the German ESPED trial. *Hämostaseologie* 2010;**30**(suppl 1):S108–11
2 Choudhuri S, Bolton-Maggs PHB. Von Willebrand disorder. *Paediatr Child Health* 2011;**21**:348–52
3 Perel P, Al-Shahi Salman R, Kawahara T, Morris Z, Prieto-Merino D, Roberts I *et al*. CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) intracranial bleeding study: the effect of tranexamic acid in traumatic brain injury – a nested randomised, placebo-controlled trial. *Health Technol Assess* 2012;**16**:iii–x11,1–54
4 Gruen RL, Reade MC. Administer tranexamic acid early to injured patients at risk of substantial bleeding. *BMJ* 2012;**345**:46–7
5 WHO Model List of Essential Medicines, 18th edn, 2013. In: http://www.who.int/medicines/publications/essentialmedicines/en/index.html [21 May 2014]
6 Verstraete M. Clinical application of inhibitors of fibrinolysis. *Drugs* 1985;**29**:236–61
7 Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ* 2012;**344**:e3054
8 Reid RW, Zimmerman AA, Laussen PC, Mayer JE, Gorlin JB, Burrows FA. The efficacy of tranexamic acid versus placebo on decreasing blood loss in pediatric patients undergoing repeat cardiac surgery. *Anesth Analg* 1997;**84**:990–6
9 Mahdy AM, Webster NR. Perioperative systemic haemostatic agents. *Br J Anaesth* 2004;**93**:842–58
10 Veien M, Sorensen JV, Madsen F, Juelsgaard P. Tranexamic acid given intraoperatively reduces blood loss after total knee replacement: a randomized, controlled study. *Acta Anaesthesiol Scand* 2002;**46**:1206–11
11 Perel P, Ker K, Morales Uribe CH, Roberts I. Tranexamic acid for reducing mortality in emergency and urgent surgery. *Cochrane Database Syst Rev* 2013;(1):CD010245
12 Sindet-Pedersen S, Ramström G, Bernvil S, Biombäck M. Hemostatic effect of tranexamic acid mouthwash in anticoagulant-treated patients undergoing oral surgery. *New Engl J Med* 1989;**320**:840–3
13 Watson A. Anaesthesia for cleft lip and palate surgery in children. In: James I, Walker I, eds. *Core Topics in Paediatric Anaesthesia*. Cambridge: Cambridge University Press, 2013; 228–36
14 Senghore N, Harris M. The effect of tranexamic acid (cyclokapron) on blood loss after third molar extraction under a day case general anaesthetic. *Br Dent J* 1999;**186**:634–6
15 Choi WS, Irwin MG, Samman N. The effect of tranexamic acid on blood loss during orthognathic surgery: a randomized controlled trial. *J Oral Maxillofac Surg* 2009;**67**:125–33
16 Dunn CJ, Goa KL. Tranexamic acid: a review of its use in surgery and other indications. *Drugs* 1999;**57**:1005–32
17 Femstrual. In: http://femstrual.co.uk/ [22 December 2012]
18 Na JI, Choi SY, Yang SH, Choi HR, Kang HY, Park K-C. Effect of tranexamic acid on melasma: a clinical trial with histological evaluation. *J Eur Acad Dermatol Venereol* 2012;**8**:1035–9
19 Wu S, Shi H, Wu H, Yan S, Guo J, Sun Y *et al*. Treatment of melasma with oral administration of tranexamic acid. *Aesthetic Plast Surg* 2012;**36**:964–70
20 Tranexamic acid. In: http://mcbiotec.com/products/?type=detail&id=33 [23 December 2012]
21 Modified Release Tranexamic Acid Formulation: US 20120135079 A1. In: http://www.google.com/patents/US20120135079 [22 May 2014]
22 Nardi K, Pelone G, Bartolo M, Di Ruzza, Storto M, Notte A *et al*. Ischaemic stroke following tranexamic acid in young patients carrying heterozygosity of MTHFR C677T. *Ann Clin Biochem* 2011;**48**:575–8
23 Schneider JA, Rees DC, Liu YT, Clegg JB. Worldwide distribution of a common methylenetetrahydrofolate reductase mutation. *Am J Hum Genet* 1998;**62**:1258–60
24 Ducloy-Bouthors A-S, Jude B, Duhamel A, Broisin F, Huissoud C, Keita-Meyer H *et al*. High-dose tranexamic acid reduces blood loss in postpartum haemorrhage. *Crit Care* 2011;**15**:R117
25 Ronsmans CI, Graham WJ; Lancet Maternal Survival Series steering group. Maternal mortality: who, when, where, and why. *Lancet* 2006;**368**:1189–200
26 Snelgrove JW. Postpartum haemorrhage in the developing world. A review of clinical management strategies. *McGill J Med* 2009;**12**:61–6
27 Kalavrouziotis D, Voisine P, Mohammadi S, Dionne S, Dagenais F. High-dose tranexamic acid is an independent predictor of early seizure after cardiopulmonary bypass. *Ann Thorac Surg* 2012;**93**:148–54
28 Guerriero C, Cairns J, Jayaraman S, Roberts I, Perel P, Shakur H. Giving tranexamic acid to reduce surgical bleeding in sub-Saharan Africa: an economic evaluation. *Cost Eff Resour Alloc* 2010;**8**:1–11
29 Vallamkondu V, Ah-See K, Rocke J, Bannister M. Tranexamic acid for the prevention and treatment of tonsillectomy-related haemorrhage in adults (Protocols). *Cochrane Database Syst Rev* 2013;(9):CD010740
30 Mazauric FX, Boudon A, Rheingold C. Value of tranexamic acid in extracapsular tonsillectomy in adults [in French]. *JFORL J Fr Otorhinolaryngol Audiophonol Chir Maxillofac* 1973;**22**:165–8
31 Verstraete M, Tyberghein J, De Greef Y, Daems L, Van Hoof A. Double-blind trials with ethamsylate, batroxobin or tranexamic acid on blood loss after adenotonsillectomy. *Acta Clin Belg* 1977;**32**:136–40
32 Castelli G, Vogt E. Result of an antifibrinolytic treatment using tranexamic acid for the reduction of blood loss during and after tonsillectomy [in German]. *Schweiz Med Wochenschr* 1977;**107**:780–4
33 George A, Kumar R, Kumar S, Shetty S. A randomized control trial to verify the efficacy of pre-operative intra venous tranexamic acid in the control of tonsillectomy bleeding. *Indian J Otolaryngol Head Neck Surg* 2011;**63**:20–6
34 Brum MR, Miura MS, de Castro SM, Machado M, Lima LH, Faibes J *et al*. Tranexamic acid in adenotonsillectomy: a double-blind randomized clinical trial. *Int J Pediatr Otorhinolaryngol* 2012;**76**:1401–5
35 Chan CC, Chan YY, Tanweer F. Systematic review and meta-analysis of the use of tranexamic acid in tonsillectomy. *Eur Arch Otorhinolaryngol* 2013;**270**:735–48
36 Falbe-Hansen J Jr, Jacobsen B, Lorenzen E. Local application of an antifibrinolytic in tonsillectomy. A double-blind study. *J Laryngol Otol* 1974;**88**:565–8
37 Scottish Intercollegiate Guidelines Network. *Management of Sore Throat and Indications for Tonsillectomy: A National Clinical Guideline* (National Clinical Guideline 117). Edinburgh: SIGN, 2010
38 Robb PJ, Bew S, Kubba H, Murphy N, Rollin AM, Tremlett M. Tonsillectomy and adenoidectomy in children with sleep-related breathing disorders: consensus statement of a UK multidisciplinary working party. *Ann R Coll Surg Engl* 2009;**91**:371–3
39 Robb PJ, Thorning G. Perioperative tranexamic acid in day-case paediatric tonsillectomy. *Ann R Coll Surg Engl* 2014;**96**:127–9
40 National Institute for Health and Clinical Excellence. *Suction Diathermy Adenoidectomy* (Interventional procedure guidance 328). London: NICE, 2009
41 Robb PJ, Ewah BN. Post-operative nausea and vomiting following paediatric day-case tonsillectomy: audit of the Epsom protocol. *J Laryngol Otol* 2011;**125**:1049–52
42 Codeine for analgesia: restricted use in children because of reports of morphine toxicity. In: http://www.mhra.gov.uk/

https://doi.org/10.1017/S0022215114001285 Published online by Cambridge University Press

Safetyinformation/DrugSafetyUpdate/CON296400 [3 August 2013]
43 Robb PJ, Ewah B. Can tranexamic acid reduce bleeding after tonsillectomy? A pilot study. *Otorinolaringologia* 2013;**63**:163–7
44 Windfuhr J, Seehafer M. Classification of haemorrhage following tonsillectomy. *J Laryngol Otol* 2001;**115**:457–61
45 Albirmawy OA, Saafan M, Shehata EM, Basuni AS, Eldaba AA. Topical application of tranexamic acid after adenoidectomy: a double-blind, prospective, randomized, controlled study. *Int J Pediatr Otorhinolaryngol* 2013;**77**:1139–42
46 Bennett JDC, Giangrande PLF. Nosebleeds – the importance of taking a history. *J R Army Med Corps* 1990;**136**:167–9
47 Joseph J, Martinez-Devesa P, Perera R. Antifibrinolytic agent tranexamic acid for nasal haemorrhage (epistaxis). *Cochrane Database Syst Rev* 2010;(12):CD004328
48 Zahed R, Moharamzadeh P, Alizadeharasi S, Ghasemi A, Saeedi M. A new and rapid method of epistaxis treatment using injectable form of tranexamic acid topically: a randomized controlled trial. *Am J Emerg Med* 2013;**31**:1389–92
49 Langille MA, Chiarella A, Côté DWJ, Mulholland G, Sowerby LJ, Dziegielewski PY *et al*. Intravenous tranexamic acid and intraoperative visualization during functional endoscopic sinus surgery: a double-blind randomized controlled trial. *Int Forum Allergy Rhinol* 2013;**3**:315–18
50 Chhapola S, Matta I. Short-term use of tranexamic acid to reduce blood loss in endoscopic nasal surgeries. *Clinical Rhinology: An International Journal* 2011;**55**:20–7
51 Thongrong C, Kasemsiri P, Carrau RL, Bergese SD. Control of bleeding in endoscopic skull base surgery: current concepts to improve hemostasis. *ISRN Surg* 2013;**2013**:191543
52 Parmar A, Hanks K-A, Muir J, Evans K. The true cost of post-tonsillectomy bleeds. *Clin Otolaryngol* 2013;**38**:106–7
53 General Election 2010: frequently asked questions. In: http://www.kingsfund.org.uk/projects/general-election-2010/faqs#hospital [18 March 2013]
54 British National Formulary. In: http://www.nice.org.uk/mpc/BritishNationalFormulary.jsp [22 May 2014]

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Mr P J Robb takes responsibility for the integrity of the content of the paper
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