Randomized clinical trial

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Topical moistening of mastectomy wounds with diluted tranexamic acid to reduce bleeding: randomized clinical trial

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Background: **Topical administration of tranexamic acid (TXA) may be an alternative to intravenous administration to reduce bleeding with a lower risk of systemic adverse events. The aim of this study was to investigate whether moistening a surgical wound with TXA before closure, leaving a thin film of drug only, would reduce postoperative bleeding.**

Methods: **This was a two-centre, stratified, parallel-group, placebo-controlled, double-blind RCT. Patients undergoing mastectomy with or without axillary lymph node clearance were randomized 1 : 1 to moistening of wound surface before closure with either 25 mg/ml TXA or 0·9 per cent sodium chloride (placebo). The primary endpoint was postoperative bleeding as measured by drain production in the first 24 h. Secondary endpoints were early haematoma, total drain production, postoperative complications and late aspirations of seroma within 3 months.**

Results: **Between 1 January 2016 and 31 August 2018, 208 patients were randomized. Two patients were converted to a different surgical procedure at surgery, and four did not receive the intervention owing to technical error. Thus, 202 patients were included in the study (101 in the TXA and 101 in the placebo group). TXA reduced mean drain production at 24 h (110 *versus* 144 ml; mean difference 34 (95 per cent c.i. 8 to 60) ml, $P = 0{\cdot}011$). One patient in the TXA group had early haematoma compared with seven in the placebo group (odds ratio (OR) 0·13 (95 per cent c.i. 0·02 to 1·07); $P = 0{\cdot}057$). There was no significant difference in postoperative complications between TXA and placebo (13 *versus* 10; OR 1·11 (0·45 to 2·73), $P = 0{\cdot}824$) or need for late seroma aspirations (79 *versus* 67 per cent; OR 1·83 (0·91 to 3·68), $P = 0{\cdot}089$).**

Conclusion: **Moistening the wound with TXA 25 mg/ml before closure reduces postoperative bleeding within the first 24 h in patients undergoing mastectomy. Registration number: NCT02627560 (https://clinicaltrials.gov).**

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Introduction

In healthy patients with no coagulation deficiency, the only systemically administered pharmacological intervention to reduce surgical bleeding universally with an acceptable safety profile is antifibrinolytic drugs[1]. Tranexamic acid (TXA) has been the drug of choice since the withdrawal of aprotinin from the market in 2007[2]. Intravenous use of TXA reduces surgical bleeding and need for blood transfusion by about one-third[3], and is used routinely in surgery associated with significant blood loss. Even high-dose intravenous TXA has not been associated with an increased rate of thromboembolic events, although large prospective studies designed to evaluate this specific risk are lacking[4]. A dose-dependent increase in non-ischaemic seizures has been described after intravenous TXA in cardiac surgery[5–7]. Although minimization of blood loss is

desirable in all operations, general use of intravenous TXA has not been advocated owing to unease regarding possible systemic adverse effects[8,9].

A prophylactic intervention to minimize postoperative blood loss should be low-cost, simple, efficient and safe. Topical use of TXA may provide a high drug concentration on the wound surface with negligible systemic concentrations[10]. Topical use is still off-label, with no consensus regarding the optimal TXA concentration in the solution applied, mode of application or duration of contact[11,12]. Most publications come from joint replacement surgery, where instilling TXA as a bolus into the joint reduces bleeding equivalent to that following intravenous administration[13–15]. The present authors have previously introduced a novel procedure in which the wound surface is simply moistened with 25 mg/ml tranexamic acid before closure, with a mean 39 per cent reduction in drain volume in a small proof-of-concept, randomized, placebo-controlled study of bilateral reduction mammoplasty[16]. Such moistening exposes the wound surface to TXA for a considerably shorter time than topical boluses[10].

The aim of this study was to investigate the effect of this moistening method in a larger population and in a different study model. Mastectomy was chosen as a suitable model for bleeding as it is a common and standard surgical procedure with homogenous wounds and little occult blood loss. As postoperative seroma is a major adverse event after mastectomy[17,18], the influence of topical TXA on seroma formation was also investigated.

Methods

The study was a two-centre, stratified, parallel-group, placebo-controlled, double-blind RCT. It was registered at ClinicalTrials.gov (NCT02627560) and approved by the involved departments, the Regional Committee for Medical and Health Research Ethics in Mid Norway (2015/1722) and the Norwegian Medicines Agency (15/11405-7). The trial was performed in accordance with the principles of the Declaration of Helsinki and monitored according to the Good Clinical Practice directive of the European Medicines Agency.

Study population

Patients above 18 years of age who were to undergo simple mastectomy, mastectomy with sentinel node biopsy (SNB) or mastectomy with axillary lymph node clearance were identified consecutively from the operation planning registries at St Olav's University Hospital (centre A) and Ålesund Hospital (centre B) between 1 January 2016 and 31 August 2018. Exclusion criteria were: known thromboembolic disease or high risk of thromboembolism warranting extra anticoagulation in connection with the procedure; pregnant or nursing patient; and known allergy to TXA. Eligible patients were informed about the study after diagnosis but before surgery by nurses and doctors connected to the respective breast cancer centres. Patients were enrolled if written informed consent was obtained.

Treatment allocation

Computer-generated randomization was done in permuted blocks of 10, 20 or 50 patients, stratified according to study centre. Sealed and numbered opaque randomization envelopes were produced accordingly. All randomization and organization of electronic case report forms was done by the Unit of Applied Clinical Research[19] at the Norwegian University of Science and Technology, Trondheim, Norway. Participants and all personnel involved in surgery and postoperative follow-up, data collection and statistical analysis were blinded to the randomization.

Study interventions

Participants were assigned randomly in a 1 : 1 ratio to moistening of the wound surface before closure with either 20 ml TXA 25 mg/ml or 0·9 per cent sodium chloride (placebo). Opening of the randomization envelope and drug preparation was done by personnel not connected to the surgery, postoperative follow-up, data collection or statistical analysis. Envelopes were opened in numerical order. TXA 25 mg/ml was prepared by extracting 5 ml from a 20-ml bottle of 0·9 per cent saline and adding 5 ml TXA 100 mg/ml to the same bottle, thus obtaining 20 ml TXA 25 mg/ml. Placebo was an identical 20-ml bottle of saline, perforated by a needle for identical appearance.

The moistening method is illustrated in a video that can be accessed at https://www.youtube.com/watch?v=-8MAE3NAHfQ. All involved surgeons were instructed visually on details of the moistening technique by watching this video, and also instructed to cover all surfaces and use the entire 20 ml, although much would spill. Breast specimen weight, height and width were measured during surgery. Wound surface area was calculated as an ellipse (height/2 × width/2 × π). Patients received active vacuum drains (Exudrain® FG 14; Wellspect, Oslo, Norway) marked with the exact time point to register drain production 24 h after completion of the operation. Preoperative evaluation, performance of the surgery, postoperative treatment and drain removal were otherwise in accordance with existing routine at the participating study centres; randomization was therefore stratified according to study centre.

It was discussed whether randomization should also be substratified according to the type of surgical procedure, as the presence or absence of lymph node clearance is known to have a significant impact on drain output. As randomization was done before surgery for practical purposes and a planned procedure might be converted during surgery, the authors chose instead to adjust for type of procedure in the statistical analysis.

Study outcomes

The primary outcome was postoperative bleeding as defined by the volume of drain production in the first 24 h after surgery. Secondary outcomes were total drain production and drain time, early haematoma, postoperative complications and seroma formation. Seroma was defined as fluid accumulation warranting aspiration after drain removal. Chronic seroma was defined as persistent seroma at 3 months. Patients experiencing postoperative complications defined as haematomas, infections and wound ruptures were excluded from the seroma analyses as these may influence seroma formation.

Drain production was recorded at 24 h after the end of surgery, and on a daily basis thereafter until drain removal. Variables that, according to protocol, could influence the defined outcomes were obtained from the medical record (*Table 1*). Staff were instructed to document seroma aspirations accurately throughout the study period, and patients were instructed to request accurate measuring should they have aspirations performed elsewhere. Patient follow-up lasted for 3 months, and all patients received a final phone call to ensure or correct registered data and identify unregistered adverse events.

Evaluation of the surgical techniques at the two centres had been performed before study initiation. Use of tumescence, dissection with diathermy and choice of surgical levels were found to be comparable. However, during data collection it was noted that drain productions in centre B were notably lower. A *post hoc* re-evaluation revealed that centre B routinely applied a circular compression bandage for the first 24 h after surgery; this had not been recognized during the study design phase. Postoperative compression is an active intervention to reduce bleeding, but was not registered accurately in the medical records or accurately remembered by patients in retrospect. It could therefore not be added as a *post hoc* variable at the individual patient level but had to be regarded an inherent factor when adjusting data for study centre.

Statistical analysis

A between-group difference in mean drain production of 25 per cent was considered clinically significant. Estimating a standard deviation of 0·6[20], α of 0·05 and power 0·80, a sample size of 92 patients in each group was needed[21]. It was planned to include a total of 210 patients to ensure additional power.

Table 1 Patient characteristics at baseline

	TXA (*n* = 101)	Placebo (*n* = 101)
Age (years)*	66·2(13·3)	62·3(12·8)‡
Women	98 (97·0)	100 (99·0)
BMI (kg/m^2)*	26·9(4·9)	27·1(4·7)
Active smoker	19 (18·8)	13 (12·9)
Recruited at centre A	77 (76·2)	77 (76·2)
Operated on by senior surgeon	50 (49·5)	50 (49·5)
Neoadjuvant treatment	32 (31·7)	41 (40·6)
Irradiated tissue	14 (13·9)	11 (10·9)
Perioperative anticoagulation	32 (31·7)	37 (36·6)
Axillary clearance	34 (33·7)	31 (30·7)
Weight of breast specimen (g)*†	780(450)	746(359)
Wound surface area (cm^2)*†	292(117)	279(84)

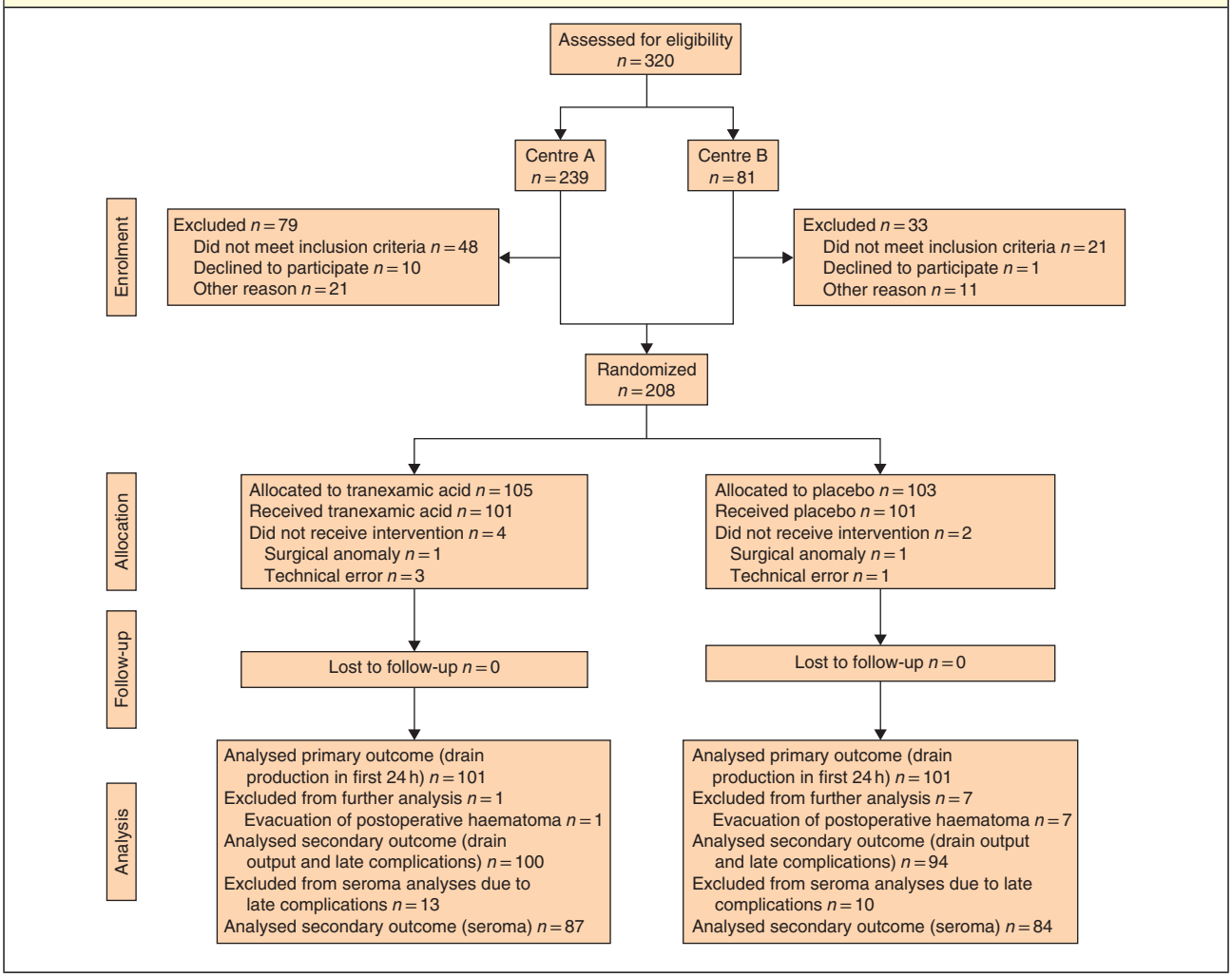
Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.) †Axillary component included. TXA, tranexamic acid. ‡$P = 0·033$ *versus* TXA (independent-samples *t* test).

Continuous patient characteristics data are presented as mean(s.d.) values and compared with independent-samples *t* tests. Categorical patient data are presented as frequency counts and percentages, and compared using the χ^2 tests, although variables with fewer than five patients were analysed with Fisher's exact test.

Continuous outcome data are presented as mean (95 per cent c.i.) values. Categorical outcome data are presented as frequency counts and percentages. For presentation of unadjusted effect size of continuous data, the mean difference (with 95 per cent c.i.) between groups was determined. Effect sizes of categorical data are presented as odds ratios (ORs) with 95 per cent confidence intervals. For statistical analysis of unadjusted effect sizes, continuous outcome data were analysed using independent-samples *t* tests, whereas categorical outcome data were compared using χ^2 or Fisher's exact tests, as appropriate.

For adjusted statistical analyses, non-normally distributed continuous data underwent logarithmic transformation. Data were then analysed using a general linear model. All variables listed in *Table 1* were included, and stepwise removal of non-significant variables ($P > 0·050$) was performed to obtain a final model that included only individually significant variables. Results were calculated as percentage differences between means, with 95 per cent confidence intervals. Non-normally distributed continuous data that could not undergo logarithmic transformation owing to the appearance of zero values were dichotomized

Fig. 1 CONSORT diagram for the study



and analysed using a logistic regression model, adjusting for significant variables. Results are shown as mean differences or ORs with 95 per cent confidence intervals. Two-tailed $P < 0{\cdot}050$ was considered statistically significant. Analyses were performed in accordance with the intention-to-treat principle and were conducted using SPSS® version 25 (IBM, Armonk, New York, USA).

Results

Between 1 January 2016 and 31 August 2018, 208 patients were randomized, of whom 202 were included in the study (*Fig. 1*). Of these, 101 received TXA and 101 placebo. Patient characteristics are presented in *Table 1*. Patients receiving TXA were on average 3·9 years older ($P = 0{\cdot}033$); otherwise there were no differences between the groups. Patient data stratified for study centre and type of surgery defined as axillary lymph node clearance or simple mastectomy/SNB are presented in *Tables S1* and *S2* (supporting information).

Outcome data

Outcome data are presented in *Table 2*, and data stratified for type of surgery and study centre are presented in *Tables S3–S5* (supporting information). Mean(s.d.) drain production at 24 h was 110(67) ml in the TXA group *versus* 144(113) ml in the placebo group (mean difference 34 (95 per cent c.i. 8 to 60) ml; $P = 0{\cdot}011$).

The following five patient variables independently and significantly affected outcome: administration of TXA; type of procedure; study centre; wound surface area; and

Table 2 Outcome data

			TXA *versus* placebo*			
			Effect size		Adjusted difference##	
	TXA	Placebo	OR†	*P*‡‡	OR†	*P****
Primary outcome	*n* = 101	*n* = 101				
Mean drain production in first 24 h (ml)*	110 (97, 123)	144 (122, 167)	−34 (−60, −8)‡	0·011§§	−32·4 (−51·4, −15·8)¶	< 0·001†††
Secondary outcomes#	*n* = 100	*n* = 94				
Early haematoma**	1 (1·0)	7 (7)	0·13 (0·02, 1·11)	0·065¶¶	0·13 (0·02, 1·07)	0·057
Mean total drain production (ml)*	189 (145, 234)	214 (165, 264)	−25 (−91, 41)‡	0·461§§	−33·0 (−60·0, −10·4)¶	0·003†††
Mean time with drain (days)*	1·7 (1·4, 1·9)	1·8 (1·6, 2·1)	−0·1 (−0·7, 0·2)§	0·341§§	−15·6 (−30·2, −2·6)¶	0·017†††
Drain removed at 24 h	65 (65·0)	47 (50)	1·86 (1·04, 3·31)	0·035	3·00 (1·44, 6·22)	0·003
Mean drain production in 24 h before removal (ml)*	93 (82, 105)	91 (80, 102)	2 (−13, 18)‡	0·783§§	−6·4 (−22·3, 8·10)¶	0·083†††
Late haematoma, postoperative infection or wound rupture	13 (13·0)	10 (11)	1·26 (0·52, 3·02)	0·721	1·11 (0·45, 2·73)	0·824
Thromboembolic event	0 (0)	0 (0)				
Seroma††	*n* = 87	*n* = 84				
Aspiration required	69 (79)	56 (67)	1·92 (0·96, 3·82)	0·062	1·83 (0·91, 3·68)	0·089
≥ 5 aspirations	19 (22)	17 (20)	1·10 (0·53, 2·30)	0·797	0·87 (0·38, 2·00)	0·740
Cumulative seroma ≥ 500 ml	34 (39)	20 (24)	2·05 (1·06, 3·98)	0·033	1·99 (0·94, 4·23)	0·073
Chronic seroma	6 (7)	11 (13)	0·49 (0·17, 1·40)	0·182	0·41 (0·14, 1·21)	0·107

Values in parentheses are percentages unless indicated otherwise; *values in parentheses are 95 per cent confidence intervals. †Odds ratio (OR) unless indicated otherwise; values are ‡millilitres, §days and ¶percentages. #Number of patients with early haematoma calculated from all patients; **patients with early haematoma excluded from other secondary postoperative outcome registrations; ††patients with early or late haematoma, infection or wound rupture excluded from seroma registrations. TXA, tranexamic acid. ‡‡χ^2 test, except §§independent-samples Student's *t* test and ¶¶Fisher's exact test. ##Regression analyses, adjusted according to axillary clearance, study centre, wound surface area and surgeon seniority: ***logistic regression model, except †††general linear model (ratio between logarithmic mean as percentage difference).

Table 3 Exploratory subgroup analysis: adjusted primary and secondary outcomes according to administration of tranexamic acid *versus* placebo, stratified for type of surgery

	TXA *versus* placebo			
	Simple mastectomy/SNB (*n* = 137)*	*P*	Axillary clearance (*n* = 65)†	*P*
Primary outcome				
Drain production in first 24 h‡§	−33·4 (−58·1, −12·6)	0·001	−27 (−56, −3)	0·026
Secondary outcomes¶				
Early haematoma	TXA 1 *versus* placebo 3††	0·620	TXA 0 *versus* placebo 4††	0·046
Total drain production‡§	−32·3 (−62·4, −9·4)	0·005	−27 (−92, 18)	0·244
Time with drain‡	−11·6 (−24·9, −0·2)	0·054	−23 (−65, 9)	0·166
Drain removed at 24 h#	2·41 (1·02, 5·68)	0·044	5·70 (1·27, 25·6)	0·023
Drain volume in 24 h before removal‡	−11·3 (−30·3, 5·3)	0·185	5·2 (−40, 26)	0·721
Late haematoma, postoperative infection or wound rupture#	1·01 (0·33, 3·06)	0·985	1·27 (0·24, 6·62)	0·778
Seroma**				
Aspiration required#	1·32 (0·59, 2·97)	0·500	5·71 (1·16, 28·2)	0·032
≥ 5 aspirations#	0·47 (0·15, 1·50)	0·203	1·88 (0·54, 6·49)	0·320
Cumulative seroma ≥ 500 ml#	1·08 (0·41, 2·81)	0·880	5·72 (1·50, 21·9)	0·011
Chronic seroma#	0·18 (0·04, 0·89)	0·035	1·50 (0·23, 9·73)	0·671

Values in parentheses are 95 per cent confidence intervals. *Tranexamic acid (TXA) (67 patients) *versus* placebo (70); †TXA (34) *versus* placebo (31). ‡Ratio between logarithmic mean as percentage difference; univariable general linear model adjusted for study centre and wound surface area; §additionally adjusted for surgeon seniority. ¶Number of patients with early haematoma calculated from all patients; patients with early haematoma excluded from other secondary postoperative outcome registrations. #Odds ratio: logistic regression model adjusted for study centre and wound surface area. **Patients with early or late haematoma, infection or wound rupture excluded from seroma registrations. SNB, sentinel node biopsy; ††Fisher's exact test owing to number of patients being too low for logistic regression analysis.

surgeon seniority. Perioperative anticoagulation did not affect the outcome variables. The independent significance of effect of all patient variables on the primary outcome is presented in *Table S6* (supporting information).

Outcome variables adjusted for the significant patient variables showed that moistening the wound surface with TXA significantly reduced 24-h drain production by 32·4 per cent ($P < 0·001$) (*Table 2*). Although total drain volume was not significantly reduced in the unadjusted analyses, adjusted outcome showed that total drain volume was reduced by 33·0 per cent ($P = 0·003$). Patients in the TXA group were significantly more likely to have drains removed on the first day (OR 3·00; $P = 0·003$) and had a significantly shorter duration of drain insertion (−15·6 per cent; $P = 0·017$).

Early haematomas warranting reoperation occurred in seven patients in the placebo group and one patient in the TXA group ($P = 0·057$). There were no differences between groups regarding other complications. No thromboembolic events were registered.

Table 4 Exploratory subgroup analysis: adjusted primary and secondary outcomes according to administration of tranexamic acid *versus* placebo in patients who had simple mastectomy/sentinel node biopsy at centre A

	TXA ($n = 52$) *versus* placebo ($n = 56$)	*P*
Primary outcome		
Drain production in first 24 h*†	−39 (−69, −14)	0·001
Secondary outcomes‡		
Early haematoma	TXA 0 *versus* placebo 3#	0·244
Total drain production*†	−46 (−81, −18)	0·001
Days with drain*	−23 (−83, −10)	0·001
Drain removed at 24 h§	6·60 (2·07, 21·22)	0·001
Drain volume in 24 h before removal*	−9 (−30, 9)	0·309
Late haematoma, postoperative infection or wound rupture	TXA 5 *versus* placebo 6#	1·000
Seroma¶		
Aspiration required§	1·11 (0·44, 2·79)	0·821
≥ 5 aspirations§	0·47 (0·15, 1·50)	0·203
Cumulative seroma ≥ 500 ml§	1·05 (0·38, 2·90)	0·930
Chronic seroma§	0·18 (0·04, 0·89)	0·035

Values in parentheses are 95 per cent confidence intervals. *Ratio between logarithmic mean as percentage difference; univariable general linear model adjusted for drug and wound surface area; †additionally adjusted for surgeon seniority. ‡Number of patients with early haematoma calculated from all patients; patients with early haematoma excluded from other secondary postoperative outcome registrations. §Odds ratio: logistic regression model adjusted for wound surface area. ¶Patients with early or late haematoma, infection or wound rupture excluded from seroma registrations. TXA, tranexamic acid. #Fisher's exact test owing to number of patients being too low for logistic regression analysis.

Subgroup analyses

Before initiation of the study, axillary clearance was assumed to have a significant influence on drain production, and subgroup analyses were planned according to type of surgery. Recognition of the significant influence of study centre led to an additional *post hoc* subgroup analysis according to study centre. The adjusted effects of type of surgery and study centre on outcome variables are presented in *Table S7* (supporting information).

Subgroup analysis for type of surgery showed that TXA had a significant effect on drain production at 24 h in patients having axillary clearance (−27 per cent; $P = 0·026$), although less than in the simple mastectomy/SNB group (−33·4 per cent; $P = 0·001$) (*Table 3*). Total drain production was not significantly reduced in patients who had axillary clearance (−27 per cent; $P = 0·244$), whereas it was significantly reduced in the simple mastectomy/SNB group (−32·3 per cent; $P = 0·005$). The subpopulation that had undergone lymph node clearance had significantly increased odds compared with placebo of needing seroma aspiration (OR 5·71; $P = 0·032$) and of having a cumulative aspirated seroma volume of 500 ml or more (OR 5·72; $P = 0·011$), but no increased risk of chronic seroma (OR 1·50; $P = 0·671$) (*Table 3*).

Patients operated on at centre A had 60·3 per cent higher drain production at 24 h than those from centre B ($P < 0·001$) (*Table S7*, supporting information). Centre A practised a significantly higher threshold value for ongoing drain production at removal (97·4 per cent greater; $P < 0·001$) and kept drains for a significantly shorter duration (−29·8 per cent; $P < 0·001$) than centre B, yet centre A had a 33·5 per cent greater cumulative drain volume at the time of removal ($P = 0·013$). This difference was postulated to be influenced by the postoperative compression used at centre B.

Patients who neither received compression nor had lymph node clearance were those in the simple mastectomy/SNB group at centre A (108 patients: TXA 52, placebo 56). To illustrate the isolated effect of TXA, this subpopulation was analysed separately; there was a 39 per cent reduction in 24-h drain production ($P = 0·001$) and a 46 per cent reduction in total drain output ($P = 0·001$) compared with placebo (*Table 4*).

Discussion

This study examined the effect of leaving a thin film of TXA fluid on the wound surface before closure[16], and confirmed that a simple single moistening of a wound surface with TXA 25 mg/ml significantly reduced both postoperative bleeding and total drain production by about

one-third. This is comparable to the effect of established intravenous prophylactic use of TXA[22], and is thus an alternative mode of administration. The authors also postulate that topical TXA may reduce the risk of postoperative haematoma warranting reoperation, as seven of eight rebleeding episodes occurred in the placebo group; in the authors' previous pilot study[16] two rebleeding episodes were observed, both in the placebo group. Thus, in the authors' two intervention studies with a total of 258 breasts, nine of ten haematomas occurred in the placebo group ($P = 0{\cdot}019$, Fisher's exact test). In the few existing studies[20,23,24] of intravenous TXA in breast surgery, a reduction in both bleeding and haematoma has been suggested.

An unexpected finding was a possible negative effect of TXA on leakage of lymph. In the subgroup of patients receiving TXA who underwent lymph node clearance, TXA had a less beneficial effect on postoperative drain production; these patients were later significantly more likely to need seroma aspiration and had an increased cumulative seroma volume, although no increase in chronic seroma.

The purpose of this study was not to demonstrate reduced bleeding in mastectomies *per se*. The need to minimize perioperative bleeding is fundamental, and the method has relevance for many procedures other than breast surgery. Mastectomy is, however, a suitable study model, in which homogenous wounds and little occult bleeding should provide relatively unbiased results. A major strength of the present study was the identification of modifying variables with a significant effect, such as wound surface area, performance of lymph node clearance and inherent differences between study centres.

Drain production is a surrogate for bleeding, and could be considered a weakness of this study. Topical application of TXA at the end of surgery will not affect perioperative bleeding, and hence comparison of preoperative and postoperative haemoglobin concentrations would not be an appropriate measure for the effect of this mode of administration. Drain fluids consist of both blood and transudate, with a transition to more serous fluids over time. The authors therefore regarded drain production at 24 h as a more appropriate measure of postoperative bleeding than total drain production.

A major weakness of this study was the failure to register 'application of postoperative compression' as a separate variable, as this was recognized in retrospect to be a routine procedure at centre B. Closure of dead space reduces bleeding[25]. Compression is thus an active intervention that may interact with the effect of TXA, possibly contributing to the reduced drain production and the lower beneficial effect of TXA observed at centre B. Use of compression to reduce bleeding and seroma has been somewhat forfeited in breast surgery, the few existing studies showing little effect, particularly on late seroma[26,27]. However, these studies describe ongoing compression for several days, which may induce both discomfort and secondary reactions to ischaemia. Moreover, seroma is a different endpoint than postoperative bleeding. A proper randomized evaluation of the effect of a 24-h postoperative compression bandage, as practised at centre B, on postoperative bleeding and haematoma is warranted.

When analysing only the subpopulation that had neither lymph node clearance nor postoperative compression (patients undergoing simple mastectomy/SNB at centre A), the isolated effect of TXA increased to a 39 per cent reduction in 24-h drain production and a 46 per cent reduction in total drain output. This may be the most appropriate model for the true isolated effect of topical TXA.

Studies on the topical use of TXA have been published since the 1970s[13]. Topical administration has, however, been done mostly by instilling boluses into closed spaces such as joints or the mediastinum, the application of soaked gauze or repeated irrigation[13]. As topical use is off-label and the possible local effects of prolonged tissue exposure are largely unknown, keeping drug concentration and contact time as low as possible would be a sensible precaution when advocating routine prophylactic use. Although bolus and gauze administrations may lead to prolonged exposure to TXA, the authors' previous study[10] demonstrated that topical moistening has predictable and swift elimination, as well as rendering systemic concentrations negligible.

Although there was no increase in wound rupture, wound infection or chronic seroma in the TXA group, the increase in seroma volume after TXA in patients having lymph node clearance raises the question of whether tissue adhesion or healing of lymph vessels may be delayed by topical application of TXA. As the present population may have presented with exceedingly high rates of seroma owing to the practice of early drain removal (more than 70 per cent needed at least one seroma aspiration subsequently), these findings need confirmation from other populations with different drain protocols.

Whether TXA may have unrecognized antiadhesive properties needs further exploration. TXA inhibits plasminogen, which is ubiquitous in tissue matrix and has numerous functions beyond the cleavage of fibrin. Studies[28,29] have suggested that TXA may affect cell adhesion, and inhibition of TXA on tumour growth and spread was investigated in the 1970s and 1980s[30]. The authors made the unexpected observation in a previous study[31] that prolonged exposure to high concentrations of topical TXA caused lack of re-epithelialization, and even

epithelial detachment, in an *ex vivo* human skin wound model.

TXA not only binds to plasminogen but may act as a competitive antagonist to the inhibitory neurotransmitters γ-aminobutyric acid type A and glycine[5,32] in the central nervous system (CNS). Both topical application of TXA to the brain in animal experimental settings[33,34] and intrathecal accidental administration of TXA in humans[35] have been shown to cause seizures, and topical TXA should not be used in surgery with exposed CNS.

These findings demonstrate that the local effect of TXA has been explored insufficiently, and that caution may be warranted with regard to dose and exposure time.

The authors propose that simple moistening of most surgical wound surfaces before closure with TXA 25 mg/ml is a low-cost, simple and quick routine prophylactic measure to reduce bleeding and possibly prevent reoperation due to haemorrhage. Further research must determine the lowest effective topical dose when using a moistening technique. Adequately powered studies or meta-analyses of the ability of topical TXA to prevent reoperation for bleeding are lacking, and possible adverse effects of topical application need further exploration.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.