Original Article

Eur J Breast Health 2023; 19(2): 134-139
DOI: 10.4274/ejbh.galenos.2023.2022-11-1

Evaluation of Topical Sclerosant Agents for Minimization of Postmastectomy Seroma: A Placebo-Controlled, Double-Blind, Randomized Trial

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ABSTRACT

Objective: Seroma after mastectomy is a bothersome problem. Topical sclerosants are one method used to reduce seroma. The aim of this study was to evaluate if spraying flaps before closure with doxycycline or bleomycin after total mastectomy can prevent seroma.

Materials and Methods: After institutional review board approval, using a computer-based randomization program, a prospective, double-blind, placebo-controlled randomized, superiority study was conducted during the period from the first of August 2017 to the first of August 2018. IRB proposal code was MS/17.08.66 and the trial was approved at 15/8/2017. The trial is available publicly at http://www.eulc.edu.eg/eulc_v5/Libraries/Thesis/BrowseThesisPages.aspx?fn=PublicDrawThesis&BibID=12553049. The primary outcome of the study was to assess the incidence of seroma following total mastectomy after intervention comprising spraying of skin flaps with doxycycline or bleomycin versus placebo. Patients who were candidates for total mastectomy were randomized into control, doxycycline, and bleomycin groups. The postoperative data included length of the hospital stay, pain score among the three groups, post-operative drained fluid volume, post-operative day of drain removal, complication rates including infection, flap necrosis and hematoma, the incidence of seroma and aspirated seroma volume, and total number of postoperative visits.

Results: Of 125 patients, 90 were candidates for total mastectomy. Analysis of these 90 showed that the incidence of seroma was similar; 43.4%, 40% and 40% in the control, doxycycline, and bleomycin groups, respectively (p = 0.99). Furthermore, wound complication rates were similar among all groups.

Conclusion: Despite improved recognition and management of risk factors, seromas remain a common clinical concern in the postoperative setting of total mastectomy. These results suggest that sclerosant agents, specifically bleomycin and doxycycline, have no utility for prevention of post mastectomy seroma.

Keywords: Mastectomy, seroma, sclerosant

Cite this article as: Khater A, Hassan A, Farouk O, Sinbel A, Saleh S, Abdelaziz M, Eldamshety O. Evaluation of Topical Sclerosant Agents for Minimization of Postmastectomy Seroma: A Placebo-Controlled, Double-Blind, Randomized Trial. Eur J Breast Health 2023; 19(2): 134-139

Key Points

- Mastectomy.
- Seroma.
- Sclerosant.

Introduction

Since mastectomy was first described by Halsted in 1894, surgeons have faced several problems, such as necrosis of the skin flaps, breakdown of the wound, hematoma, seroma, and infection (1). Seromas can disrupt the healing process, lengthen the convalescence, be upsetting for the patient, and delay adjuvant therapy (2). The incidence of post-mastectomy seroma has been reported to vary widely from 15% to 81% (1). Various methods have been tried aiming to decrease the occurrence of seroma, with limited success. These include insertion of suction drains, obliteration of mastectomy or the axillary space by sutures, topical application of sclerotherapy with tetracycline, application of fibrin glue, and external application of compressive dressings. Spraying of mastectomy flaps with doxycyclines and bleomycin were previously reported as having a positive effect in seroma prevention (3). The aim of this study was to evaluate if seroma can be prevented after total mastectomy by the spraying of flaps before closure with doxycycline or bleomycin. The primary outcome was to assess the incidence of seroma after total mastectomy when flaps were sprayed with doxycycline or bleomycin versus placebo. The secondary endpoints were the operative outcomes and complication rates, including hematoma, flap necrosis and wound infection.

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Received: 01.11.2022
Accepted: 09.02.2023
Available Online Date: 01.04.2023

Materials and Methods

After Institutional Review Board approval, a prospective, double-blind, placebo-controlled randomized, superiority study was conducted during the period from the first of August 2017 to the first of August 2018. After obtaining informed consent, ninety female patients, aged between 25 and 75 years old who were candidates for elective total mastectomy were enrolled. Patients were included if they had operable breast cancer with no distant metastases and consented to participate. Those with incapacitating cardiac disease, uncontrolled diabetes, advanced liver disease, coagulopathy, or collagen vascular disease were excluded. Exclusion criteria also included patients aged less than 25 years, patients using steroids or anticoagulants, patients with ongoing systemic infection at the time of surgery, those with history of chest irradiation or prior axillary surgery, patients with planned immediate breast reconstruction, pregnant and lactating patients, those who were unfit for general anesthesia, patients with locally advanced cancer with no neoadjuvant chemotherapy, patients with metastatic cancer and those unwilling to participate in the trial. After using a computer-based randomization program, patients were assigned to groups by a closed envelope method (Figure 1). Patients were divided into three groups: Doxycycline, bleomycin, and placebo control. Participants in the doxycycline group were sprayed with 500 mg doxycycline [5x100 mg tablets of Doxymycin (EL-NILE CO) diluted in 100 mL saline] onto the undersurface of the skin flaps after the mastectomy and after achieving hemostasis. Patients in the bleomycin group were sprayed with 60 units of bleomycin (2 ampules of Bleomycin 30 IU; Salius Pharma), also diluted in 100 mL saline. Patients in the control group were sprayed with 100 mL of saline. Surgeons were blinded to the three preparations, which were prepared by a third party. Skin was closed routinely in all patients after placing two Nelaton catheters 18French drains, one in the axilla and the second underneath the mastectomy flaps. Drains were clamped for three hours postoperatively to keep solutions in contact with the skin flaps. In all patients, a dry light dressing was placed. Arm exercise was allowed from the first postoperative day but lifting more than 5 kg or lifting the arm above the shoulder was prohibited until two weeks after surgery. All participants were followed up by routine postoperative visits for 1-2 months. Drains were removed when daily output was less than 50 mL in any 24-hour period.

Ultrasonographic evaluation was the main tool for diagnosis of seroma formation. Grading was performed as described by Kuroi et al. (4) in 2005. This grading system was: G1, asymptomatic seroma; G2, symptomatic seroma that resolves with aspiration; and G3, symptomatic seroma that resolves with surgical or radiologic intervention.

The preoperative data included patient age, body mass index (BMI) in kg/m^2, is the patient is premenopausal or postmenopausal, medical comorbidities (diabetes, chronic liver disease, hypertension, and heart disease), receipt of neoadjuvant therapy, the affected breast side, size and the tumor size. The operative data included the duration of the procedure, estimated blood loss, the number of retrieved axillary nodes, the number of positive axillary nodes, the final pathologic diagnosis including cancer stage, specimen weight and the removed skin surface area. Postoperative data included length of hospital stay, post-operative drained fluid volume, the day of drain removal, the mean pain score of the groups, reported by visual analogue scale (VAS) measured after 4 and 8 hours after surgery and then every 12 hours until discharge. Rate of complications including infection, flap necrosis and hematoma, the incidence of seroma, aspirated seroma volume, and the total number of postoperative visits were also recorded.

Statistical Analysis

Analysis of the qualitative and quantitative data was performed using chi-square analysis and analysis of variance, respectively. Analyses of quantitative variables were evaluated by Bartlett's test for equal variances. If this test identified heterogeneity of variance, the data was subjected to log transformation or the Box-Cox transformation procedure and reanalyzed after heterogeneity of variance had been corrected. If transformation procedures were unsuccessful in correcting heterogeneity of variance, treatment differences were compared using the Wilcoxon rank-sum test. A value of $p<0.05$ was considered statistically significant. The calculated sample size with 90% power and p-value of 0.05 was 106. Interim analyses of overall events rates during the study provided a guide as to whether the sample size needed to be altered as the study proceeded. Due to limited time and resources, the sample size was modified to be 90 with three equally sized groups to detect a 0.3 effect reduction in the incidence of postmastectomy seroma at 80% power with p-value 0.05.

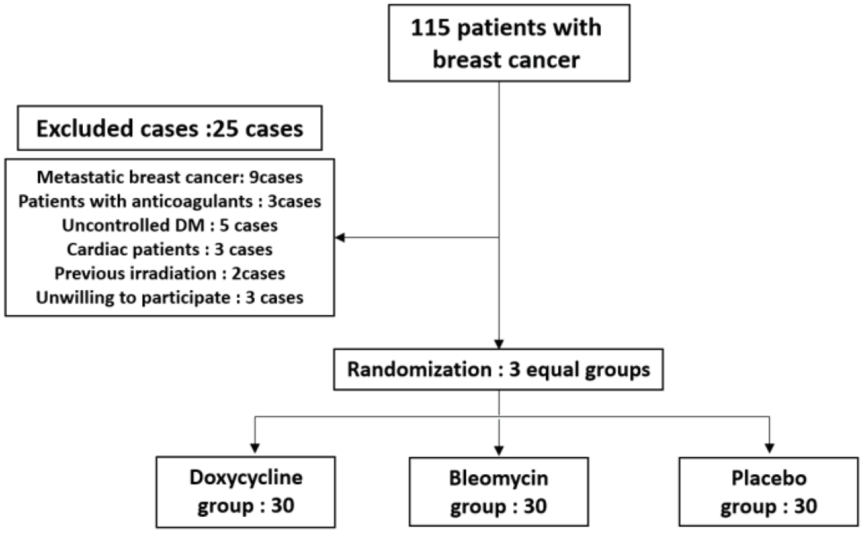

Figure 1. Flowchart and randomization of patients

Results

All patients were biopsied to prove malignancy before planning of treatment. Of 125 patients (Figure 1), 90 patients underwent total mastectomy with axillary surgery. Sentinel lymph node biopsy was performed in five patients in the doxycycline group and three patients in the bleomycin group. Comparison of demographic data and comorbid conditions for control, doxycycline and bleomycin groups showed no difference. The three groups were comparable with regard to age, BMI and comorbidities. Within the bleomycin group, there was a lower incidence of hypertension compared with the other two groups while only patients in the doxycyline had prexeisting heart disease (Table 1). There was a significantly higher number of patients with clinically locally advanced breast cancer in the doxycycline group compared to the other two groups (p = 0.005), but there was no difference in breast size between the groups. There was no difference in mammographic size of the malignant breast mass/masses among the study patients, neither was there any difference in the number of clinically detected axillary lymph nodes during the preoperative examination. There was no significant difference as regards the side of the diseased breast among all groups (p = 0.392). There was a significantly greater number of patients with early breast cancer in the bleomycin group (Table 1). There were no significant differences between number of the cases who underwent neoadjuvant therapy or exhibited tumor downsizing after receiving neoadjuvant therapy. As regards tumor size, there was a significant difference following pathological dissection after surgery with relatively smaller tumor size in the bleomycin group (p = 0.002) with no significant difference as regard the breast size itself or surface area of the excised skin. There was no significant difference in the number of cases who underwent axillary clearance and those who did not among all groups. There was no difference in the total number of excised axillary lymph nodes, nor in the number of the axillary lymph nodes with malignant infiltration. Table 2 shows a comparison of operative outcome and postoperative complications between the three groups. Analysis revealed that all measured parameters were similar between all groups. However, some differences emerged. Using the VAS scoring system, there was a significant difference in the postoperative pain with higher number of cases suffering from pain in the bleomycin group, especially in the early postoperative hours (p<0.001). There was also a significantly higher incidence of post mastectomy hematoma in the bleomycin group (p = 0.008). Overall complication rate was similar in all groups as regard the incidence of independent complications, including, infection, flap necrosis and hematoma. The incidence of seroma was comparable among the three groups with no significant difference either as a whole or when stratified by grade of seroma. No seroma occurred in 18/30 in the doxycycline and bleomycin groups and in 17/30 in the placebo group. The incidence of G1, G2 and G3 seroma in the three groups is shown in Table 3. This did not differ between groups. There was no difference in postoperative fluid

Table 1. Comparison of patients and tumor characteristics between the three groups

	Doxycycline (n = 30)	Placebo (n = 30)	Bleomycin (n = 30)	p
Mean age (years)	55.47±11.74	53.30±13.14	50.60±11.50	0.304
Mean BMI (kg/m^2)	37.79±7.40	39.47±7.94	36.48±7.64	0.322
Incidence of diabetes mellitus	9 (30.0%)	8 (26.7%)	3 (10.0%)	0.136
Chronic pulmonary disease	3 (10.0%)	1 (3.3%)	0 (0.0%)	0.160
Hypertension	10 (33.3%)	14 (46.7%)	3 (10.0%)	0.007*
Heart disease	3 (10.0%)	0 (0.0%)	0 (0.0%)	0.045*
Proportion with large breasts (cup C&D)	24 (80.0%)	24 (80.0%)	25 (83.3%)	0.930
Proportion with positive axillary LNs	11 (36.7%)	10 (33.3%)	12 (40.0%)	0.866
Mean radiological tumor size (cm)	3.07±1.83	3.20±1.98	2.78±1.02	0.607
Left sided cases	13 (43.3%)	18 (60.0%)	17 (56.7%)	0.392
Tumor stage				
0	1 (3.3%)	0 (0.0%)	3 (10.0%)	<0.001*
I	1 (3.3%)	5 (16.7%)	18 (60.0%)	
II	12 (40%)	11 (36.7%)	0 (0.0%)	
III	16 (53.3%)	14 (46.6%)	9 (30.0%)	
Neoadjuvant therapy	18 (60.0%)	16 (53.3%)	18 (60.0%)	0.833
Response to neoadjuvant therapy	11 (36.7%)	8 (26.7%)	15 (50.0%)	0.174
Mean largest diameter of tumor (cm)	3.94±1.99	3.81±1.87	2.28±2.06	0.002*
Mean removed skin surface area (cm^2)	17.60±7.04	17.83±5.91	16.50±5.92	0.684
Axillary clearance	25 (83.3%)	30 (100.0%)	27 (90.0%)	0.074
Mean total number of LNs removed	13.73±9.15	18.10±7.65	16.50±9.32	0.153
This is to be corrected into: Median number of malignant LN: 4 with a range of 2-7	3.67±4.86	4.77±7.28	5.10±8.07	0.700

BMI: body mass index; LN: lymph nodes

drainage volume among the three groups. Furthermore, there was no difference in the proportion of patients in each group who underwent seroma aspiration or the volume of aspiration fluid. Finally, there was no difference between groups in terms of the incidence of drain reinsertion in refractory cases for simple aspiration.

Discussion and Conclusion

The most common sequel after mastectomy is the formation of a post-operative seroma. It should be noted that the clinical definition of seroma differs from the ultrasonographic definition. The clinical definition of seroma is the presence of fluctuant serous collection after drain removal that necessitates aspiration or drain re-insertion. The ultrasonographic definition adds that the subclinical (G1) seroma that may not affect the post-operative recovery (4). Various surgical and medical techniques have been tried with the aim of decreasing the incidence and magnitude of this problem, and currently there is no consensus for preventative therapy (5).

The pathophysiology of post-operative seroma remains unclear. The most widely accepted hypothesis for seroma formation is lymph fluid collection associated with transection of wide areas of lymph bearing tissues resulting in a large dead space after surgery. Therefore it has been recommended to obliterate the dead space to avoid seroma formation (6, 7). Woodworth et al. (8) in a study of 252 patients showed that the rate of seroma was around 25.5%. Porter et al. (9) concluded that the incidence of seroma was around 26% in an analysis of 80 patients (9). The incidence of seroma in the current study was much higher than in these earlier studies at around 41.1%. The use of electrocautery dissection decreases blood loss, but it increases the incidence of seroma (9, 10). In contrast, argon beam coagulation and harmonic scalpel were reported to decrease seroma formation (11, 12). The use of sclerotherapy as a preventive measure for post-operative seroma has been described. This sclerotherapy consists of filling the dead space with an irritating substance to induce a fibrotic reaction with the clinical aim of sealing the space. Commonly used irritating substances included doxycycline, bleomycin, ethanol, and talc (13). To our knowledge, a few published reports have documented the use of sclerotherapy for prevention

Table 2. Comparison of operative outcome and postoperative complications between the three groups

	Doxycycline (n = 30)	Placebo (n = 30)	Bleomycin (n = 30)	*p*
Operation time (minutes)	83.50±33.04	92.83±42.84	85.00±31.27	0.563
Estimated blood loss (mL)	45.33±32.35	55.00±39.46	37.33±26.90	0.127
Mean VAS after 4h	5.27±1.34	7.03±0.89	6.80±1.10	<0.001*
Mean VAS after 8h	3.13±0.35	4.07±0.87	4.90±1.24	<0.001*
Mean VAS after 12h	3.10±0.31	3.70±0.65	4.50±1.31	<0.001*
Postoperative hematoma, n (%)	0 (0.0%)	1 (3.3%)	6 (20.0%)	0.008*
Flap ischemia, n (%)	6 (20.0%)	5 (16.7%)	6 (20.0%)	0.930
Postoperative infection, n (%)	1 (3.3%)	2 (6.7%)	3 (10.0%)	0.585

VAS: visual analog scale

Table 3. Comparison between the three groups in terms of incidence of seroma, clinical features of seroma and its management

	Doxycycline (n = 30)	Placebo (n = 30)	Bleomycin (n = 30)	*p*
Time of drain removal (days)	19.43±5.50	19.13±7.13	18.20±5.26	0.711
Seroma incidence				
No seroma	18 (60.0%)	17 (56.7%)	18 (60.0%)	0.992
G1 seroma	3 (10.0%)	2 (6.7%)	3 (10.0%)	
G2 seroma	4 (13.3%)	4 (13.3%)	3 (10.0%)	
G3 seroma	5 (16.7%)	7 (23.3%)	6 (20.0%)	
Postoperative drainage (mL)				
Amount in the first 3 days	629.00±451.07	601.83±330.71	568.00±209.23	0.791
Total amount of drained fluid	2891.17±2048.38	3415.33±3788.49	3389±1679.82	0.694
Amount in the last 3 days	139.50±20.73	141.83±16.69	140.50±20.02	0.895
Amount on last day	21.83±13.93	23.33±11.55	25.00±10.42	0.597
Number of patients undergoing aspiration of seroma, n (%)	10 (33.3%)	10 (33.3%)	9 (30.0%)	0.950
Total aspirated volume (mL)	66.50±142.09	108.67±367.29	57.00±119.49	0.670
Drain reinsertion, n (%)	5 (16.7%)	6 (20.0%)	6 (20.0%)	0.930

or treatment of seromas. The existing reports suggested that this treatment was effective and well-tolerated. However, a comprehensive comparative analysis of the different possible options was lacking. The hypothesis for the sclerosing action of doxycycline was the destruction of the mesothelial cells lining the pseudocyst, as well as inhibition of fibrinolysis and induction of fibroblast growth factors (14). The concentration of the recommended material in most studies was 500 mg of doxycycline dissolved in 50 to 100 mL of sterile saline. This was prescribed for pleurodesis, but the main disadvantage of doxycycline was the associated pain, so analgesic and/or conscious sedation was usually added (15). Bansal et al. (14) applied doxycycline to trunk, thigh, and gluteal seromas in 16 patients. In this study, 500 mg of doxycycline in 25 mL normal saline was injected into the seroma cavities and compression garments were applied postoperatively. Most seromas resolved within four weeks, whereas seromas of the anterior abdominal wall resolved within eight weeks (14). Our study showed no significant difference in the incidence of post-mastectomy seroma with or without doxycycline administration at the same dose. Our study showed no increased incidence of postoperative complications between doxycycline and the control group as regard postoperative hematoma, flap necrosis, pain, and infection.

For bleomycin, most studies recommended its use in pleurodesis in a dosage of 60 IU mixed with 50 to 100 mL sterile saline. In comparison with tetracycline, similar or higher success rates were reported when bleomycin was used as a sclerosing agent (16-18). A direct trial comparing doxycycline with bleomycin in pleurodesis using a small-bore catheter has demonstrated a similar success rate (79% doxycycline and 72% bleomycin) (15). Our study showed no significant difference as regard to the incidence of postmastectomy seroma between bleomycin, doxycycline, and control group. The main disadvantage of bleomycin as a sclerosing agent was its relatively higher cost when compared to other sclerosing agents, such as doxycycline and talc (18, 19). Our study showed a higher number of cases suffering from pain and postoperative hematoma in the bleomycin group in the early postoperative hours. Our study showed that there was no significant difference among the three groups in the amount of drainage within the first three postoperative days. Kuroi et al. (1) showed that the duration of drainage did not have a significant influence on seroma formation. In contrast, Pogson et al. (6) reported that the *in situ* dwelling time of drains is an important risk factor for seroma formation and early drain removal with a larger amount of wound drainage can participate in postoperative seroma formation (6). Varshney and Goddord (20) found that longer drainage duration is usually associated with a very minimal incidence of postmastectomy seroma formation, but early removal can markedly increase seroma formation. Gupta et at. (21) reported that 8-day drainage after modified radical mastectomy resulted in a lower incidence of seroma than 5-day drainage. In our study, the drains were removed only after the daily drainage output was less than 50 mL in the preceeding 24 hours. There was no significant difference between the three groups in terms of postoperative time of drain removal. In our study, non-suction drainage was used in all cases to eliminate the suspected risk associated with type of drainage on seroma formation.

Despite improved recognition and management of risk factors, seromas remain a common concern after total mastectomy. The use of sclerosing agents, such as bleomycin and doxycycline with non-suction drainage did not decrease the incidence of post-mastectomy seroma when compared to placebo in this population.

Ethics Committee Approval: Ethical approval was granted by the Institutional Review Board Mansoura Faculty of Medicine Mansoura University (approval number: MS/17.08.66, date: 15.08.2017).

Informed Consent: Written informed consent forms were obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.K., A.H., O.F., A.S., S.S., M.A., O.E.; Concept: A.K.; Design: A.K., A.H., O.F., A.S., S.S., M.A., O.E.; Data Collection or Processing: A.K., A.H., O.F., A.S., S.S., M.A., O.E.; Analysis or Interpretation: A.K., A.H., O.F., A.S., S.S., M.A., O.E.; Literature Search: A.K., A.H., O.F., A.S., S.S., M.A., O.E.; Writing: A.K., A.H., O.F., A.S., S.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Kuroi K, Shimozuma K, Taguchi T, Imai H, Yamashiro H, Ohsumi S, et al. Evidence-based risk factors for seroma formation in breast surgery. Jpn J Clin Oncol 2006; 36: 197-206. (PMID: 16684859) [Crossref]
2. Boostrom SY, Throckmorton AD, Boughey JC, Holifield AC, Zakaria S, Hoskin TL, et al. Incidence of clinically significant seroma after breast and axillary surgery. J Am Coll Surg 2009; 208: 148-150. (PMID: 19228516) [Crossref]
3. Soon PS, Clark J, Magarey CJ. Seroma formation after axillary lymphadenectomy with and without the use of drains. Breast 2005; 14: 103-107. (PMID: 15767179) [Crossref]
4. Kuroi K, Shimozuma K, Taguchi T, Imai H, Yamashiro H, Ohsumi S, et al. Pathophysiology of seroma in breast cancer. Breast Cancer 2005; 12: 288-293. (PMID: 16286909) [Crossref]
5. Saydam S, Harmancioglu O. Seroma prevention. Eur Surg Res 2001; 33: 8-245. [Crossref]
6. Pogson CJ, Adwani A, Ebbs SR. Seroma following breast cancer surgery. European Journal of Surgical Oncology, Vol. 29, No.9, 2003, pp. 711-717. [Crossref]
7. Khater A, Elnahas W, Roshdy S, Farouk O, Senbel A, Fathi A, et al. Evaluation of the Quilting Technique for Reduction of Postmastectomy Seroma: A Randomized Controlled Study. Int J Breast Cancer 2015; 2015: 287398. (PMID: 26246912) [Crossref]
8 Woodworth PA, McBoyle MF, Helmer SD, Beamer RL. Seroma formation after breast cancer surgery: incidence and predicting factors. Am Surg 2000; 66: 444-450. (PMID: 10824744) [Crossref]
9. Porter KA, O'Connor S, Rimm E, Lopez M. Electrocautery as a factor in seroma formation following mastectomy. Am J Surg 1998; 176: 8-11. (PMID: 9683123) [Crossref]
10. Hoefer RA Jr, DuBois JJ, Ostrow LB, Silver LF. Wound complications following modified radical mastectomy: an analysis of perioperative factors. J Am Osteopath Assoc 1990; 90: 47-53. (PMID: 2312369) [Crossref]
11. Ridings P, Bailey C, Bucknall TE. Argon beam coagulation as an adjunct in breast-conserving surgery. Ann R Coll Surg Engl 1998; 80: 61-62. (PMID: 9579131) [Crossref]
12. Khater A. Harmonic scalpel as a single instrument in modified radical mastectomy. Is it more cost effective than electrocautery and ligature? Egypt J Surg 2010; 29: 59-63. [Crossref]
13. Shermak MA, Rotellini-Coltvet LA, Chang D. Seroma development following body contouring surgery for massive weight loss: patient risk factors and treatment strategies. Plast Reconstr Surg 2008; 122: 280-288. (PMID: 18594418) [Crossref]
14. Bansal A, Bhatia N, Singh A, Singh AK. Doxycycline sclerodesis as a treatment option for persistent Morel-Lavallée lesions. Injury 2013; 44: 66-69. (PMID: 22204771) [Crossref]

15. Patz EF Jr, McAdams HP, Erasmus JJ, Goodman PC, Culhane DK, Gilkeson RC, et al. Sclerotherapy for malignant pleural effusions: a prospective randomized trial of bleomycin vs doxycycline with small-bore catheter drainage. Chest 1998; 113: 1305-1311. (PMID: 9596311) [Crossref]
16. Hartman DL, Gaither JM, Kesler KA, Mylet DM, Brown JW, Mathur PN. Comparison of insufflated talc under thoracoscopic guidance with standard tetracycline and bleomycin pleurodesis for control of malignant pleural effusions. J Thorac Cardiovasc Surg 1993; 105: 743-747. (PMID: 7682268) [Crossref]
17. Moffett MJ, Ruckdeschel JC. Bleomycin and tetracycline in malignant pleural effusions: a review. Semin Oncol 1992; 19(2 Suppl 5): 59-62. (PMID: 1384146) [Crossref]
18. Martínez-Moragón E, Aparicio J, Rogado MC, Sanchis J, Sanchis F, Gil-Suay V. Pleurodesis in malignant pleural effusions: a randomized study of tetracycline versus bleomycin. Eur Respir J 1997; 10: 2380-2383. (PMID: 9387969) [Crossref]
19. Windsor PG, Como JA, Windsor KS. Sclerotherapy for malignant pleural effusions: alternatives to tetracycline. South Med J 1994; 87: 709-714. (PMID: 7517579) [Crossref]
20. Varshney S, Goddord J. The optimal timing of drains removal following mastectomy and axillary clearance. Eur J Surg Oncol 2004; 29: 46. [Crossref]
21. Gupta R, Patel K, Royle GT. A comparison of 5-day and 8-day drainage following mastectomy and axillary clearance. Eur J Surg Oncol 2002; 28: 15-18. (PMID: 11237488) [Crossref]