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Intraoperative Topical Tetracycline Sclerotherapy Following Mastectomy: A Prospective, Randomized Trial

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Background and Objectives: Postoperative wound seromas are a frequent and troublesome occurrence after mastectomy. Recent reports have suggested the efficacy of topical sclerosants at reducing their formation.

Methods: A prospective, randomized, double-blinded trial was performed to examine the effect of intraoperatively administered topical tetracycline on the occurrence of postoperative mastectomy seromas. Thirty-two women were randomized to the control arm (normal saline) and 30 women to the tetracycline arm. In the treatment group, 100 ml (2 g) of tetracycline solution was administered topically to the chest wall and skin flaps prior to skin closure. The control group received an equal volume of normal saline. Patients were monitored for the development of postoperative wound seroma.

Results: There were no significant differences between groups regarding total volume of closed suction drainage, numbers of patients leaving hospital with drains in place, or duration of catheter drainage. Seroma formation 2 weeks postoperatively was greater in the tetracycline group than the control group (53% vs. 22%, $P = 0.01$). There were no differences between groups regarding the degree of postoperative pain, wound infection, or seroma formation 1 month postoperatively.

Conclusions: Topical tetracycline is not effective at preventing postmastectomy wound seromas.

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KEY WORDS: **breast cancer; breast neoplasms; seroma; suction; closed suction drainage; tetracycline; postoperative complications; mastectomy sclerotherapy**

INTRODUCTION

Seromas occur in 4.3% to 63% of patients after modified radical mastectomy [1–5] secondary to the disruption of lymphatic channels. The risk of seroma formation is related to the extent of axillary dissection [6]. Although postoperative seromas generally resolve with repeated aspiration, they are a source of great annoyance and concern to patients. Many techniques have been suggested to reduce seroma development [1,7–9], but no single method has been shown to consistently and reliably reduce their occurrence. Even use of closed-suction drainage is controversial [10].

Two reports have suggested the efficacy of tetracycline (TCN), as a topical sclerosing agent, in the treatment of postoperative wound seromas [11,12]. Based on these reports, a trial was carried out at our institution to examine whether postoperative irrigation of wound drains with TCN would hasten resolution of wound seromas after mastectomy [13]. This trial was stopped be-

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cause of pain experienced by patients receiving TCN. To readdress this concept, the current trial was designed so that TCN would be administered intraoperatively, with the patient under general anesthesia.

MATERIALS AND METHODS

A prospective, randomized, double-blinded, clinical study was designed. Approval was obtained from our Institutional Review Board. Women undergoing modified radical mastectomy were eligible for inclusion. Patients who were pregnant or lactating, had a known sensitivity to TCN, or were to have immediate breast reconstruction were excluded from the study. All patients underwent a standard modified radical mastectomy and received perioperative cefazolin (1 g by i.v. injection preoperatively and 1 g i.v. postoperatively). At the completion of the procedure, a round silastic closed-suction catheter was placed in the axilla and another beneath the skin flaps. Patients were then randomized, by drawing an envelope, to the control or TCN-treated group. In the TCN group, 50 ml of TCN solution (1 g in 50 ml 0.9% NaCl) were applied to the chest wall and undersides of the skin flaps prior to closure of the wound. After skin closure, another 25 ml of TCN solution were instilled through each of the 2 drains, which were then capped. A loose dressing was applied. The control group was treated identically with an equal volume of 0.9% NaCl containing light yellow food coloring so that the solution would be identical in color to the TCN solution. After 30 min, the drains in both groups were placed to low-pressure, continuous wall suction.

Once on the surgical nursing unit, a study nurse coordinator, blinded to the treatment, recorded daily drain output and monitored wounds for seroma formation, infection, necrosis, or other complications. Pain was graded as absent, minimal, mild, moderate, or severe. Infection was considered present when purulent drainage occurred from the wound or when there was clinical evidence of cellulitis. Patients were discharged at the surgeon's discretion, with or without drains in place. Drains were removed once the daily output was $\leq$30 ml for 2 consecutive days. Follow-up was obtained at 2 weeks and 1 month after operation.

Prior to beginning the study, a power calculation showed that 200 patients (100 in the control group and 100 in the TCN group) were required to provide a 90% probability of detecting a 1-day difference in duration of drainage with a P value of 0.05. A planned interim analysis, performed after the first 30 patients had been enrolled in each group, suggested that the trial be stopped after entering 32 patients in the control and 30 in the TCN group.

Continuous variables were compared using the Wilcoxon rank sum test, and categorical variables were compared using the χ^2 or Fisher's exact test, as appropriate.

RESULTS

Patients were similar with respect to age, weight, and height (data not shown). Characteristics of histology and staging are shown in Table I. There were no significant differences regarding tumor histology. Although the primary tumors in the TCN group tended to be slightly larger than in the controls, the difference was not significant nor were there any differences in nodal status or numbers of lymph nodes removed during axillary dissection (median 18 vs. 17.5, $P = 0.71$).

Although the total volume of wound drainage was higher in the TCN group compared to the control group (901 vs. 689 ml), the difference was not statistically significant (Fig. 1). Similarly, neither the number of patients leaving hospital with drains in place (47% vs. 52%) nor the median day the catheters were removed (8 vs. 10.5 days) was statistically significantly different (Table II).

The degree of postoperative wound pain was similar between groups, both in the immediate postoperative period and during follow-up examinations (Table III). Early (2 weeks) wound seromas occurred in 16 of 30 patients (53%) in the TCN group but in only 7 of 32 patients (22%) in the control group ($P = 0.01$). One month postoperatively, no differences in seroma incidence were noted [30% (9/30) vs. 19% (6/32), respectively, $P = 0.199$]. There were no differences between groups in incidence of wound infection or necrosis of skin flaps. Based on the planned interim analysis, which showed the inefficacy of TCN and the greater incidence of wound seromas at 2 weeks postoperatively, the study was terminated.

DISCUSSION

Wound seromas represent a significant cause of morbidity after modified radical mastectomy. Despite numerous trials of new techniques which have attempted to reduce the incidence of seroma formation, no single method appears to be uniformly effective. Topical sclerotherapy with TCN has long been used successfully in the treatment of malignant pleural effusions to cause obliteration of the pleural space [14]. The first report of TCN sclerotherapy for treating seromas after mastectomy was by Sitzmann et al. [11], who instilled 2 g of TCN in 150 ml of 0.9% NaCl following aspiration of seromas in 5 patients. All patients had a marked decrease in the size of seromas within 48 hr. Another anecdotal report, by Nichter et al. [12], demonstrated efficacy of TCN in 4 patients with persistent postoperative seromas. Based on these reports, a prospective trial was initiated at Mayo Medical Center to examine the utility of TCN instillation in patients with persistent postmastectomy seromas [13]. This study was terminated prematurely because instillation of TCN caused severe pain.

The current study evaluated intraoperative topical ad-

TABLE I. Breast Cancer Histopathology and Staging for Study Patients

Variable	Control (%) (n = 32)	TCN (%) (n = 30)	*P* value
Histology			
Invasive ductal	25 (78)	24 (79)	0.385
Intraductal	5 (16)	2 (7)	
Other	2 (6)	4 (14)	
Staging			
T			
is[a]	5 (16)	2 (7)	0.062[b]
1	19 (59)	14 (46)	
2	7 (22)	12 (40)	
3	0	2 (7)	
4	1 (3)	0	
N			
0	24 (75)	21 (70)	0.659
1	8 (25)	9 (30)	
M			
0	32 (100)	29 (97)	0.298
1	0	1 (3)	

[a]is = in situ.
[b]Rank sum test (others are χ^2 test).

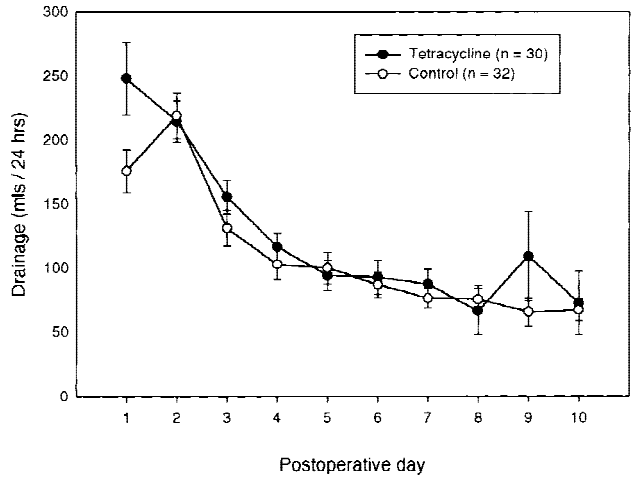

Fig. 1. Postoperative wound drainage expressed as mean ± standard error of mean, $P = 0.199$.

TABLE II. Postoperative Wound Drainage Volumes and Duration of Wound Drainage by Study Group

Variable	Control (%) (n = 32)	TCN (%) (n = 30)	*P* value
	Median (interquartile range)		
Total drainge in hospital (ml)	689 (437–1,026)	901 (553–1,208)	0.199
Drains in place at hospital dismissal	16 (50)	14 (47)	0.699
Post-op day drains removed	10.5 (6–14.75)	8 (6.5–11)	0.509

TABLE III. Postoperative Wound Complications by Study Group

Complication	Control (%) (n = 32)	TCN (%) (n = 30)	*P* value
Postop pain			
None	2 (6)	1 (3)	0.453[a]
Minimal	15 (47)	12 (40)	
Mild	12 (38)	15 (50)	
Moderate	3 (9)	2 (7)	
Seroma at 2 weeks	7 (22)	16 (53)	0.010
Seroma at 1 month	6 (20)	9 (30)	0.371
Infection	2 (6)	1 (3)	0.593
Necrosis of skin flap	2 (6)	1 (3)	0.593

[a]Indicates rank sum test (others are χ^2 test).

ministration of TCN. No differences were noted in immediate postoperative pain between control and TCN groups. Unfortunately, there was also no evidence to suggest that TCN reduced seroma formation; indeed, there were significantly more seromas in the TCN group 2 weeks postoperatively compared to the control group.

Numerous reports describe the use of TCN sclerotherapy in a diverse range of conditions. While TCN is used most commonly for the treatment of malignant pleural effusions [14], hydroceles of the testes [15], endometrial cysts [16], hepatic cysts [17], pericardial effusions [18], and even the gallbladder lumen [19] have been successfully obliterated using topical TCN. There is less evidence to support the efficacy of TCN in the management of postoperative wounds where a greater disruption of lymphatic channels occurs, as with a lymphadenectomy. Although Sitzmann et al. [11] reported good results of sclerotherapy after mastectomy, their study was retrospective and anecdotal in only 5 patients. In the experience of Nichter et al. [12], there were postmastectomy seromas; 3 patients developed lymphoceles associated with a myocutaneous flap and 1 had a persistent adventitial bursa of the gluteal region. Furthermore, none of these patients had a regional lymph node dissection. It appears that the combination of the rich lymphatic supply to the chest wall and axilla, the excision of lymphoid tissue, and the extensive subcutaneous dissection required in a modified radical mastectomy enhances seroma formation and minimizes the effectiveness of TCN sclerotherapy.

Alternatives to TCN for tissue adhesion exist. Sclerosis of malignant pleural effusions may be performed very effectively using either talc or bleomycin [20]; however, neither appear appropriate for treating postmastectomy seromas. Talc carries with it the risk of wound infection because of the presence of foreign material, while bleomycin, which is prohibitively expensive [21], may interfere with wound healing. Fibrin glue has shown promise in rat studies [9,22]. Unfortunately, 2 recent clinical trials have failed to show efficacy at preventing postmastectomy seromas in humans [23,24].

What, therefore, can be done to limit the frequent incidence of postmastectomy seromas? Retrospective evidence supports the use of closed-suction drains, which should be left in place until their output is <30 to 50 ml for 2 consecutive days [3], although Liu and McFadden [10] suggest that they may be successfully removed after only 24 hr. Suturing of skin flaps to the underlying musculature has been advocated to reduce "dead space," and a recent prospective, randomized trial, albeit with small numbers of patients, suggests that this technique may reduce the incidence of seromas [7]. These 2 methods, in conjunction with meticulous ligation of axillary lymphatics, are probably the most important factors in preventing postmastectomy seromas. Use of TCN as a topical sclerosant cannot be advocated in this situation based on our findings.

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