Original Research Article

DOI: http://dx.doi.org/10.18203/2349-2902.isj20172579

Role of fibrin glue in seroma reduction after modified radical mastectomy

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Received: 20 May 2017 Accepted: 29 May 2017

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ABSTRACT

Background: Seroma is one of the most common morbidity occurring post modified radical mastectomy (MRM). It can delay post-operative initiation of adjuvant therapy. This study was designed to determine the role of fibrin glue spray in reduction of seroma volume and duration after breast surgeries.

Methods: A prospective, randomized, controlled study over forty female patients who underwent (MRM) was done. The study cohort was randomized into control group where only conventional drain placement was used and experimental group where double dose of fibrin glue has been sprayed to the axillary and mammary beds plus conventional drain placement. Data regarding the amount of drained fluid in the first post-operative day, hospital stay, length of drain placement, amount and duration of post-operative seroma, number of excised lymph nodes (L. Ns) and pathological results were recorded.

Results: No difference in mean age, number of excised L. Ns and rate of post-operative infection between both groups was detected. There was significant reduction in hospital stay time favouring fibrin glue group (p=0.006). Fibrin glue group had a significant reduction in the length of drain placement (p=0.001). The amount of post-operative serous fluid was reduced and the incidence of occurrence of post-operative seroma was (7/20) 35% in control group compared to (1/20) 5% in fibrin glue group giving significant reduction in incidence and amount.

Conclusions: Use of fibrin glue sealant during MRM resulted in noticeable and significant decrease of post-operative rate of seroma formation, its amount and the length of drain placement.

Keywords: Fibrin glue, Modified radical mastectomy, Seroma

INTRODUCTION

Breast cancer is the second leading cause of cancer death among women. The surgical treatment is the best choice for those patients. Since the first mastectomy which was carried out by Halsted in 1882, surgeons have faced several problems such as skin flaps necrosis, wound breakdown, seroma, infection, nerve injuries, lymphedema, phantom breast syndrome and hematoma.

Seroma, which is a subcutaneous collection of serous fluid, is a common problem in breast surgery where it develops under the skin flaps during mastectomy or in the axillary dead space after axillary dissection. It usually resolves within a few weeks, so many surgeons view this problem as an unavoidable nuisance rather than a serious complication.³

Seroma formation is the most frequent postoperative complication after breast cancer surgery. Incidence of seroma formation after breast surgery varies between 2.5% and 51%. Although seroma is not life threatening, it can lead to significant morbidity (e.g. flap necrosis, wound dehiscence, predisposes to sepsis, prolonged recovery period, multiple physician visits) and it may delay adjuvant therapy. The pathogenesis of seroma has not been fully elucidated. It has been hypothesized that seromas form as an exudate from an acute inflammatory

reaction following surgical trauma and acute phase of wound healing. This leads to increased fibrinolytic activity in serum and lymph therefore increased serous fluid collection. Low fibrinogen levels in seromas compared to those in plasma during the postoperative period supports the hypothesis that seroma most likely originates from lymph.³⁻⁵

Methods applied to reduce lymphatic drainage include compression dressings, postoperative shoulder immobilization and fibrin glue application to the axillary dissection site. There are other methods used as trials to decrease seroma formation such as; decreasing the extent of mastectomy, use of ultrasonic scalpel or laser scalpel in dissection, good post-operative drainage, and suture flap fixation. Test

Fibrin sealant/glue is a ready to use preparation that is believed to function by promoting closure of microvascular leaks caused by surgical trauma, it showed reduction in seroma formation in animal models. Its role in seroma prevention has been studied with varying results in mastectomy and thyroidectomy patients. 9-10

Human fibrin glue (HFG) is formed of two components contained in separate vials; the first component is a freeze-dried concentrate of clotting proteins, mainly fibrinogen, Factor XIII and fibronectin (the sealant) and the second substance is freeze dried thrombin (the catalyst). The first component is reconstituted with an aprotinin solution that inhibits tissue fibrinolysis. The second component (thrombin), available in 500 I.U. concentration, is dissolved with calcium chloride. HFG is a set of substances involved in the hemostasis and wound healing processes, giving it the hemostatic and sealing properties. ¹¹

In the current study, we focused on the role of fibrin glue 'in double dose' in seroma reduction after mastectomy.

METHODS

During the period from December 2014 to January 2017, a prospective, randomized study was performed over forty female patients with stage I and II breast cancer. Patients underwent modified radical mastectomy after obtaining the patients' consent. The surgery done under general anesthesia after history taking, complete clinical, imaging and laboratory examinations and completed their pre-operative metastatic work up in Al-Menofia University Hospitals.

Inclusion criteria

- Female gender
- Age >18 years old
- Newly diagnosed breast cancer
- Scheduled to undergo an elective breast procedure (modified radical mastectomy)
- Had platelet counts ≥100,000/mL

- Have no uncompensated diabetes or advanced liver disease
- Have no psychological changes
- Are not severely obese or slim
- Have not had previous surgery on the axillary lymphatic system
- Being outside of any exclusion criteria.

Exclusion criteria

- Severely obese or severely slim patients
- Current steroid use,
- Systemic anticoagulation or significant coagulation disorder,
- Platelet count ≤99,000/mL
- History of chest radiation
- Receiving preoperative chemotherapy
- Planned immediate breast reconstruction
- Pregnant or lactating
- Patients planned to sentinel node biopsy
- No consent.

The patients were randomized using closed envelop method into two groups, control group where only conventional drain placement was used and experimental group where double dose of fibrin glue sealant have been sprayed to the axillary and mammary beds plus conventional drain placement. All patients underwent (MRM) by the same surgical team with minimizing the use of electro-cautery as much as possible and meticulous hemostasis in both groups. Data regarding age, comorbidities (diabetes-chronic liver disease-hypertension), serum albumin level, breast mass size, post-operative infection, amount of drained fluid in the first postoperative day, hospital stay, length of drain placement, amount and duration of post-operative seroma plus lastly number of excised L. Ns and pathological results were recorded.

Study used the (FIBROGLOO of Cairo Medical Centre Blood Bank) two packs for each patient one pack for the dead space under the skin flaps and the other one to the axillary bed. By this we gave the doubled ordinary dose to each patient in a trial to check to efficacy of increasing the dose of fibrin glue in seroma reduction after mastectomy.

The fibrin sealant was prepackaged each pack contains

R1: Human thrombin vial (1000 I.U) freeze, dried (lyophilized) and sterile cake like.

R2: Human fibrinogen vial (6.5 gm. /dl) freeze, dried (lyophilized) and sterile in powder.

When thrombin is added to fibrinogen, it is transformed into fibrin and coagulum occurs.

Two syringes each 3 ml.

- One vial of sterile water
- One double barrel needle and disposables.

The fibrin sealant prepared according to the manufacturer instructions as the following: A vial of thrombin and a vial of fibrinogen were allowed to reach room temperature, then the metal tabs and rubber bungs from both vials were removed, the container of sterile water for injection was opened and aspirated, 1 ml was injected in the thrombin and 1 ml fibrinogen vials (1ml in each). The vials were gently shacked and swirled for 1 min and then allowed to stand at room temperature for 5 min to ensure complete protein rehydration. Syringes were then placed in the duploject injector, which was specially designed so that depressing the common plunger exerted simultaneous and equal pressure on both the syringes. A mixer nose cone, topped by a blunt applicator needle, was attached to the nozzle to facilitate the mixing of the two syringe components.



Figure 1: The fibrin sealant prepared according to the manufacturer instructions. A) content of the pack. B) mixing of the two syringe components.

Then the mixture was sprayed, after complete drying of the field, as previously mentioned one pack for the dead space under the skin flaps and the other one to the axillary bed (Figure 2). After spraying the mixture, we have exerted gentle pressure for not less than 5 minutes over the flaps and axilla and closed the wound in layers rapidly as much as possible. Lastly, we put small compressing cotton bad in axilla and post-operative data were recorded.

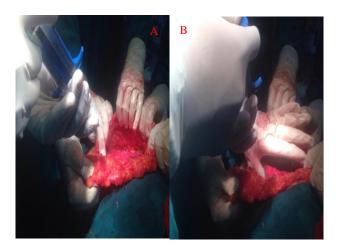


Figure 2: Spraying prepared fibrin glue to. A) dead space under skin flaps. B) on the axillary bed.

RESULTS

Statistical analysis

Results were statistically analyzed by SPSS version 20 (SPSS Inc., Chicago, IL, USA). Student's t-test: It is a single test used to collectively indicate the presence of any significant difference between two means for a normally distributed quantitative variable. Mann-Whitney test is a nonparametric test of Student's t-test. Chi-Squared (χ^2): It is used to compare between two groups or more regarding one qualitative variable Fisher's exact test is used to compare between two groups regarding one qualitative variable in 2x2 contingency table when the expected count of any of the cells less than 5. P value is set to be significant if ≤ 0.05 , P value of < 0.001 was considered statistically highly significant.

The statistical analysis of received pre-and postoperative data showed the following results:

Clinical characteristics of studied groups showed that there is no significant difference between control and experimental groups in the age of patients, serum albumin level or their co-morbidities in form of (diabetes, chronic liver disease and hypertension) (Table 1).

Table 1: Clinica	l characteristics	of studied	l groups.
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Characteristics		ups		Test of significant	P value	
		Fibrin glue, (N=20)		trol, (N=20)		Test of significant
Age(Year), Mean ±SD	43.3	5±9.90	43.25	5±9.10	t=0.03	0.974
Serum albumin (mg/dl), Mean ±SD	4.18	±0.38	4.10	±0.29	t=0.78	0.439
	No.	%	No.	%		
DM	5	25.0	4	20.0	Fisher's exact=0.14	1.0
Hypertension	6	30.0	5	25.0	$\chi 2 = 0.14$	0.723
Chronic liver disease	5	25.0	5	25.0	-	-

Table 2: Tumour characteristics of the studied groups.

Characteristics		Groups			Test of significant	P
		Fibrin glue, (N=20)		ntrol, (N=20)	Test of significant	value
	N	%	N	%		
Tumour size						
Small (T1)	10	50.0	10	50.0	-	-
Moderate (T2)	10	50.0	10	50.0		
Pathology						
Invasive duct carcinoma	19	95.0	19	95.0		
(No special type)					-	-
Special types	1	5.0	1	5.0		
Total number of lymph nodes, mean±SD	16.45	±3.17	16.3	35±2.97	0.10	0.916
Positive lymph nodes, mean ±SD	5.45	±2.03	5.50) ±1.82	Mann-Whitney-0.12	0.899

Tumour characteristics of the studied groups showed that there is no significant difference between control and experimental groups in the size of the tumour mass, number of excised L.Ns or number of positive L.Ns for metastasis also there was no significant difference in pathological types of breast cancer (Table 2).

Outcome of the studied groups showed that there is no statistically significant difference in post-operative complication rate as regard to infection or skin necrosis. However, there is statistically significant difference favoring fibrin glue group in amount of fluid drained in first post-operative day, incidence of seroma and its amount, hospital stay time, and time passed to remove the drain. The drained fluid in first post-operative day (mean

±SD) was (152.50±41.27 cc) for fibrin glue group compared to (192.50±49.40 cc) in control group (P value 0.008). The incidence of seroma occurrence in fibrin glue group was 5% compared to 35 % in control group (P value 0.044). The hospital stay time (mean±SD) in fibrin glue group was (1.35 ± 0.48) day compared to (1.85 ± 0.58) day in control group (P value 0.006). Lastly there were highly significant differences between the two groups regarding the post-operative cumulative amount of serous fluid and the time passed to remove drain. Where the amount (mean±SD) was (411.5±56.9 cc) in fibrin glue group compared to (521.7±68.6 cc) in control group with (P value 0.001), and the time passed to remove drain (mean±SD) was (10.60±0.94) days to fibrin glue group compared to (11.80±1.19) days in control group (P value 0.001) (Table 3).

Table 3: Outcome of the studied groups.

	Grou	ıps		Took of significant	Davolaro	
	Fibri	in glue, (N=20)	Cont	rol, (N=20)	Test of significant	P value
Amount of drained fluid in the first post-operative day (cc), Mean ±SD	152.5	50±41.27	192.5	50±49.40	t=2.77	0.008*
Time to drain removal (days), Mean ±SD	10.60)±0.94	11.80)±1.19	t=3.52	0.001**
Hospital stay (days), Mean ±SD	1.35=	±0.48	1.85±	-0.58	Mann-Whitney- 2.92	0.006*
Cumulative amount of serous fluid (cc), Mean ±SD	411.5	5±56.9	521.7	′±68.6	t = 5.52	0.001**
	No.	%	No.	%		
Seroma	1	5.0	7	35.0	Fisher's exact=5.62	0.044*
Infection	1	5.0	1	5.0	-	-
Skin necrosis	1	5.0	1	5.0	-	-

^{*=} significant, ** = highly significan

DISCUSSION

Prolonged axillary lymphatic drainage or seroma may not be a serious complication after axillary dissection or MRM in breast cancer, but it still the principle cause of prolonged hospital stays resulting in increased health care costs. Seroma, or the prolonged presence of drains may share to increase the incidence of wound infection, skin

flap necrosis, wound dehiscence, nerve injury and lymphedema. Therefore, several approaches have been used to reduce axillary lymphatic drainage, such as the use of fibrin glue and immobilization of the affected arm. 12,13 The use of fibrin glue may reduce lymphatic drainage by reducing the number of transected small vessels and lymphatics during axillary lymph node removal.¹⁴ However, conflicting results exist regarding fibrin glue use in breast cancer surgery. 15 Eroglu et al in their study on animal models using guinea pigs with preparing fibrin glue from fresh human plasma documented that it had a significant effect on seroma reduction and opened the door for using the human fibrin glue instead of previously used bovine one. 16 Other animal study found that increasing the concentrations of both the fibrinogen and the thrombin components up to a threshold level produced a trend of increasing effectiveness in preventing seroma formation.¹⁷ Burak et al documented that the trial failed to show a significant reduction in the incidence of seromas using bovine thrombin only and recommended to examine combining human thrombin with concentrated fibringen in an effort to produce a stronger and more effective sealant. 18

On the light of previous researches, we designed present study where we implemented good randomization of patients and used combination of human thrombin with fibrinogen in a more concentrated dose. Present study showed that neither the clinical characteristics of patients nor the tumour characteristics of the studied groups have any significance on seroma production. Adding the fibrin glue did not affect the post-operative rate of infection or wound dehiscence and this is compatible with most of published series.

Our results showed that the incidence rate of seroma was 5% for fibrin glue group to 35% to control group and this falls in the previously mentioned range of incidence rate 2.5% to 51 % .¹ Very similar results were mentioned by Moore et al with seroma incidence 29 %. Jain et al mentioned that the seroma incidence, without using neither fibrin glue nor drain, was 40% of all patients. ¹³,¹¹² Lastly Tejler et al said that seroma incidence was 36.5% and 26.8% after MRM and segmental resection respectively in their study done over 386 patients. ²⁰

In present study, there was significant difference in seroma incidence rate with favor to fibrin glue group. This is in line with results documented by many authors. 6,13,14,16,17,19,20,22 Eunyoung Ko et al documented that fibrin glue use can decrease the drainage duration and overall drain output after breast lumpectomy and axillary dissection in patients undergoing level II or III axillary dissection. Moore et al reported that the application of fibrin sealant following axillary dissection at the time of lumpectomy or modified radical mastectomy can significantly decrease the duration and quantity of serosanguinous drainage. 13

In present study, we used fibrin glue in doubled manufactured dose using 1000 I.U of human thrombin and (6.5 gm. /dl) of human fibringen to both axilla and breast bed and this gave us significant difference in rate of seroma incidence and its amount. Similar results mentioned by Moore et al who used 3200 I.U of human thrombin and 1.2 gm. of human fibrinogen to axilla and I.U of human thrombin and 0.6 gm. of human fibrinogen to skin flap. 13 Jain et al prepared their solution from four components: human pooled fibrinogen (75-115 mg/ml), aprotinin (3000 kallidinogenase-inactivator units/ml), human thrombin powder (500 units/ml) and calcium chloride (40 µmol/ml).¹⁹ The fibrinogen and aprotinin were mixed in one vial. Also, increasing the dose and use of human thrombin and fibrinogen was recommended by many authors. 13,16-18

The cumulative amount of seroma in fibrin glue group in our results showed highly significant reduction compared to the control group. This harmonizes with results obtained by all previously mentioned authors who documented decrease incidence of seroma in their series. 6,13,14,16,17,19-22 Adding to them many other authors like Tasinato et al in his study over 186 patients reported a reduction in seroma magnitude, duration, and the number of evacuative suctions when fibrin glue spray was used, in comparison to patients whose axillary fossa was only washed with povidone-iodine or saline solution.²³ Florio G et al documented in his study over 24 patients that the fibrin glue group showed a significant reduction of postoperative axillary secretion.²¹ Tirelli et al noted a reduction in the magnitude and duration of seromas in patients on whom fibrin glue was used in his study over 20 patients.²⁴ Langer et al documented that fibrin sealant application in 26 patients out of 55 patients resulted in a 60 % reduction in overall drainage amount after total mastectomy and a 32 % reduction after modified radical mastectomy which allowed earlier removal of closed suction drainage catheters.²⁵

On the other hand, some authors mentioned that there was no significant reduction in incidence of seroma with using fibrin glue. They only reported that there was reduction of the amount of post-operative serous fluid. From these authors Ruggiero et al who mentioned that seroma magnitude and duration were significantly reduced and there were fewer evacuative punctures, in patients receiving fibrin glue compared with the conventional treatment group in his study over 90 patients.²⁶ Bonjar et al documented that the cumulative aspirate volumes for seromas in the drain group were significantly greater in control group than in the fibrin glue group.²⁷ Cumulative seroma volume in fibrin glue and control groups was 110 and 210 mL, respectively (P = 0.0015). Gilly L et al concluded that the use of fibrin glue in axillary lymphadenectomy for breast cancer leads to a significant reduction in postoperative drainage volume, hospital stay period but does not affect delayed seroma formation.²⁸

Regarding the hospital stay our results showed that, there was significant decrease favoring fibrin glue group and compensating its high cost by decreasing the hospital bill. This can be explained as a normal reflection of decreased amount and incidence of seroma. This result agrees with most publications. 6,13,19-26,28,29 Accompanying with hospital stay time reduction there was also significant reduction in time passed to remove the drain. 6,13,21,24,25,29

Conflicting results were found by some authors telling that the effect of using the fibrin glue is doubtful or nonbeneficial. For example, Cha et al who applied it in immediate breast reconstruction utilizing a latissimus dorsi myocutaneous flap. ¹⁰ Burak et al whose results using only bovine thrombin failed to get significant outcome, similar results obtained by Cipolla et al in their study over 159 patients. ^{18,30} Vaxman et al reported that with the use the fibrin glue the total drain output increased. ³¹ Moreover, Dinsmore et al stated that not only the drainage volume increased but also the overall complication rate increased. ³²

Dinsmore et al in spite of his criticism to fibrin glue usage, he put a hypothesis suggesting that the lack of benefit was due to the presence of drains that may interfere with the stabilization of a fibrin clot and with closure of the lymphatic capillaries.³² Fibrin glue interacts with the damaged tissues during the surgery, favoring the growth of fibroblasts and wound healing. It favors hemostasis by preventing hematomas that can delay the surgical healing processes, makes the lymphatic branches impermeable, reducing seroma formation, and makes it possible to close the dead spaces through tissue adhesion. Other explanations may be that other authors may have used fibrin glue in a low or non-suitable concentration or used bovine thrombin and fibrinogen which may have less effect than human one or even used one of these two components only.

Lack of direct compression or rapid closure may affect the results as it was noted that closure of wound rapidly just after fibrin sealant application seems to be very important in maximizing the sealing effect and adhesive strength of the fibrin sealant.²⁹ If the wound is rapidly closed after sealant application, the wound surfaces can effectively bond during the period of sealant polymerization but if there is a delay in bringing opposing wound surfaces into contact, polymerization of the sealant may occur before tissue adherence is achieved. The polymerized sealant may, in this situation, have a reverse action with an anti-adhesive rather than an adhesive effect, acting as a barrier between the opposing tissue surfaces.^{13,29}

In present study, we had a great care about this condition and exerted immediate mild compression to the wounds just after spraying the fibrin glue not less than 5 minutes then closed the wounds as rapid as possible. But we cannot judge if this happened with others or not and this may be one of the important explanations for different results between us.

CONCLUSION

Seroma is one of most common morbidity occurring after modified radical mastectomy that cause much nuisance for both patients and surgeons and may delay postoperative initiation of adjuvant therapy. With unclear pathogenesis, many methods were suggested to decrease its incidence and amount. Fibrin glue was one of these modalities with a conflicting result. Present study supports the use of human extracted fibrin glue in a suitable concentration in this aspect. The use of fibrin glue showed a significant reduction of both seroma volume and incidence. Therefore, it had also a significant decrease in hospital stay time and time passes till the drains removed and this led to decrease in the bill compensating to what extent its relatively high cost. Further lager prospective studies and bigger retrospective meta-analysis studies are recommended to reach final decision about this technique.

Funding: No funding sources
Conflict of interest: None declared

Ethical approval: The study was approved by the

institutional ethics committee

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Cite this article as: Fawzy A, Gaber A, Farid AM. Role of fibrin glue in seroma reduction after modified radical mastectomy. Int Surg J 2017;4:2103-9.