European Journal of Plastic Surgery (2019) 42:559–562
https://doi.org/10.1007/s00238-019-01527-9

ORIGINAL PAPER

Does tranexamic acid increase the risk of thromboembolic events in immediate or delayed breast reconstruction? A review of the literature

Ian C. C. King[1] · Andrew J. Mellington[1] · Anita Hazari[1] · Martin E. Jones[1]

Received: 29 September 2018 / Accepted: 17 March 2019 / Published online: 2 April 2019
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Abstract

Background Tranexamic acid (TXA) is effective in reducing blood loss and minimizing transfusion requirements in acute trauma and in selected elective surgical procedures. Its utility within plastic surgery is presently limited. The role of TXA in both immediate and delayed breast reconstruction is contentious, with concerns centring on thromboembolic risk in oncological and microsurgical settings. We examined the current evidence for the safety and efficacy of TXA in breast surgery.

Methods We searched PubMed, EMBASE and MEDLINE for studies in which TXA was used in breast surgery. The following terms were used: tranexamic acid, DVT (and deep vein/venous thrombosis), PE (and pulmonary embolus/emboli), mastectomy, mastopexy, breast augmentation, breast reconstruction, microsurgery/microsurgical and thromboembolic events/thromboembolus. All eligible studies were identified and full texts scrutinized.

Results Three papers were identified in which TXA was directly considered in relation to surgical procedures of the breast. None were related to breast reconstruction, either autologous or implant-based. Two papers studied mastectomy and TXA; one paper examined topical TXA use following mammoplasty. These studies demonstrated that TXA reduced or made no difference to haematoma incidence and might reduce drain outputs. Thromboembolic events were not discussed in any of the studies.

Conclusions Studies examining the role of TXA in breast surgery are limited. There is currently no evidence to support concerns that using TXA in patients undergoing mastectomy and/or breast reconstruction is associated with an increased risk of thromboembolic events. There remains, however, a lack of level 1 evidence for TXA use in breast surgery, including reconstruction.

Level of Evidence: Not ratable.

Keywords Tranexamic acid · Bleeding · Breast reconstruction

Introduction

The use of tranexamic acid (TXA) in breast reconstruction is contentious and practice varied with regard to its use. For many breast surgeons, concern exists about the risk of symptomatic thromboembolic events (TE) following the use of TXA during and after mastectomy and particularly for immediate breast reconstruction. As a department performing hundreds of free tissue breast reconstructions annually (both immediate and delayed), we sought to examine this concern as the protocols which we use include the use of TXA in the perioperative period. The value of TXA is recognized widely within the surgical world; however, the evidence to support its use in plastic surgery is limited to craniofacial surgery, where it has been used extensively [1–3]. We set out to ask whether the available literature is supportive of TXA use in breast oncological and reconstructive surgery.

Method

A systematic literature search using PubMed, EMBASE (OvidSP) and Medline (OvidSP) was undertaken using the following heading and free text terms centred on tranexamic acid combined with combinations of the following: DVT (and deep vein/venous thrombosis), PE (and pulmonary embolus/emboli), mastectomy, mastopexy, breast augmentation, breast reconstruction, microsurgery/microsurgical and

✉ Ian C. C. King

[1] Queen Victoria Hospital, East Grinstead RH19 3DZ, UK

thromboembolic events/thromboembolus. The primary searches were as follows, but a number of smaller combinations were attempted to interrogate the databases more thoroughly. All data ranges for all searches were employed: [Breast reconstruction OR mastectomy OR mastopexy OR breast augmentation] AND [TXA OR tranexamic acid]; [TXA OR tranexamic acid] AND [microsurgery OR microsurgical]; [Thromboembolism OR PE OR pulmonary embolism OR pulmonary emboli OR DVT OR deep vein thrombosis] AND either [TXA OR tranexamic acid] or [microsurgery OR microsurgical].

All eligible studies were identified and abstracts scrutinized by two authors with no limit set to date, language or publication status. Studies not pertaining to breast surgery were rejected.

Results

Our search identified three papers in which TXA was directly considered relating to surgical procedures of the breast. None related to breast reconstruction (either autologous or implant-based reconstruction), two papers discussed mastectomy and TXA [4, 5], and one paper explored topical TXA use following reduction mammoplasty [6]. No papers were found which studied TXA use in the microsurgical setting in any surgical specialty.

Considering TXA administration alongside mastectomy, Oertil et al. found no difference in haematoma formation amongst those receiving TXA compared with those not receiving TXA but passed no comment on incidence of TE [4]. The more recent study by Wolter et al. compared 712 patients undergoing subcutaneous mastectomy, dividing their patients into two cohorts—one with standard of care ($n = 346$) and one who received measures to prevent haematoma formation ($n = 366$) [5]. These measures included perioperative administration of TXA, intraoperative blood pressure elevation prior to wound closure, bedrest and compression dressings. This study demonstrated a significantly reduced haematoma incidence in the intervention group (4.4% vs. 9.2% in the control group, $p < 0.05$), yet it is difficult to ascertain the independent effect of TXA, as there were no controls for the other interventions used [5]. Indeed, the authors considered that raising blood pressure prior to definitive closure was the most important preventative factor for acute haematomas. As with the Oertil study, no comment was made concerning their incidence of TE following TXA use: Indeed, TE complications were not mentioned.

Ausen et al.'s randomized double-blind placebo-controlled study examined 28 consecutive patients undergoing bilateral reduction mammoplasty, applying saline topically to one breast and TXA topically to the other prior to closure [6]. They observed a 39% reduction in drain production in the breasts which had received TXA. No haematomas were reported in either group, and there was no mention of TE arising post-operatively.

Discussion

TXA has been shown to be of great value in reducing mortality for trauma and major haemorrhage [7–12], yet the benefit of TXA in minor bleeding and elective surgery is less clear; it has been suggested that the risk of TE is too poorly documented and inadequately evaluated to justify the risk of exposure [13]. This research stalemate therefore poses a challenge to plastic surgery as a broad specialty which has a great deal to gain by reducing bleeding, minimizing transfusion requirements and developing enhanced patient recovery systems to get patients up and out of hospital promptly post-operatively.

Tranexamic acid is a synthetic lysine analogue antifibrinolytic that acts by competitively inhibiting the activation of plasminogen to plasmin, thus reducing the degradation of fibrin clots by plasmin [14]. TXA also blocks plasmin-induced platelet activation to prevent platelets being used needlessly. TXA further provides an anti-inflammatory effect through inhibition of plasmin formation, as plasmin plays a role in inflammation mediation [15]. Since d-dimers are a fibrin degradation product, the formation of d-dimers is impaired by TXA use. This has been shown to result in false-negative d-dimer readings in some patients with TEs following treatment for menorrhagia [16]. A recent systematic review and meta-analysis of tranexamic acid-centred randomized controlled trials demonstrated that surgical bleeding and blood transfusion requirement is reduced by about a third using tranexamic acid [17, 18]. The suggested single intravenous dose of TXA is 1–2 g [19, 20], but the minimal effective plasma concentration is unknown [19, 21]. It is suggested that TXA should be avoided in patients with a history of coagulopathy or clotting disorders and either arterial or venous thrombosis or embolism. Caution is often taken with renal impairment and in those at risk of seizures, though definitive causal relationships have not been clearly established in these populations [22, 23].

The majority of the literature discussing TXA for elective surgery focusses on either orthopaedic surgery, cardiothoracic surgery, or obstetrics and gynaecology [24–28]. A large number of reviews have shown TXA to be safe in knee and hip arthroplasty, demonstrating no increase in TE following TXA use [20, 24, 25, 28, 29]. Poeran et al.'s retrospective cohort study examined the outcomes of 20,051 patients who received TXA during either hip or knee arthroplasty and compared them with 852,365 patients who did not and found that TXA reduces blood transfusion requirements without increasing risk of vascular occlusive events [20]. Gillette et al. found a low and statistically insignificant complication rate when using TXA alongside three different chemical prophylactic regimens (warfarin, aspiring and dalteparin) following hip and knee arthroplasty [30].

Concerns also exist within the literature over the uncertainty that antifibrinolytic administration has on the risk of

vascular occlusive events, and in particular on the heart [31], as perioperative myocardial infarction can often go undetected as patients may not experience ischaemic symptoms [32]. Poeran's study, however, demonstrated a reduction in myocardial infarction risk in their TXA patient cohort [20]; whether the inhibition of plasmin (and therefore of inflammation) by TXA reduces inflammation which in turn lowers myocardial infarction risk has been hypothesized [31, 33]. The aspirin and tranexamic acid for coronary artery surgery trial examined 4631 patients, however, which suggests that TXA use does not increase the risk of thromboembolic events [34].

How TXA is administered is considered by some to be an important factor in safety and efficacy [35]. Topical TXA has been posited to have an equal or superior effect to intravenous TXA on transfusion requirements and bleeding [6, 24, 28]; however, most studies are in orthopaedics and study design often flawed. A systematic review by Ker et al., however, addressed this and considered 29 randomized trials and found a similar efficacy between topical and intravenous TXA, but they noted that the effect on the risk of TE was nonetheless uncertain [36]. Alshryda et al. for example failed to directly compare topical and intravenous TXA, noting no difference in TE rates following TXA administration compared with placebos, but nonetheless concluding that topical TXA is superior to intravenous TXA [24]. Wang et al. found no statistical significance between topical and IV administration of TXA in terms of blood loss, transfusion requirements and TE [28]. Rohrich explains that the use of topical TXA is more convenient, safer and can be applied directly during surgery to an appropriate surgical field [35], suggesting that surgical preference is a factor in administration. Rohrich further discusses intravenous dosing either by a 10 mg/kg bolus given thrice or four times daily as required, or by a 10 mg/kg bolus followed by a 1 mg/kg/h infusion to maintain a constant blood concentration of TXA [35]. This differs from our practice wherein we administer a solitary 1 g intravenous bolus peri-operatively to aid control, which we find to be adequate and safe.

There is very little literature considering the use of TXA with skin flaps, either pedicled or free. This is of particular interest when considering the thrombogenic potential of microvascular anastomoses in the immediate operative and postoperative period. Valero et al. examined a cohort of 173 extremity flap reconstructions between 2003 and 2012, where TXA was used in 11% of patients. One hundred flaps were pedicled and 73 flaps were free tissue transfers [37]. They found an overall VTE rate of 23.7%, but there were no documented VTEs in patient who had received TXA. Furthermore, there were no significant differences in flap complications in the military patients receiving TXA and those who did not [37]. Whilst a comparatively small study, this is nonetheless reassuring and it tallies with our experience of a low flap failure rate and the maintenance of patent microvascular anastomoses despite TXA administration.

The population of patients undergoing immediate breast reconstruction mostly have active breast cancer. Whilst patients undergoing treatment for cancer are recognized to be at risk of TEs, the absolute risk depends on the type and stage of the tumour and upon the use of cytotoxic medications. Age, co-morbidities and immobilization following surgery are important factors. Tumour cells have a capacity to release fibrinolytic factors, procoagulants (such as tissue factor) and inflammatory cytokines in addition to their direct interaction with other blood cells, such as monocytes and platelets. The effect of TXA-like drugs has not been extensively studied, but a recent systemic review and meta-analysis considering the safety and efficacy of lysine analogues in cancer patients found that there was no increased risk of TE in patients who received lysine analogues compared to controls, but that transfusion risk was significantly reduced in the intervention group [38].

Conclusion

Our review has illustrated that there is currently no evidence to support concerns that TXA use in patients undergoing mastectomy and/or breast reconstruction is associated with an increased risk of TE. In a field in which enhanced patient treatment pathways are evolving to ensure hospital stays are kept to a minimum following surgery, tranexamic acid certainly may have an important role in recovery, particularly from the perspective of intra-operative blood loss and drainage output after surgery. Further specific studies are required in this field, however, as robust evidence for the value of this drug would be essential for the future of breast surgery—and indeed plastic surgery more widely.

Compliance with ethical standards

Conflict of interest Ian CC King, Andrew J. Mellington, Martin E. Jones and Anita Hazari declare that they have no conflicts of interest.

Ethical approval For this type of study, formal consent is not required.

Informed consent n/a

Patient consent Patients provided written consent for the use of their images.

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