The Use of Tetracycline Sclerotherapy as an Option in Management of The Refractory Postmastectomy Seroma

Mohamed I Abdelaziz, MD, Salah S. Soliman,MD, Hany F Habashy
General Surgery Department, Fayoum University, Fayoum, Egypt.

ABSTRACT

Seroma is the commonest complication after modified radical mastectomy and breast conserving surgery. The aim of this study was to evaluate the efficiency and safety of tetracycline sclerotherapy in the treatment of refractory post mastectomy seroma. 44 female patients after modified radical mastectomy and breast conserving surgery developed persistent post mastectomy seroma and were managed with tetracycline sclerotherapy on an outpatient basis through installation of 1 gm tetracycline diluted in 25 ml normal saline plus 10 ml lidocaine 2% after aspiration of the seroma. Results were analysed as rgard amount of seroma, number of sclerotherapy session required to achieve cure, any side effects recorded and whether the patient was satisfied with the procedure or not. Resolution was achieved in 28 (63.6%) patients after single dose of sclerotherapy and 13 (29.5%) patients were cured after two sessions, while 3 (6.8%) patients required a third TCN sclerotherapy to achieve cure. 91% of patients were satisfied while 9% were not because of severe pain. ***Conclusion:*** *tetracycline sclerothaerpy is a simple, effective , cheap and safe method of treatment of refractory postmastectomy seroma with no serious side effects.*
Keywords: *postmastectomy, seroma, tetracycline, sclerotherapy.*

INTRODUCTION

Seroma is an abnormal collection of serous fluid in the dead space of post mastectomy skin flaps, axilla or breast following modified radical mastectomy (MRM) or breast conserving surgery (BCS) and is the most common early postoperative complication.[1]Seroma formation accounts for prolonged patient discomfort due to pain, delayed wound healing, skin flap necrosis and infection that required repeated outpatient attendance and aspiration.[2] A direct correlation was found between incidence of seroma and patient age, breast size,hypertension, uncontrolled diabetes, early postoperative shoulder exercise, neoadjuvant radiotherapy, presence of malignant nodes in axilla and their number, extent of lymph node dissection, previous surgical biopsy, perioperative use of heparin, use of electrocautery in dissection and whether intraoperative lymphatic vessels ligation was done or not.[3] Every women undergoing breast cancer surgery is at risk for developing seroma with incidence may be as high as 90%, but most of studies report rates around 20–30%.[4] Many studies indicated that no single way is effective to prevent seroma formation but there are many proven methods to reduce it significantly.[4]The main pathophysiology of seroma is still poorly understood and remains controversial[3]. It seems to be multifactorial with surgery at its core.[4] Many authors believe that the source of seroma is mainly due to disruption of lymphatic channels together with an inflammatory reaction.[2,3,4,5]

Management options for seroma can be classified into prophylactic or therapeutic measures; prophylactic options include insertion of vacuum drain postoperatively, proper hemostasis, avoid using electrocautery in dissection as much as possible[6,7], ligation of lymphatic channels with closure of dead space[8], intraoperative administration of sclerosant agents or tissue glue to the wound cavity [9,10] , postoperative pressure bandage[3], and patients should encouraged to use their arm in normal routines but physiotherapy should not be started before at least one week postoperatively[4]. Whereas therapeutic measures include percutaneous aspiration[11], obliteration of dead dead space by steroids, fibrin glue, or sclerosants[6] and in some cases excision of the seroma capsule may be necessary[12]. However management of post mastectomy seroma can be difficult and frustrating for both patient and physician. The exact constituents of seroma are a place of controversy, one theory proposes that it originates from disrupted lymphatic vessels but if this was true so seroma fluid should contain predominantely lymphocytes, however granulocytes have been found to be the primary

white cells moreover protein analysis suggests that the fluid is an exudates.[13] Nevertheless,the possibility remains that disrupted lymphatic vessels contribute to the formation of seroma which makes the use of tissue glue or sclerosants beneficial for sealing such damaged vessels and the dead space.[14,15]Other chronic fluid collections such as liver and renal cysts, primary hydrocele, pelvic lymphocele and pleural effusion have been treated succefully with injection of sclerosing agents which is known as sclerotherapy.[16] Concenterated alcohol is the most commonly used but other possible agents have been tried with variable success rates like talc powder, hypertonic saline , povidone iodine, acetic acid, tetracycline (TCN)[16] and erythromycin.[6] Although the use of TCN sclerotherapy for postmastectomy seroma did not begin before Sitzman[17] followed by McCarthy[18], the topical TCN has been used for a long time with great success in the management of benign and malignant pleural effusion [19,20] .

In 1983 Sitzmann et al[17] presented in their study tetracycline as a sclerosant agent for treatment of postmastectomy refractory seroma in five patients with significant improvement within 48 hours after the procedure. In 1986 McCarthy et al[18] designed the first randomized controlled trial to study the effect of TCN as a sclerosant in management of prolonged postmastectomy seroma but the trial was aborted as the tetracycline was painful and not effective. In 2009 Hokkam et al[21] reported that topical application of TCN is effective and feasible method in the management of refractory postmastectomy seroma and also some other studies designed to evaluate the effect of TCN sclerotherapy in treatment of post mastectomy seroma with a wide range of controversy.[16]

The aim of our study was to evaluate efficiency and safety of topical application of TCN as a sclerosant agent in treatment of postmastectomy refractory seroma.

PATIENTS & METHODS

This prospective study was carried out at the general surgery department ,Fayoum university hospital during the period between June 2010 and September 2014.The study included forty four (44) female patients with primary diagnosis of breast cancer who did Modified Radical Mastectomy or Breast Conservative Surgery and developed refractory post-operative seroma that appeared after removal of drains. Patients who were hypersensitive to TCN and with uncontrolled diabetes were excluded from the study. After adequate explanation of all about the procedure to every patient ,informed consent was taken from every patient.All patients were subjected to proper history taking, careful clinical examination and ultrasound (US) assessment of seroma was done. In our study we defined refractory seroma as persistent accumulation of abnormal fluid in the operative bed for at least 4 week postoperatively, after drain had been removed, in spite of weekly regular aspiration for 3 successive weeks. All patients were studied for the efficacy and safety of TCN sclerotherapy as a treatment option for the post mastectomy refractory seroma as an outpatient procedure. After the seroma was aspirated using 16 gauge wide bore needle, connected to three way stopcock valve, then TCN sclerosant solution was installed into the dead space (1 gm TCN dissolved in 30 ml 0.9%NaCl plus 10 ml lidocaine 2%). After installation was completed, gentle local massage was done to ensure adequate distribution of the solution inside the dead space then pressure bandage was applied with emphasis on the patient to limit the shoulder exercise for one week.

Patients were observed for 12 hours and then were discharged home. Prophylactic oral antibiotics (amoxicillin clavulanate 625mg) every 8 hour and non-steroidal anti-inflammatory analgesic (ibuprofen 400mg) every 8 hour were prescribed for all patient for 5 days. The procedure was repeated after one week if seroma recollected again. Patients were reviewed weekly until cure achieved, then after one month, three months and six months. On every follow up visit, careful clinical examination and US assessment were performed to evaluate the efficiency of the procedure, moreover, symptomatic improvement and any complications were recorded .Patients were asked about their satisfaction with the procedure and if they were not the reasons for unsatisfaction were recorded.

Data about; age, type of previous breast surgery, size of seroma by US, amount of seroma aspirated prior to sclerotherapy, number of sclerotherapy sessions required, pain and any complications like fever, infection, flap necrosis and cosmotic disfigurement were collected and analysed.

RESULTS

Forty seven female patients were allocated in this study, three patients were excluded (as two patients were missed during follow up and one patient get infected seroma before sclerotherapy and was treated by open drainage). Demography of patients are summarized in table (1).

Table (1): Patients Demography.

Variable	**Value**
Age (mean ± SD*)	43.2 ± 6.8
Duration of postmastectomy drain in days (mean ± SD*)	11.3 ± 4.1
Amount of seroma by US in ml.(mean±SD*):	
All patients	125.5 ± 18.7
Post MRM	137.3 ± 23.1
Post BCS	109.7 ± 16.3
Type of surgery done:	
MRM	35 patients (79.5%)
BCS	9 patients (20.5%)
BMI (mean ± SD*)	29.1± 4.8

** Standard deviation*

The mean age was 43.2±6.8 years and mean BMI was 29.1±4.8 and 79.5% of patients presented with seroma post MRM whereas 20.5% post BCS, the mean time for drain after primary surgery was 11.3±4.1 days, the mean seroma size in the first presentation detected by US was 125.18.7 ml. more in patients post MRM 137.3±23.1 ml. than patients post BCS 109.7±16.3 ml. with p.value < 0.05.

Table (2): Number of patients and sclerotherapy sessions required to achieve cure.

Sclerotherapy session	**Number of patients**	**Amount of the aspirated seroma in ml (mean±SD)**
First session	44 (100%)	120.3±2.8
Second session	16 (36.4%)	59.2±4.4
Thirs session	3 (6.8%)	36.1±3.5

During first session, the mean amount of the aspirated seroma was 120.3±2.8 ml. then TCN sclerotherapy was installed, after one week follow up sufficient cure was achieved in 28 (63.6%) patients after single dose of sclerotherapy while 16 (36.4%) patients presented again with recollected seroma that necessitated reaspiration with mean amount of 59.2±4.4 ml. then second session of TCN sclerotherapy was given, after one week 13 (29.5% of all study sample) patients of these 16 were cured successfully while 3 (6.8%) patients were still had recollected seroma and subjected to third aspiration that revealed meam amount of 36.1±3.5 ml. followed by third session of TCN sclerotherapy that cured all of them as proved by regular follow up. None of patients in our study required further aspiration and thus no further sclerotherapy sessions required.

Three (6.8%) patients developed mild to moderate local infection without suppuration after TCN installation, two patients (4.5%of total study patients and 12.5% of second session patients) after second session on the second postsclerotherapy day and one patient (2.3% of total study patients and 33.3% of third session patients) after third session on the third postsclerotherapy day. All the three patients were treated with oral ciprofloxacin 500mg every 8 hours (in conjunction with amoxicillin clavulanate that already was given with sclerotherapy session) with repeated topical warm compresses.

As shown in table 3, 23(52.3%) patients get mild pain after sclerotherapy, 12(27.2%) patients complained of moderate pain and 4(9.1%) patients suffered from severe pain that required parenteral analgesics (diclofenac sodium 75 mg intramuscular injection) two injections were required on the same sclerotherapy day with 8hours interval.

Table(3): Postsclerotherapy pain

pain	Number of patients	Percentage
Mild	23	52.3%
Moderate	12	27.2%
severe	4	9.1%

All patients were discharged to home 12 hours after the procedure; none of them were readmitted after the discharge in the hospital. Forty(91%) patients were satisfied with the procedure while 4(9.1%) patients were not satisfied because of severe pain experienced.

DISCUSSION

Seroma formation is the most common non tumor related morbidity[22,23], that can occur in rates as high as 90% after modified radical mastectomy and breast conserving surgery ,however most studies report rates around 20-30%.[4]

As sclerotherapy was successful for treatment of other chronic fluid collections as pleural effusion, liver and renal cysts, and pelvic lymphocele hence many studies began to offer this treatment as an option for difficult refractory postmastectomy seroma.[16]

The exact mechanism of postmastectomy seroma formation is still unknown and believed to be multifactorial [3,5], however the important factors include the amount of dead space created[24,] and the extent of lymphatic dissection in the axilla (since level I axillary sampling results in a lower incidence in addition the majority of seromas occur in the axilla) and the use of electrocautery in dissection and creation of skin flaps.[7] Although there is no single way to prevent seroma formation however there are many proven methods that significantly reduce it.[4] As the amount of seroma formation is directly related to the amount of dead space created so the treatment depends mainly on obliteration of such space which can be obtained through chemical and mechanical means.[4,7] The mechanical means to reduce seroma formation is through minimizing dead space intra operatively that have been proved to be a very effective [4,8], while the chemical means to reduce the seroma formation is through stimulating an inflammatory reactions that result in obliteration of the dead space through the adhesions developed between the flaps and chest wall that also obliterate the damaged lymphatic channels. [4,7,17] Various sclerosing agents have been investigated for such purpose in many studies with a controversy about their efficacy ranging from complete success to complete failure.[5,17,18,21]

The most commonly reported sclerosant in the literature is tetracycline (TCN), and similar to fibrin glue and other sclerosants some reports found it useful[17,21,28], whereas others did not.[9,18] TCN sclerotherapy can be administerated either intraoperatively before closure of skin via topical application directly to chest wall and skin flaps as a prophylaxis against seroma formation[9], or postoperatively if seroma persisted where aspiration of seroma should be done first (either directly or under US guidance) followed by installation of TCN diluted in 0.9%NaCl[17,21]. Although Sitzmann et al[17] reported good results of TCN sclerotherapy as a successful management of post mastectomy refractory seroma (the study was retrospective and included only five patients), after that McCarthy et al[18] designed his controlled trial to study TCN sclerotharpy efficacy on patients with prolonged drainage after mastectomy but the trial was aborted as TCN was painful and not effective. Later in 2000 Rice et al[9] started their trial at Mayo clinic with intraoperative TCN sclerotherapy (1 gm TCN dissolved in 100 ml 0.9%NaCl) as a prophylactic measure but also the trial was stopped because two weeks postoperatively TCN group had more seromas than the saline group. In Hokkam et al[21] study treatment of forty patients with postmastectomy persistant seroma by aspiration and installation of TCN sclerosant solution (2 gm TCN dissolved 100 ml 0.9%NaCl plus 10 ml lidocaine) they reported a very good results, as thirty six (73.4%) patients were treated successfully with one sclerotherapy session while nine (18.4%) patients required two sessions and four (8.2%) patients required three sessions, moreover 85.7% of patients had no complications after procedure.

We designed our study to evaluate the efficacy and safety of TCN (1 gm TCN dissolved in 25 ml 0.9%NaCl plus 10 ml lidocaine 2%) as a sclerosant agent for treatment of refractory seroma that developed after MRM or BCS.The procedure was applied on 44 patients (35 post MRM and 9 post BCS) and the results were very promising and similar with the studies of

Sitzmann et al[18] and Hokkam et al[21]. In our study large number of patients were cured successfully from refractory postmastectomy seroma formation by the end of study where 63.6% of patients cured after single session of TCN sclerotherapy, 27.3% of patients after two sessions and 6.8% of patients after three sessions. None of the patients in the study developed recollection of seroma after third session of TCN sclerotherapy,duing the period of six months follow up.Morbidity of the procedure was in the form of mild to moderate wound infection in the form of erythema with no suppuration occurring in three (6.8%) patients, two (4.5%) patients after first session (both of them cured completely from seroma after same session of TCN sclerotherapy) and one (2.3%) patient after second session (cured completely from seroma after the same session of TCN sclerotherapy), all the three patients were cured completely with oral antibiotics and apart from these three patients we did not get any other complications.

We believe that the main reason of failure of previous studies was the severe pain, so adding lidocaine to the sclerosant formula will be beneficial. Four patients in our study were unsatisfied by the end of study as they experienced severe pain after the procedure (all were after the first session) and oral analgesic was not enough and they required parenteral diclofenac sodium 75 ml twice after procedure and all cured successfully from seroma after the first session. we believe that such severe pain was a form of a topical hypersensitivity reaction with subsequent exaggerated inflammation to TCN and this might be less if we used more diluted TCN formula and/or added more lidocaine .

CONCLUSION

Management of refractory postmastectomy seroma represents a challenge and may be frustrating to both patient and physician as there is no a single treatment option successful in all patients .Tetracycline sclerotherapy is a simple, effective , cheap and safe treatment with no serious side effects. Further studies are recommended to get optimal TCN sclerosant formula and whether TCN sclerotherapy is superior to other treatment options for the management of postmastectomy refractory seromas.

REFERENCES

1. **Kumar S, Lal B and Misra MC.** Postmastectomy seroma: a new look into the aetiology of an old problem. J R Coll Surg. Edinb 1995;40:292-294
2. **Tadych K.** postmastectomy seromas and wound drainage. Surg Gyn Obst 1987;165:483-7
3. **Sampathraju S and Rodrigues.** Seroma formation after mastectomy: pathogenesis and prevention. Indian J Surg Oncol 2010; 1(4):328-333 .
4. **Van Bemmel AJM, Van del Velde CJH, Schmitz RF and Liefer GJ.** Prevention of seroma formation after axillary dissection in breast cancer: a systemic review. Europ J Surg Oncol 2011; 37:829-835.
5. **Kuroi K, shimozuma K, Taguchi T, Imai H, Yamashiro H, Ohsumi S and Saito S.** Evidence based risk factors for seroma formation in breast surgery. Jpn J Clin Oncol 2006; 36:197-206.
6. **Ali-Khan AS, Orlando A and Kenealy J.** Erythromycin sclerotherapy in the management of seroma. J Plast Reconst Aesthet surgery. 2009; 62:e55-e56
7. **Keogh GW, Doughty JC, McArdle CSM and Cook TG.** Seroma formation related to electrocautery in breast surgery:a prospective randomized trial. The breast journal 1998; 7:39-41. .
8. **Habashy HF, Fayek IS and Abdelaziz MI.** Impact of dead space closure and lymph vessel ligation during MRM on postoperative seroma formation: a two institutional randomized study. Kasr elaini journal of surgery 2013; 14(2):33-38.
9. **Rice DC, Morris SM and Starr MG.** Intraoperative topical tetracycline sclerotherapy following mastectomy: aprospective randomized trial. J surg Oncol 2000; 73:224-227..
10. **Moore M, Burak Jr WE and Nelson E.** Fibrin sealant reduces the duration and amount of fluid drainage after axillary

dissection: a randomized prospective clinical trial. J am Coll Surg 2001; 192:591-599.

11. **Wiener M, Mackie I and Ralston DR.** Drainage of large symptomatic seromas: let the vacuum do the work. J Plast Reconstr Aesthet Surg 2007; 60:573-574.
12. **Stanzyk M, Grala B, Zwierowicz T and Maruszynski M.** Surgical resection for persistent seroma, following modified radical mastectomy. World Surg J oncol 2007;5:104.
13. **Watt-Boolsen S, Nielsen VB, Jensen J and Bak S.** Post mastectomy seroma a study of the nature and origin of seroma after mastectomy. Dan Med Bull 1989; 36:487-489.
14. **Butler CE.** Treatment of refractory donor site seromas with percutaneous instillation of fibrin sealant. Plast Reconst Surg 2006; 117:976-985.
15. **Chung TL, Holton 3rd. LH, Goldberg NH and Silverman RP.** seroma prevention using mytilus edulis protein in a rat mastectomy model. Breast J 2006; 12:442-445.
16. **Throckmorton AD, Giesmann JA, Hoskin TL, Bjarnason H, Donohue JH, Boughey JC and Degnim AC.** Sclerotherapy for treatment of postmastectomy seroma. Am J Surg 2008; 196:541-544.
17. **Sitzmann JV, Durfresne C and Zuidema GD.** The use of sclerotherapy for treatment of postmastectomy wound seromas. Surg 1983; 93:345-347.
18. **McCarthy PM, Martin JK, Wells DC, Welch JS and IIstrup DM.** An aborted, prospective randomized trial of sclerotherapy for prolonged drainage after mastectomy. Surg Gyn Obst 1986; 162:418-420.
19. **Hausheer FH and Yarbro JW.** Diagnosis and treatment of malignant pleural effusion. Semin Oncol 1980; 12:54-75.
20. **McKnight KM, Adair NE and Agudelo CA.** Successful use of tetracycline pleurodesis to treat massive pleural effusion secondary to systemic lupus erythematosus. Arthritis and Rheumatism 1991; 34(11):1483-1484.
21. **Hokkam E, Farrag S and El-Kammash S.** Tetracycline sclerotherapy in treating postmastectomy seroma: A simple solution for a frequently occurring problem. Egyp J Sur 2009; 28(3):99-104.
22. **Hoefer Jr RA, DuBois JJ,Ostrow LB and Silver LF.** Wound complications following modified radical mastectomy: an analysis of perioperative factors. J Am Osteopath Assoc 1990; 90:47-53.
23. **Wedgwood KR and Benson EA.** Non-tumor morbidity and mortality after modified radical mastectomy. Ann R Roll Surg Engl 1992; 74:314-317.
24. **O'Dwyer PJ, O'Higgin NJ and James AG.** Effect of closing dead space on incidence of seroma after mastectomy. Surg Gyn Obst 1991; 172:55-56.
25. **Pogson CJ, Adwani A and Ebbs SR.** Seroma following breast cancer surgery. Europ J Surg Oncol 2003; 29:711-717.
26. **Saeb-Parsy K, Athanassoglou V and Benson Jr.** Talc powder seromadesis: a novel technique for the treatment of chronic seromas following breast surgery. Breast J 2006; 12:502-504.
27. **Gruver DI.** Hypertonic saline for treatment of seroma. Plast Reconst Surg 2003; 112: 934.
28. **Widgerow AD, Song C, Ritz M and Potgieter E.** Wound modulation via sclerotherapy and tissue adhesion observation and discussion. S Afr J Surg 1997;35:88-92