Effect of Intraoperative Wound Irrigation with Topical Phenytoin on Postoperative Seroma Formation Post Modified Radical Mastectomy

Salah Mansour Abdel-Aal 1, Mohamed Ibrahim Abdelhamid Elsayed 1, Mohamed Mohamed Abdelsalam 1 and Loay Mohamed Elhady Gertallah 1

(1) Department of General Surgery, Zagazig University Hospitals, Zagazig, Egypt.

Correspondence to: Mohamed Mohamed Abdelsalam
E-mail: Docmohammed19921992@gmail.com

Tel: 01000682578

Abstract:
Background: Modified radical mastectomy (MRM), as a surgical treatment in MRM breast cancer patients, may lead to important complications with significant morbidities including seroma formation. In this study aimed to evaluate the effect of wound irrigation with topical phenytoin on breast and axillary wound drainage and seroma formation after Modified radical mastectomy (MRM). Patients and methods: This is a double-blinded randomized clinical trial carried out at the General Surgery outpatient clinic of Zagazig University Hospital during the period 6 months. The patients were randomly assigned to two groups. Group A: (30 cases) 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 procedure while MRM. Group B: (30 cases) (control group) underwent irrigation of the wound with the 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: Average daily Axillary drainage (in milliliters) of drains according to their location and day of evaluation. According to Days of Evaluation in Axillary Drain in Group A (Phenytoin) day 5 group drained a mean of 60.93 with SD of 30.57 in day 7 Mean of drainage was 44.24 and SD was 33.29 in days 8 to 10 Mean of drainage was 30 and SD was 13.76 in days 11 to 13 Mean of drainage was 22.67 and SD was 6.86. Group B (Control) day 5 group drained a mean of 75.83 and SD was 27.80 in days 8 to 10 Mean of drainage was 62.76 and SD was 39.07 in days 11 to 13 Mean of drainage was 45 and SD was 29.22 and in days 14 to 16 Mean of drainage was 27.73 and SD was 13.48. Conclusion: Topical irrigation of the surgery site with phenytoin was effective in reducing axillary surgical wound drainage.

Keywords: Modified radical mastectomy, Seroma, breast surgery
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\(^1\).

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\(^2\).

It is probably secondary to the disruption of lymphatic vessels during surgery that leads to the accumulation of lymphatic fluid beneath the skin. It may cause patient discomfort, requires repeated aspirations, and is a potential source of wound infection, as well. The incidence of seroma has been reported to vary from 15 to 55 percent in different studies\(^3\).

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\(^4\).

Other methods like using fibrin glue, topical phenytoin, and quilting sutures have been applied to reduce seroma formation, as well. The efficacy of these methods is controversial and yet must be determined\(^5\).

The effect of phenytoin on wound healing has been investigated in several studies and evidence suggests that phenytoin can accelerate the healing process. To the best of our knowledge, no previous study has evaluated the effect of topical phenytoin in women undergoing MRM\(^6\). The aim of this study is to determine the effect of wound irrigation with topical phenytoin on postoperative seroma formation after modified radical mastectomy.

Patients and Methods:

This study is a double-blinded randomized clinical trial carried out at the General Surgery outpatient clinic of Zagazig University Hospital during the period 6 months. Included 60 patients from 50-78 years with a mean value of 53.30±11.5 years. BMI mean was 26.52 and SD was 4.87 who were candidates for modified radical mastectomy (MRM). 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 were randomly assigned to two groups:
Group A: (30 cases) 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 procedure while MRM while Group B: (30 cases) (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 were prepared and the pH values were determined using a 691 pH meter (Metrohm, Swiss). Values of the phenytoin PH 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 form. 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.

Statistical analysis

Obtained data were presented as mean ± SD, ranges, numbers and percentages as appropriate. Nominal variables were analyzed using Chi-squared (χ2) test. Continuous variables were analyzed using unpaired Student’s t-test or Univariate two-group repeated measures “mixed-design” analysis of variance (ANOVA) with post hoc Dunnett’s test as appropriate. Nominal and non-normally distributed variables were analyzed using Mann-Whitney U test. Statistical calculations were performed using Microsoft® Office Excel 2020 and SPSS (Version 28, 2021). P value < 0.05 was considered statistically significant.

Results:

According to Days of Evaluation in Axillary Drain in Group A (Phenytoin) day 5 group drained a mean of 65.92 with SD of 35.57 in day 7 Mean of drainage was 43.24 and SD was 30.28 in days 8 to 10 Mean of drainage was 33 and SD was 15.76 in days 11 to 13 Mean of drainage was 21.67 and SD was 6.26. in Group B (Control) day 5 group drained a mean of 64.57 with SD of 19.75 in day 7 Mean of drainage was 73.93 and SD was 25.80 in days 8 to 10 Mean of drainage was 42 and SD was 23.22 and in days 14 to 16 Mean of drainage was 29.73 and SD was 13. Austrian population.
Figure (1): Shows Means of daily Axillary drainage (in mililiters) of drains according to their location and day of evaluation.

Group A (Phenytoin) day 5 group drained a mean of 23.23 with SD of 33.81 in day 7 Mean of drainage was 27.89 and SD was 13.34 in days 8 to 10 Mean of drainage was 31.4 and SD was 11.95 in days 11 to 13 Mean of drainage was 15.55 and SD was 6.87. Group B (Control) day 5 group drained a mean of 39.03 with SD of 13.03 in day 7 Mean of drainage was 29.1 and SD was 13.01 in days 8 to 10 Mean of drainage was 22.03 and SD was 12.01 in days 11 to 13 only one patient in control group had breast drain after 11th postoperative day drainage was 45.62 and in days 14 to 16 drainage was 23 Figure (2).
Figure (2): Shows Means of daily Axillary drainage (in mililiters) of drains according to their location and day of evaluation.

In Group A (Phenytoin) Edema was detected in 3 (10%) cases & congestion in 4 (13.33%) cases. In Group B (Control) Edema was detected in 10 (33.33%) cases & congestion in 13 (43.33%) cases Figure(3).

Figure(3): Shows detected edema and congestion.
Group A (Phenytoin) seroma was detected in 3 (10%) and in Group B (Control) seroma was detected in 5 (16.67%) Figure (4).

![Figure (4): Shows Detected cases of seroma formation.](image)

**Discussion:**

In this study Average daily Axillary drainage (in mililiters) of drains according to their location and day of evaluation. According to Days of Evaluation in Axillary Drain in Group A (Phenytoin) day 5 group drained a mean of 65.92 with SD of 35.57 in day 7 Mean of drainage was 43.24 and SD was 30.28 in days 8 to 10 Mean of drainage was 33 and SD was 15.76 in days 11 to 13 Mean of drainage was 21.67 and SD was 6.26. Group B (Control) day 5 group drained a mean of 64.57 with SD of 19.75 in day 7 Mean of drainage was 73.93 and SD was 25.80 in days 8 to 10 Mean of drainage was 65.76 and SD was 41.07 in days 11 to 13 Mean of drainage was 42 and SD was 23.22 and in days 14 to 16 Mean of drainage was 29.73 and SD was 13.

In Elyasinia et al. (3) According to Average daily Axillary drainage (in mililiters) of drains according to their location and day of evaluation. According to Days of Evaluation in Axillary Drain in Group A (Phenytoin) day 5 group drained a mean of 60.93 with SD of 30.57 in day 7 Mean of drainage was 44.24 and SD was 33.29 in days 8 to 10 Mean of drainage was 30 and SD was 13.76 in days 11 to 13 Mean of drainage was 22.67 and SD was 6.86. Group B (Control) day 5 group drained a mean of 67.57 with SD of 18.75 in day 7 Mean of drainage was 75.83 and SD was 42.76 in days 8 to 10 Mean of drainage was 62.76 and SD was 39.07 in days.
11 to 13 Mean of drainage was 45 and SD was 29.22 and in days 14 to 16 Mean of drainage was 27.73 and SD was 13.48.

In an old study Parikh et al.\(^{(7)}\) early drain removal following modified radical mastectomy was at mean of total 340.92 ml after 3 days and total of 589.49ml after 6 days.

In Kabbash et al.\(^{(8)}\) Early drain removal in ml was at mean of 6.56 with SD of 2.4, in last 3 days was 155.67 with SD of 90.8 and drained fluid last day was 35.22 with SD of 10.5.

Average daily Breast drainage (in mililiters) of drains according to their location and day of evaluation. Group A (Phenytoin) day 5 group drained a mean of 23.23 with SD of 33.81 in day 7 Mean of drainage was 27.89 and SD was 13.34 in days 8 to 10 Mean of drainage was 31.4 and SD was 11.95 in days 11 to 13 Mean of drainage was 15.55 and SD was 6.87. Group B (Control) day 5 group drained a mean of 39.03 with SD of 13.03 in day 7 Mean of drainage was 29.1 and SD was 13.01 in days 8 to 10 Mean of drainage was 22.03 and SD was 12.01 in days 11 to 13 only one patient in control group had breast drain after 11th postoperative day drainage was 45.62 and in days 14 to 16 drainage was 23.

In Elyasinia et al.\(^{(3)}\) Average daily Breast drainage (in mililiters) of drains according to their location and day of evaluation. Group A (Phenytoin) day 5 group drained a mean of 24.62 with SD of 32.79 in day 7 Mean of drainage was 28.89 and SD was 18.33 in days 8 to 10 Mean of drainage was 32 and SD was 10.95 in days 11 to 13 Mean of drainage was 15 and SD was 7.07. Group B (Control) day 5 group drained a mean of 35.88 with SD of 12.93 in day 7 Mean of drainage was 28.18 and SD was 12.68 in days 8 to 10 Mean of drainage was 21.43 and SD was 11.07 in days 11 to 13 only one patient in control group had breast drain after 11th postoperative day drainage was 50 and in days 14 to 16 drainage was 20.

According to edema and congestion. In Group A (Phenytoin) Edema was detected in 3 (10%) cases & congestion in 4 (13.33%) cases. In Group B (Control) Edema was detected in 10 (33.33%) cases & congestion in 13 (43.33%) cases. Postoperative seroma formation. Group A (Phenytoin) seroma was detected in 3 (10%) and in Group B (Control) seroma was detected in 5 (16.67%).

In Elyasinia et al.\(^{(3)}\) Seroma formation Group A (Phenytoin) seroma was detected in 7.1% and in Group B (Control) seroma was detected in 9.5%.

Rhodes et al.\(^{(9)}\) has reported that topical phenytoin increases granulation tissue formation and decreases wound discharge in trophic leprosy ulcers and improves the healing of decubitus ulcers.

El-Nahas et al.\(^{(10)}\) reported the positive impact of phenytoin in treating neuropathic diabetic ulcers. Shaw et al.\(^{(11)}\) 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.
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. (12) 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. They also reported that fibrosis was significantly increased and angiogenesis was reduced following topical phenytoin application.

**Conclusion:**
Topical irrigation of the surgery site with phenytoin was effective in reducing axillary surgical wound drainage

**References:**
