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Effects of Wound Irrigation with Topical Phenytoin Solution During Modified Radical Mastectomy on Postoperative Seroma Formation

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ABSTRACT

Background: Modified radical mastectomy (MRM), as a surgical treatment in breast cancer patients, may lead to important complications with significant morbidities including seroma formation. In this study, we used topical phenytoin to evaluate its impact on breast and axillary wound drainage and seroma formation after MRM.

Methods: In a double-blinded randomized clinical trial, patients with breast cancer who were candidates for modified radical mastectomy (MRM) were enrolled. The patients were randomly assigned to two groups using a simple randomization method. Group A received topical phenytoin 1% solution for the irrigation of the mastectomy wound during the MRM procedure while group B (control group) underwent wound irrigation with normal saline solution. In addition to demographic data, postoperative variables including daily drainage of breast and axillary drains, drain removal days, and possible complications including seroma formation and their management were recorded.

Results: Except for daily drainage recorded on the fifth postoperative day, the drainage of both axillary and breast drains were significantly different between group A and B in the following days. Compared to group B, axillary drains could be removed significantly earlier in group A. In regard to the breast drains, they were removed earlier in group A with no statistically difference compared to group B, the difference was not statistically significant. Seroma was detected in 7(8.3%) patients, 3 patients in group A and 4 patients in group B, with no significant differences between the two groups. All the patients underwent repeated aspirations.

Conclusions: Our findings showed that topical irrigation of the surgery site with phenytoin was effective in reducing axillary surgical wound drainage.

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Introduction

Modified radical mastectomy (MRM) is defined as complete removal of the breast and the underlying fascia along with the removal of level I and II axillary lymph nodes. Although this procedure has been replaced by conservative breast surgery in most patients with early stage breast cancer, it is still the

treatment of choice in patients diagnosed with more advanced disease. In contrast to its therapeutic benefits, MRM may lead to important complications with significant morbidities. Lymphedema and compromised range of motion of the shoulder are known complications that can be quite troublesome. Seroma formation is a relatively common complication in MRM which may occur on early post-operation days.[1,2] It is probably secondary to the disruption of lymphatic vessels during surgery that leads to the accumulation of lymphatic fluid beneath the skin.[3,4] It may cause patient discomfort, requires repeated aspirations, and is a potential source of wound infection, as well.[5]

The incidence of seroma has been reported to vary from 15 to 55 percent in different studies.[6,7] Adopting measures to prevent seroma formation helps to reduce morbidity and improve postoperative well-being of the patients. Placing drains in the axilla is widely used and has been shown to have considerable effects on reducing seroma formation.[8-10] Other methods like using fibrin glue, topical phenytoin, and quilting sutures have been applied to reduce seroma formation, as well.[11,12] The efficacy of these methods is controversial and yet must be determined.

The effect of phenytoin on wound healing has been investigated in several studies and evidence suggests that phenytoin can accelerate the healing process.[13,14] To the best of our knowledge, no previous study has evaluated the effect of topical phenytoin in women undergoing MRM. In this study, we used topical phenytoin during the MRM procedure to evaluate its impact on breast and axillary wound drainage and seroma formation.

Methods

Study design and participants

This double-blinded randomized clinical trial was conducted in a referral hospital affiliated with Tehran University of Medical Sciences between 2013 and 2014. The study protocol was reviewed and approved by the local ethics committee. The patients were informed of the study protocol and procedures and written informed consent were taken from each patient prior to enrollment. The patients with pathologically confirmed breast cancer were enrolled in the study. The patients were candidates for MRM based on the disease stage. The patients with a previous diagnosis of epilepsy, history of convulsive attacks, history of head trauma and cardiac arrhythmia were not eligible for enrollment.

Study Intervention

The patients were randomly assigned to two groups using a simple randomization method. Group A received topical phenytoin 1% solution (at a dose of 4 mg/kg for each patient) for irrigation of the wound at the end of the MRM procedure while group B (control group) underwent irrigation of the wound with the normal saline solution. For selecting an appropriate dosage form, pH values of available phenytoin sodium dosage forms were determined. Several solutions (Table 1) were prepared and the pH values were determined using a 691 pH meter (Metrohm, Swiss). PH values of the phenytoin solutions prepared from injectable dosage form did not change significantly following serial dilution. This phenomenon may be related to the buffering agent (sodium hydroxide) in this dosage from. In order to prepare phenytoin 1% solution, 1g phenytoin was dissolved in 1000cc normal saline solution (with pH of 6.5). Two groups of solutions containing phenytoin 1% solution (for group A) and normal saline (for group B) were prepared and coded. Both the patients and surgeons were blinded to the study and only the moderator of the project was aware of the coded solutions.

During the MRM procedure, the skin flaps were fully developed, the fascia of the pectoralis major muscle and the overlying breast tissue were elevated off the underlying musculature, and the breast tissue was completely removed. An axillary lymph node dissection was also performed which included levels I and II lymph nodes. At the end of the procedure, the surgeon used the prepared solutions to irrigate the surgical wound. Two closed suction drains were also inserted for each patient, one in the axillary area and one under the skin flaps. The suction drains were closed for four hours after the end of the procedure to provide adequate time for phenytoin absorption through the tissues. Drainage of suction drains was recorded on a daily basis and they were removed

Table 1. Pheytoin solutions and corresponding pH values

Characteristics of solutions prepared from phenytoin AMP*:				
Concentration(mg/ml normal saline)	250mg/20ml	250mg/50ml	250mg/100ml	250mg/200ml
pH	11.8	11.1	10.2	10.00
Characteristics of solutions prepared from phenytoin Cap**:				
Concentration(mg/ml normal saline)	100mg/10ml	100mg/20ml	100mg/50ml	100mg/100ml***
pH	9.7	8.9	7.6	6.5

** AMP 250mg/5ml (Caspian Tamin Pharmaceutical Company, Rasht, IRAN), ** Cap 100mg (Loghman Pharmaceutical Company, Tehran, IRAN), *** The selected concentration for irregation of surgery site in group A*

when the daily drainage of the drain was less than 30 cc. Patients were also evaluated for any possible complication. In case of seroma formation, aspiration of the seroma fluid was performed as necessary and data were also recorded.

Outcome measurement

All pre- and postoperative data were collected using a form prepared by the researchers. Preoperative data including age, body mass index (BMI), histologic type of the breast cancer, history of previous breast and/or axillary surgery, and history of neoadjuvant therapy (and number of neoadjuvant sessions) were all recorded. Postoperative variables included daily drainage of the breast and axillary drains, drain removal days, and complications including seroma and their management.

Statistical analysis

Data were analyzed using SPSS version 20. Qualitative data are presented as mean ± standard deviation. Study variables were compared between two groups using Chi-square, Fisher, and t-test as applicable. P value less than 0.05 were considered statistically significant.

Results

In this clinical trial, a total of 84 patients with breast cancer were randomized to two equal groups of 42 patients. The mean age of the patients in group A (phenytoin) and B (control) were 53.40±11.07 and 53.19±11.53 years, resepctively.

Comparison of the demographic and pre-operative variables between two groups showed that the only variable with a significnat difference was the history of neoadjuvant chemotherapy. A total of 18 (21.4%) patients received neoadjuvant chemotherapy, including 13 (31%) patients in group A and 5 (11.9%) in group B (P = 0.033) (Table 2).

Postoperative drainage of both axillary and breast drains were recorded regularly after the fifth postoperative day. Except for the daily drainage

Table 2. Demographic and preoperative characteristics of study population

	Total	Group A (Phenytoin)	Group B (Control)	P-value
Age	53.30±11.24	53.40±11.074	53.19±11.538	0.931
Body Mass Index (BMI)	26.52±4.87	27.43±5.785	25.62±3.595	0.090
Side of breast cancer				0.826
Right	47 (56%)	23 (54.8%)	24 (57.1%)	
Left	37 (44%)	19 (45.2%)	18 (42.9%)	
History of Neoadjuvant Therapy				0.033
Yes	18 (21.4%)	13 (31%)	5 (11.9%)	
No	66 (78.6%)	29 (69%)	37 (88.1%)	
History of recent axillary surgery				0.645
Yes	5 (6%)	2 (4.8%)	3 (7.1%)	
No	79 (94%)	40 (95.2%)	39 (92.9%)	
History of recent breast surgery				0.242
Yes	14 (16.7%)	9 (21.4%)	5 (11.9%)	
No	70 (83.3%)	33 (78.6%)	37 (88.1%)	
Pathology of the breast cancer				0.191
Invasive Ductal Carcinoma (IDC)	70 (83.3%)	32 (76.2%)	38 (90.5%)	
Invasive Lobular Carcinoma (ILC)	9 (10.7%)	6 (14.3%)	3 (7.1%)	
Other pathologies	5 (6%)	4 (9.5%)	1 (2.4%)	

Table 3. Average daily drainage (in mililiters) of drains according to their location and day of evaluation

Day of Evaluation	Group A (Phenytoin)	Group B (Control)	P-value
Axillary Drain			
5	60.93±30.57	67.57±18.75	0.234
7	44.24±33.29	75.83±27.80	< 0.001
8-10	30.00±13.76	62.76±39.07	< 0.001
11-13	22.67±6.86	45.00±29.22	< 0.001
14-16	-	27.73±13.48	N/A
Breast Drain			
5	24.62±32.79	35.88±12.93	0.042
7	28.89±18.33	28.18±12.68	0.903
8-10	32.00±10.95	21.43±11.07	0.133
11-13	15.00±7.07	50.00*	0.154
14-16	-	20.00*	N/A

** only one patient in control group had breast drain after 11th postoperative day*

Table 4. Postoperative seroma formation

	Total	Group A (Phenytoin)	Group B (Control)	P-value
Seroma formation				0.693
Yes	7 (8.3%)	3 (7.1%)	4 (9.5%)	
No	77 (91.7%)	39 (92.9%)	38 (90.5%)	
Nubmer of seroma aspirations				
0	77 (91.7%)	39 (92.9%)	38 (90.5%)	0.226
1	2 (2.4%)	2 (4.8%)	0	
2	3 (3.6%)	1 (2.4%)	2 (4.8%)	
3	2 (2.4%)	0	2 (4.8%)	

recorded on the fifth postoperative day, the drainage of both axillary and breast drains were significantly lower in group A compared with group B in the next following days (Table 3). The mean day of axillary drain removal was 8.83±1.92 days in the phenytoin group and 12.17±3.91 days in the control group ($P < 0.001$). Although the breast drains were removed earlier in the phenytoin group (5.79±1.70) compared to controls (6.57±2.03), the difference failed to reach statisticall significane ($P = 0.059$).

Seroma was detected in 3 (7.1%) patients in group A and 4 (9.5%) patients in group B without any significant differences between the groups ($P = 1.000$). The mean number of aspirations in group A and B was 0.10±0.370 and 0.24±0.759 times, respectively ($P=0.226$). Detailed information regarding the number of aspirations are shown in Table 4.

Discussion

The effect of phenytoin on wound healing has been investigated and the available evidence suggests that phenytoin can accelerate the healing process.[15] This effect was first shown in oral and gingival wounds.[16,17] Subsequent studies reported the beneficial effect of phenytoin in skin ulcers.

It has been reported that topical phenytoin increases granulation tissue formation and decreases wound discharge in trophic leprosy ulcers and improves the healing of decubitus ulcers.[18,19] El-Nahas *et al.* reported the positive impact of phenytoin in treating neuropathic diabetic ulcers.[20] Shaw *et al.* published a systematic review that summarized fourteen studies on the effect of phenytoin in healing of diabetic and chronic wounds. They suggested that phenytoin might have a positive effect on wound healing.[21]

In our study, the administration of topical phenytoin was not associated with a significant reduction in the frequency of seroma formation in the breast or axilla but significantly declined wound drainage and was associated with earlier drain removal. Some researchers have found that phenytoin is associated with augmented fibroblastic proliferation, granulation tissue formation, neo-vascularization, and collagenization.[22] Such characteristics may explain how phenytoin can accelerate the healing process and prevent seroma formation.

Although topical phenytoin and methods like sclerosing agents, glues, and closure of the dead space have been employed for reducing seroma formation, they have not gained widespread adoption due to the lack of hard evidence and some concerns regarding their morbidity and complications.[23]

Studies evaluating the effect of topical phenytoin on the reduction of seroma formation after mastectomy or axillary dissection are scarce in the literature. Eser *et al.* evaluated the effect of topical phenytoin on seroma formation after mastectomy and axillary dissection in mice. They found that topical phenytoin reduced the seroma volume after surgery.[24] They also reported that fibrosis was significantly increased and angiogenesis was reduced following topical phenytoin application.

It is expected that reducing wound drainage will result in a lower rate of seroma formation but it did not occur in our study. The evidence of association between drainage volume and seroma formation is not consistent. Although it has been reported that the drainage flow rate greater than 50 mL/day after 48th hours is a predicting factor for seroma formation in breast cancer patients, such association was not found between the first 48-hour wound drainage and seroma formation in another study.[4,25]

As a limitation of our study, we did not measure wound drainage during the first four days after the operation. Some studies have reported that a higher total drainage volume is associated with an increased risk of seroma formation.[26,27] A meta-analysis of 65 studies regarding the risk factors of seroma formation concluded that there was moderate evidence supporting the association between greater wound drainage in the first three postoperative days and seroma formation.[6]

Our study was primarily intended to evaluate the effect of topical phenytoin on seroma formation; but, the reduction of wound drainage and the resulting earlier drain removal itself is associated with lower postoperative morbidity and more patient convenience.

There are still concerns regarding the possible complication of applying topical phenytoin in wounds, especially considering the potential sclerosing and fibrosis-enhancing effects of phenytoin. In our study, we did not notice any wound

complications within our follow-up period. Evaluation of the longterm results of topical phenytoin administration and its effect on the range of motion, pain, and lymphedema is recommended for future studies.

In conclusion, our study showed that irrigation of the modified radical mastectomy wound with topical phenytoin was effective in reducing axillary surgical wound drainage after the MRM procedure.

Further studies are required to confirm the benefits and possible complications of applying topical phenytoin in breast and axillary surgical wounds.

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