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Perioperative and postoperative tranexamic acid reduces the local wound complication rate after surgery for breast cancer

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A randomized double-blind trial has shown that, in 160 women with breast cancer undergoing lumpectomy or mastectomy with axillary clearance, perioperative and postoperative administration of tranexamic acid 1 g three times daily resulted in a significant reduction in the mean postoperative drainage volume compared with patients given placebo (283 *versus* 432 ml, $P < 0{\cdot}001$). The frequency of postoperative seroma formation was also decreased by tranexamic acid administration (27 *versus* 37 per cent, $P = 0{\cdot}2$). Haematoma formation was infrequent in both groups and was not altered by administration of tranexamic acid. No infectious complications occurred. Age over 60 years was a significant risk factor for overall wound complications but tumour size and regional lymph node metastases were not. Tranexamic acid may be used to reduce the frequency of postoperative wound complications following surgery for breast cancer.

The most common local complication after surgery of the breast is formation of seroma and haematoma, reported rates at different periods of follow-up varying between 4·2 and 62 per cent and from 0 to 8 per cent respectively[1–11].

Fibrinolytic activity of the plasmin system in serum and lymph may contribute to fluid accumulation in the dead space under the skin flap and in the axillary fossa. Fibrin complexes already formed within and around vessels may be degraded, resulting in further leakage of blood and lymph from the vessels.

Tranexamic acid (Anvitoff; Knoll, Liestal, Switzerland, or *trans*-4-aminomethylcyclohexanecarboxylic acid, of molecular weight 157·2 Da) is a synthetic antifibrinolytic agent. Structurally it resembles ε-aminocaproic acid but is ten times more potent. Fibrinolysis is inhibited by blockade of plasminogen activation. Tranexamic acid also has a direct antiplasmin action, inhibiting fibrin degradation. A third effect that protects fibrin arises from a direct change in the conformation of fibrinogen[12].

Tranexamic acid has been used in gastroenterology[13], gynaecology[14] and otology[15] to reduce the incidence of postoperative bleeding complications.

Patients and methods

A prospective randomized study was carried out on 160 women with breast cancer who underwent mastectomy or lumpectomy including axillary clearance. Patients were excluded if they had a history of thromboembolic events, severe varicose veins, coagulation disorders or were receiving anticoagulant drugs. No perioperative drug prophylaxis against thromboembolism was used.

Drug regimen

Tranexamic acid (3 × 1 g in 5 ml daily) or placebo (normal saline 3 × 5 ml daily) was administered in a double-blind regimen. Intravenous doses were given initially on induction of anaesthesia and continued for 24 h. Thereafter an oral regimen was administered until the fifth day after surgery. During the first period of the trial (71 patients) the three parenteral doses were given intravenously as bolus injections. Drug-related side-effects were noted significantly more frequently in the treated group than in that receiving placebo (16 of 36 *versus* three of 35, $P < 0{\cdot}001$). Marked nausea, dizziness and hypotension during injection led to a change of administration after an interim statistical analysis. The same dose of 1 g tranexamic acid or placebo was diluted in 100 ml normal saline and administered by short infusion over 20 min during the second study period (89 patients). During this latter period the frequency of side-effects was the same in both groups at three of 43 and three of 46 for tranexamic acid- and placebo-treated patients respectively.

The trial was performed over two consecutive periods: May 1987 to July 1989 and March 1990 to November 1991. The gap between the two periods occurred because of a delay in the preparation of 100-ml ampoules by the manufacturer.

Surgical technique

The surgical procedures were standard as described previously[16–18] and remained unchanged throughout the whole trial. The decision on the extent of dissection was based on the tumour size and the patient's age. Mastectomy was usually carried out in patients with tumours larger than 5 cm in diameter (i.e. T_3 and T_4 carcinoma). In patients fulfilling the criteria for lumpectomy, intraoperative frozen-section analysis of the resection margins was carried out. Axillary node clearance was performed uniformly by a standard method[18]. At least one suction drain was placed in the breast wound and at least one in the axillary fossa. The volume of drainage fluid was measured on a daily basis and drains were not removed unless the amount was less than 50 ml per drain per 24 h. No compression bandages were applied. Mobilization of the affected shoulder was allowed on day 5 after operation. Surgery was carried out by 15 different surgeons, although 95 (59·4 per cent) of the 160 operations were performed by one individual.

Local complications

The occurrence of bruising, haematoma and seroma was recorded prospectively. The final check was performed on day 14 when the skin sutures were removed by the surgeon or general practitioner.

Bruising was defined as skin discoloration surrounding the wound and extending more than 5 cm from the incision site without evidence of an underlying fluctuating collection of blood. A blood collection beneath the skin flaps that was removable by either puncture or revisional surgery was considered to be a haematoma. A seroma was defined as a fluctuating collection of serum or lymph (usually salmon pink-coloured fluid) under one or more skin flaps

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and removable by puncture. The emergence of pus from the incision wound or suction drain with positive bacterial culture defined an infection.

Statistical analysis

It was estimated that 140 patients would be needed to establish statistical significance with an α error of 5 per cent and a β error of 20 per cent if one treatment was twice as effective as the other. The decision was made to perform interim analysis after treating half of the patients. The measurements were analysed using the Z test for independent samples. The frequencies of local complication and adverse reaction in the two treatment groups were compared using a two-tailed χ^2 test. The threshold for significance was taken as $P<0{\cdot}05$. SAS statistical software (SAS Institute, Cary, North Carolina, USA) was used for all data processing and analysis.

Results

Patient age, risk factors, tumour size, type of surgical procedure and length of follow-up were similar in the two treatment groups (*Table 1*).

The patients were randomly allocated to receive either tranexamic acid ($n=79$) or placebo ($n=81$). The mean(s.d.) volume drained after surgery was significantly lower in patients treated with tranexamic acid than in those given placebo (283(187) *versus* 432(315) ml, $P<0{\cdot}001$). The mean(s.d.) duration of drainage was longer for patients receiving placebo (5·2(2·4) days) than for those treated with tranexamic acid (4·1(1·6) days), but this difference was not significant.

Postoperative wound complications are summarized in *Tables 2* and *3*. They occurred at a significantly higher frequency in patients aged 60 years or more (52 per cent of all older patients *versus* 33 per cent of all younger ones, $P=0{\cdot}015$). This difference was especially marked for placebo-treated patients. Tumour size and lymph node metastases were not additional risk factors for local wound complications (*Table 3*).

Tranexamic acid was well tolerated during oral administration, but side-effects were frequently observed after intravenous bolus injection during the first trial period. Severe side-effects led to discontinuation of tranexamic acid treatment in five patients (nausea in three, severe hypotension in one, allergic reaction in one) and one placebo-treated patient suffered side-effects (nausea and vomiting) during the first trial period. The use of diluted tranexamic acid in a short infusion over 20 min in the second study period resulted in no treatment discontinuation in the experimental group but two in the placebo-treated group (because of hypotension in one and 'allergic reaction' with skin rash in the other). The overall frequency of side-effects was significantly higher in tranexamic acid-treated patients (24 *versus* 7 per cent, $P<0{\cdot}004$).

The mean(s.d.) hospital stay was 9·2(2·3) days for tranexamic acid-treated patients and 10·1(2·5) days for those given placebo ($P<0{\cdot}02$).

The cost of treatment was estimated to be 36 SFr (£16) per patient and the average cost for 1 hospital day 399 SFr

Table 1 Patient characteristics and type of surgical intervention

	Tranexamic acid	Placebo
Total no. of patients*	79 (100)	81 (100)
Mean (s.d.) (range) age (years)	58·1 (10·4) (39–83)	59·4 (14·6) (31–87)
Tumour localization*		
Left breast	36 (46)	39 (48)
Right breast	43 (54)	42 (52)
Tumour size*†		
pT_1	26 (33)	30 (37)
pT_2	31 (39)	34 (42)
pT_3	13 (16)	9 (11)
pT_4	4 (5)	5 (6)
Surgery*		
Lumpectomy	40 (51)	33 (41)
Mastectomy	39 (49)	48 (59)
Axillary clearance	76 (96)	78 (96)

*Values in parentheses are percentages. †According to the postoperative tumour node metastasis classification. There were no statistically significant differences between the two groups

Table 2 Local wound complications

	Tranexamic acid ($n=74$)	Placebo ($n=79$)	P*
Bruising	3 (4)	8 (10)	0·15
Haematoma	5 (7)	4 (5)	0·66
Seroma	20 (27)	29 (37)	0·20
Infection	0 (0)	0 (0)	—
Total	28 (38)	41 (52)	0·08

Values in parentheses are percentages. *Two-tailed χ^2 test

Table 3 Influence of age, tumour size and node status on wound complication rate after breast cancer surgery

	Tranexamic acid			Placebo		
	No. of patients	Wound complication rate (%)	P	No. of patients	Wound complication rate (%)	P
Age (years)						
<60	41	29	n.s.	39	36	0·035
⩾60	33	42		40	60	
Tumour size						
T_1	26	39	n.s.	30	47	n.s.
T_2	31	39		34	44	
T_3 or T_4	17	24		14	50	
Lymph node status						
Negative	44	32	n.s.	40	45	n.s.
Positive	30	40		38	53	

All complications were included, i.e. bruising, haematoma and seroma. *Two-tailed χ^2 test; n.s., not significant

Table 4 Surgical complications after modified radical mastectomy

Reference	Year	No. of patients	Rate of seroma formation (%)	Rate of haematoma formation (%)	Rate of infection (%)
Aitken *et al.*[1]	1984	117	4·3	—	1·7
Hayes and Bryan[2]	1984	100	25·0	—	18·0
Tejler and Aspegren[3]	1985	324	36·5	4·3	2·8
Salmon *et al.*[4]	1985	219	33·3	—	—
Tadych and Donegan[5]	1987	49	53·0	—	0
Bryant and Baum[6]	1987	108	30·6	—	—
Watt-Boolsen *et al.*[7]	1988	104	47·1	0·0	1·9
Guenier *et al.*[8]*	1990	100	63·0	—	25·0
Vinton *et al.*[9]	1991	387	28·9	3·9	15·0
Total		1508	33·4	3·6	9·7

*Advanced stage III breast cancer, preoperative radiotherapy

Table 5 Surgical complications after conservative surgery for breast cancer

Reference	Year	No. of patients	Rate of seroma formation (%)	Rate of haematoma formation (%)	Rate of infection (%)
Schwartz *et al.*[10]	1984	154	3·9	—	5·8
Tejler and Aspegren[3]	1985	71	27	4	7
Siegel *et al.*[11]	1990	259	4·2	0·4	0·8
Vinton *et al.*[9]	1991	173	17·0	12·7	8·1
Total		657	10·2	5·2	4·6

(£181). Patients treated with tranexamic acid were discharged 0·9 days earlier than those not receiving this treatment, resulting in savings of 359 SFr (£163) per patient. The final benefit can be calculated from the difference between the saving on the shorter hospital stay and the cost of tranexamic acid medication. This amounts to 323 SFr (£147) per patient resulting in a total of over 25 500 SFr (£11 600) for the 79 patients treated. Additional costs arising from a total of 76 clinic visits for tapping of seroma in the placebo-treated group compared with 42 visits for the tranexamic acid-treated patients were not estimated.

Discussion

Formation of seroma following surgery for breast cancer is common with an average frequency of 33 per cent (*Table 4*). After conservative surgery the occurrence of seroma is lower (*Table 5*). After removal of the drains a seroma is usually harmless and is treated by repeated tapping. It may, however, impair wound healing resulting in skin flap necrosis or infection, and may delay adjuvant treatment such as radiotherapy and chemotherapy[3]. Several risk factors have been recognized as contributing to seroma formation: extent of surgery[19], advanced age[4,9,20], obesity[9], arterial hypertension[4], involved lymph nodes[6] and technical factors[3]. Drains reduce the incidence of seroma[21,22], and in an uncontrolled trial[23] the incidence of seroma was three of 33 when the skin flaps were sutured to the underlying muscle. Aitken *et al.*[1] closed the dead space of the axillary fossa by narrowing and suturing the pectoralis major, serratus anterior and latissimus dorsi muscles and reported rates of 19 and 4 per cent after radical and modified radical mastectomy respectively. Late mobilization of the shoulder may help[24,25] but intraoperative use of fibrin glues provides contradictory evidence[26–28].

In the present study, tranexamic acid had little or no effect on the occurrence of bruising and haematoma, but it reduced the rate of seroma formation from 37 to 27 per cent ($P = 0·2$) and produced a significant ($P < 0·001$) decrease in the overall postoperative drainage volume. The rate of wound complication in the control group in this trial was at the upper limit of that found previously; this may be due to the frequency and rigour of the follow-up checks, as seroma formation often does not occur before discharge from hospital. Tranexamic acid had various side-effects when administered parenterally as a bolus injection, but when diluted in 100 ml normal saline and infused over 20 min (the drug regimen used during the second trial period) there were significantly fewer problems.

The perioperative and postoperative use of tranexamic acid produces a trend towards prevention of local wound complication and results in a significant reduction in the postoperative drainage volume.

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