The Role of Fibrin Glue in Reducing Seroma Formation after Modified Radical Mastectomy in Patients with Breast Cancer: A Prospective Randomized Study

Engy E. Tolba, MSc; Eldahshan ME, MD; Mohammed A. Mlees, MD; Salah Eldin A. Elgohary, MD

Department of General Surgery, Surgical Oncology Unit, Faculty of Medicine, Tanta University, Egypt

Objective: Seroma is one of the postoperative complications after modified radical mastectomy which can be reduced by using Fibrin Glue. This study prospectively evaluated the role of Fibrin Glue in reducing seroma formation after modified radical mastectomy in patients with breast cancer.

Patients and methods: The study was carried out between February 2021 and February 2022, 30 patients with breast cancer were enrolled in this study, patients were randomly divided into two groups: group (A) (Fibrin Glue group) that included 15 patients and group (B) (the control group) that included 15 patients. Patients' characteristics, postoperative complication, amount of drained fluid in the first day and cumulative amount of serous fluid, time needed to remove the drain in days and hospital stay days were analyzed.

Results: The cumulative amount of drained fluids and the overall incidence of seroma were less in group (A) (Fibrin Glue group) than in group (B) (the control group).

Conclusion: 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 were removed.

Key words: Seroma, Fibrin Glue, Modified radical mastectomy, breast cancer.

Introduction

Breast cancer is the most common neoplastic disease worldwide for women and the second most common cancer overall. It accounts for 25% of all female cancers and 12% total of all cancers. And it is the second leading cause of death in women accounting for 20% of all cancer deaths in women. Although breast cancer is thought to be a disease of the developed world, almost 50% of breast cancer cases and 58% of deaths occur in less developed countries.[1]

Since the late 1970s there has been a steady increase in the number of treatment options for breast cancer. Nowadays, there is an assortment of targeted therapies and other strategies including surgery, radiation and chemotherapy. The selection of a breast cancer treatment plan is based on the identification of the molecular subtype of the patient, which can be ER+, HER2+, or triple-negative. While various targeted treatment options are available for ER+ and HER2+ breast cancers. Triple negative breast cancer, which lacks a characterized target, can only be treated by chemotherapy. All these therapies however can be applied as neoadjuvant or adjuvant therapy that is before or after surgery, respectively.[1]

Mastectomy is one of the treatment options which is widely used as a treatment for breast cancer and is often conducted alongside a sentinel lymph node biopsy (SLNB) or an axillary node clearance (ANC) despite the trend toward breast-conserving treatments and the standardization of surgical techniques, all of these procedures are not free from complications.[2]

Potential complications are represented by hematoma, wound infection, bleeding, nerve lesion, seroma and lymphorrhea requiring delayed drain removal. These lead to patient discomfort, longer in-hospital stay, prolonged outpatient treatment, and increased costs of care.[3]

Seroma formation is the most common postoperative complication, with an incidence ranging from 15% to 80%. It is a collection of serous fluid that accumulates in dead space and presents as a fluctuant swelling beneath a wound. In breast cancer surgery, this can be deep to the mastectomy skin flaps and in the axilla after dissection. Thought to be a combination of several factors, seroma development is complicated and multifactorial. Thermal injury to the tissue while achieving hemostasis, disruption of lymphatics and capillaries, release of inflammatory mediators, and creation of dead space have been shown to result in a higher incidence of postoperative fluid accumulation. Additional patient risk factors include increased age, invasive cancer, and obesity. The seroma may lead to dehiscence of the surgical wound and necrosis of the skin flaps, further increasing the risk of infection and reoperation, as well as interfering with the recovery of upper limb mobility and delaying the start of any adjuvant therapies.[2,4-6]

The most common approach for preventing seroma is the placement of surgical drains within the wound area, though the efficacy of this approach is not universally acknowledged and the problem persists in spite of the use of drains. Other approaches have

DOI: 10.21608/ASJS.2023.325732

been evaluated to reduce the incidence of seroma formation, include topical application of tetracycline, laser scalpel, a bipolar vessel sealing system, shoulder immobilization, quilting sutures, axillary dissection with axilloscopy, external compression, use of harmonic scalpel and application of fibrin glue. The success of all these interventions seems to have common ground: reduction of the dead space.[2,7-9]

Fibrin sealants in the form of Fibrin Glue (FG) and fibrin spray have been used in surgery for almost three decades. It is used as tissue glue to adhere subcutaneous tissue in plastic, reconstructive and burn surgery, as a replacement or an adjunct to sutures or staples. In addition, it can function as an adjunct to hemostasis on subcutaneous tissue surfaces. Their potential role as a hemostatic and sealing agent has expanded across a wide range of surgical disciplines. Since the first reports of FG alleviating seroma production in 1996 following mastectomy in animal models, it has been considered one of the most frequently reported modalities in humans after breast and axillary surgery.[10,11]

FG combines fibrinogen and thrombin, the fibrin adhesion system initiates the last phase of physiological blood coagulation under the presence of factor XIII and calcium chloride, which produces a 'fibrin clot' as would occur through the natural clotting cascade. FG is thought to act as both a hemostatic agent and as an adhesive; closing over any small vessels including lymphatics that are too small for conventional surgical closure.[10]

Patients and methods

The study was carried out between Februarys 2021 and February 2022, 30 patients with breast cancer were enrolled in this study, and patients were randomly divided into two groups: group (A) (Fibrin Glue group) that included 15 patients and group (B) (the control group) that included 15 patients. A written informed consent had been obtained from every patient included in the study. The study was approved by ethical committee.

Patient selection

Inclusion criteria

Women diagnosed as having breast cancer undergoing modified radical mastectomy.

Exclusion criteria:

Patients who had undergone previous breast or axillary surgeries, conservative breast surgery, patients with coagulopathy or liver disease, patients who prefer breast reconstruction in the same operation and pregnant patients with breast cancer due to possible allergy or anaphylaxis from Fibrin Glue.

Preoperative work up

Every patient was subjected to careful history taking, general and local abdominal examination and investigations; laboratory investigations, radiological investigation (including bilateral breast Ultrasonography or mammography), metastatic work up (including abdomino-pelvic ultrasonography, Computed Tomograghy (CT) scan abdomen and pelvis, chest CT scan, Magnetic Resonance Imaging (MRI) and bone scan if needed) and the diagnosis was confirmed by FNAC and/or Tru-cut.

Operative details

Modified radical mastectomy was done and two non-suction drains were inserted; one in the breast bed and one in the axilla.

In Group A (The fibrin glue group): the fibrin glue (EVICEL FIBRIN SEALANT (HUMAN) ETHICON) was prepared by adding 1ml water to each vial then shaking both of them simultaneously for 5 minutes until whole powder dissolved then we put each 1 ml in a syringe and put the two syringes in the applicator **(Figs. 1,2)**. Equal adhesive droplet placement was ensured on the pectoralis major muscle and in the axilla using an adhesive applicator. Droplet distribution was performed in a schematically spaced manner on the pectoralis major muscle and in the axilla **(Figs. 3,4).** Then the skin flaps were compressed against the muscle. After 5 minutes of manual compression, the wound was closed. Following wound closure, the flaps were compressed again and immobilized and compression was applied by an elastoplast bandage, wrapped around the thorax.

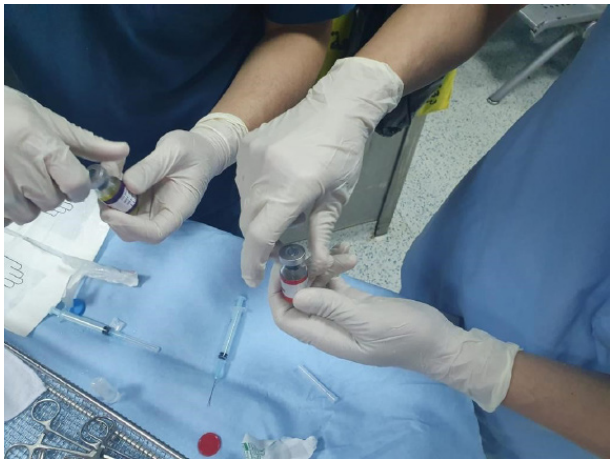

Fig 1: A picture showing adding 1ml water to each vial then shaking both of them simultaneously for 5 minutes.

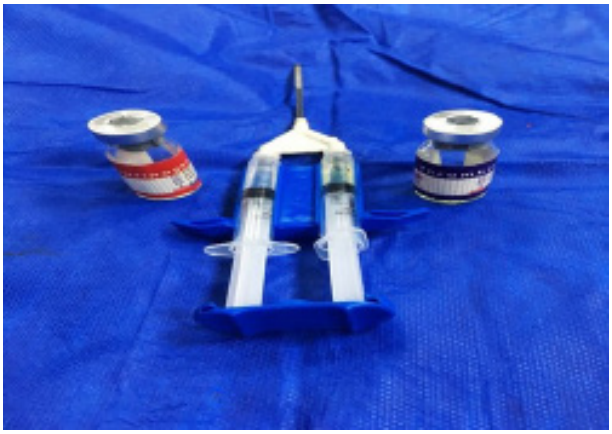

Fig 2: A picture showing putting each 1 ml in a syringe and put the two syringes in the applicator.

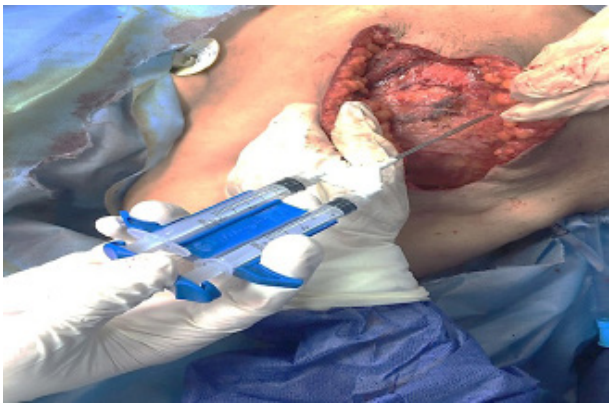

Fig 3: A picture showing equal Fibrin Glue droplets distribution on pectoralis major muscle.

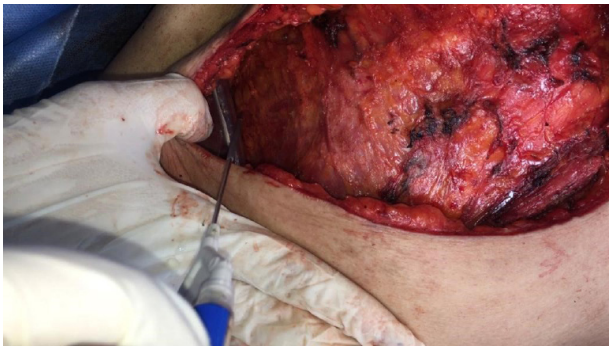

Fig 4: A picture showing equal adhesive droplet distribution was performed in the axilla.

In Group B: Modified radical mastectomy was done and two non-suction drains were inserted; one in the breast bed and one in the axilla. Then the wound was closed immediately without use of Fibrin Glue.

Postoperative follow up:

The volume drained was recorded every 24-h. The drain was removed when the amount collected per 24-hour was 30 cc or less. At postoperative follow up, patients were examined for presence of seroma (As a lump or the swelling annoying the patient).

At the second week of postoperative visit, the presence and severity of seroma was recorded. This was graded with ultrasound guide into Mild (From 0-30 cc which is asymptomatic), moderate (From 30-100 cc which is symptomatic but not requiring intervention) or severe (More than 100 cc which is symptomatic and requiring intervention).

The amount of drained fluid, the length of hospital stay and wound complications were compared between the two groups and statistical analysis was done using the mean, standard deviation and Chi-square test by SPSS Version 22 and p value ≤ 0.05 considered significant.

Results

This randomized who prospective study was conducted on 30 patients was presented with breast cancer at the Surgical Oncology Unit, General Surgery Department, Tanta University Hospitals during the period from February 2021 to February 2022.

14 patients in each group presented with breast lump, only one patient in each group presented with breast pain and bloody nipple discharge, and three patients in each group presented with nipple retraction, about 7 patients of the Fibrin Glue group and 9 of the control group presented by skin peau d'orange while none of the studied patients presented by skin ulceration or arm oedema.

Mammography with complementary U/S and Tru-cut were done for all patients in our study, only one patient in each group had to do MRI, all patients did CT chest, with 12 patients of the Fibrin Glue group and 13 of the patients of the control group did abdominal & pelvic CT, 3 patients of the Fibrin Glue group and 2 of the patients of the control group did abdominal & pelvic U/S, 14 patients of the Fibrin Glue group and 13 of the patients of the control group did bone scan and one patient of the Fibrin Glue group and 2 of the patients of the control group did PET-CT.

14 patients of each group had invasive ductal carcinoma and only one of each group had invasive lobular carcinoma and as regard to tumor stage with 5 of the patients of the Fibrin Glue group and 3 of the control group were on T3 stage and 10 of the Fibrin Glue group and 12 of the patients of the control group were on stage T4.

As regard to the number of resected axillary lymph nodes; the mean number was 23 in both groups (P value= .0680).

Postoperative complications. Two patients of the Fibrin Glue group had arm lymphedema, while 2 of the patients of the control group had infection and one of them had flap necrosis and another one had wound dehiscence **(Table 1).**

The drained fluid in first postoperative day (Mean ±SD) was (103.33±22.89 cc) for the Fibrin Glue group compared to (216.67±52.33 cc) in the control group (P value < .001). There were significant differences between the two groups regarding the postoperative cumulative amount of serous fluid and the time passed to remove the drain. Where the amount (Mean ± SD) was (593.33±67.79 cc) in the Fibrin Glue group compared to (1340±202.84 cc) in control group with (P value <0.001), The hospital stay (Mean ± SD) in the Fibrin Glue group was (2±0) day compared to (4.27±1.03) day in the control group (P value <0.001) and the time passed to remove drain (Mean ± SD) was (7.67±0.72) days to the Fibrin Glue group compared to (15.07±1.98) days in the control group (P value <0.001) **(Tables 2,3).**

Table 1: Comparison between the two studied groups according to postoperative complication

	Group A (N = 15)		Group B (N = 15)		X^2	^{FE}p
	No.	%	No.	%		
Infection						
No	15	100.0	13	86.7	2.143	0.483
Yes	0	0.0	2	13.3		
Hematoma						
No	15	100.0	15	100.0	-	-
Yes	0	0.0	0	0.0		
Flap necrosis						
No	15	100.0	14	93.3	1.034	1.000
Yes	0	0.0	1	6.7		
Wound dehiscence						
No	15	100.0	14	93.3	1.034	1.000
Yes	0	0.0	1	6.7		
Arm lymphedema						
No	13	86.7	13	86.7	0.0	1.000
Yes	2	13.3	2	13.3		

Table 2: Comparison between the two studied groups according to amount of drained fluid in the first day and cumulative amount of serous fluid

	Group A (N = 15)	Group B (N = 15)	T	P
Amount of drained fluid in the first day				
Min. – Max.	50.0 – 150.0	100.0 – 350.0		
Mean ± SD.	103.33 ± 22.89	216.67 ± 52.33	7.685*	<0.001*
Median (IQR)	100.0 (100 - 100)	200.0 (200 - 250)		
Cumulative amount of serous fluid				
Min. – Max.	500.0 – 700.0	900.0 – 1700.0		
Mean ± SD.	593.33 ± 67.79	1340.0 ± 202.84	13.522*	<0.001*
Median (IQR)	600.0 (550 - 650)	1300.0 (1200 - 1450)		

Table 3: Comparison between the two studied groups according to time needed to remove the drain and hospital stay days

	Group A (N = 15)	Group B (N = 15)	U	P
time needed to remove the drain (days)				
Min. – Max.	7.0 – 9.0	12.0 – 21.0		
Mean ± SD.	7.67 ± 0.72	15.07 ± 1.98	0.000*	<0.001*
Median (IQR)	8.0 (7.0 – 8.0)	15.0 (14.0 – 16.0)		
Hospital stay (days)				
Min. – Max.	2.0 – 2.0	4.0 – 8.0		
Mean ± SD.	2.0 ± 0.0	4.27 ± 1.03	0.000*	<0.001*
Median (IQR)	2.0 (-)	4.0 (4.0 – 4.0)		

Discussion

Prolonged seroma formation may not be a serious complication after modified radical mastectomy in breast cancer, but it is still the principle cause of prolonged hospital stay. Fibrin Glue is one of the methods that is used to reduce seroma formation, 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.[12-14]

The present study included 30 patients with breast cancer (15 patients in the Fibrin Glue group and 15 patients in the control group). The patients in surgery group were younger than the patients in control group. The age of patients in the Fibrin Glue group ranged from 40 to 80 years while the age of patients in control group ranged from 48 years to 67 years with (P value=.492). These findings coincide with the study performed by Miri Bonjar MR et al,[15] with a total of 60 women enrolled into the study. The mean age of all participants in this study was 59.1 (S.D:±12.0 years (Range 33 to 78).

In the current study, the patients subjected to assessment of comorbidities and the study showed that there was no significant difference between the Fibrin Glue group and the control group. This agrees with the study performed by Fawzy A et al,[16] during the period from December 2014 to January 2017 over forty female patients with stage I and II breast cancer and found that there is no significant difference between the Fibrin Glue group and the control groups in the patients' comorbidities.

In the present study, there were no statistically significant differences between the groups regarding the clinical presentation with most cases (14 patients (93.3%) in each group) presented by breast lump. This agrees with the finding of Ayoade BA et al,[17] who conducted his study at Olabisi Onabanjo University Teaching Hospital on 121 patients and found that most cases (91.7%) presented by breast lump.

In this study, there were no statistically significant differences between the groups as regard to preoperative diagnostic and metastatic work-up. Mammography and Tru-cut biopsy were the main diagnostic tools and CT chest, CT abdomen &pelvis and bone scan were the routine metastatic work up. This coincides with the finding of Mann RM et al,[18] who included 18 studies in his study and found that the sensitivity of mammography and physical examination ranged between 88% and 98%.

In our study, there were no statistically significant differences between the two studied groups regarding the tumor characteristics in the form of the preoperative tumor size, pathology and the clinical stage. This agrees with the finding of Cipolla C et al,[19] who conducted a randomized clinical trial at a single center with a specialist breast unit to test the efficacy and safety of fibrin glue in the prevention of postoperative axillary seroma formation. Between July 2007 and August 2009, 160 patients were enrolled in the study.

In the present study, there were no statistically significant differences between the two studied groups as regards to receiving preoperative chemotherapy or number of resected axillary lymph node. While Zieliński J et al,[20] who conducted a prospective study on 150 patients with breast cancer revealed that receiving neoadjuvnt chemotherapy and the number of the resected axillary lymph nodes had effect on the volume of the postoperative seroma. Patients who received prior neoadjuvant chemotherapy had lower cumulative total seroma volume collected through drainage (Mean 1126 ml vs 1427 ml; p=0.024) and patients who had 16 or more resected axillary lymph nodes had significantly higher volume of seroma collected compared with patients who had 15 or less resected lymph nodes (Mean 652 ml vs 558ml; P value=.05).

The current study showed that there is no statistically significant difference in postoperative complication rates. However, there is statistically significant difference favoring fibrin glue group in the incidence of seroma formation and its cumulative amount, the amount of fluid drained in first postoperative day, hospital stay time, and time passed to remove the drain. The drained fluid in first postoperative day (Mean ±SD) was (103.33±22.89 cc) for fibrin glue group compared to (216.67±52.33 cc) in control group (P value <0.001), The postoperative cumulative amount of serous fluid (Mean ± SD) was (1340.0±202.84 cc) in fibrin glue group compared to (521.7±68.6 cc) in control group with (P value <0.001). The hospital stay time (Mean ± SD) in fibrin glue group was (2.0±0.0) day compared to (4.27±1.03) day in control group (P value <0.001), and the time passed to remove drain (Mean±SD) was (7.67±0.72) days to fibrin glue group compared to (15.07±1.98) days in control group (P value< 0.001). This agrees with the study performed by Azhar Y et al,[21] who reported that there is no statistically significant difference in postoperative 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 postoperative day, incidence of seroma and its amount, hospital stay time, and time passed to remove the drain. The drained fluid in first postoperative 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).

Consistent with these findings, the study by Gilly FN et al,[22] who reported information from 108 patients showed that there is significant difference in the hospital stay favoring the Fibrin Glue group. The mean postoperative hospital stay was 10.1 days (2.1) in the control group and 8.0 days (1.6) in the Fibrin Glue group (P= 0.006). Also, Moore et al,[13] 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. Similarly, Langer et al,[23] 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.

In contrast to the present study, Fu MR et al,[24] who collected his data from 130 patients and revealed that there was significant difference for postoperative arm lymphedema between the patients who had seroma and who did not, also, Burak et al,[25] whose results using only bovine thrombin failed to get significant difference between the study group and the control group regarding the period till drain removal , similar results obtained by Vaxman et al,[26] who reported that with the use the fibrin glue the total drain output increased. Moreover, Dinsmore et al,[27] stated that not only the drainage volume increased but also the overall complication rate increased. 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.

Conclusion

Many methods were suggested to decrease the seroma incidence and amount. Fibrin glue was one of these modalities. Our 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 passed till the drains were removed.

We recommend performing further studies on larger population scale with long follow up duration to validate our results.

Consent and ethical approval

The details of the operation technique and complications were explained to the patient and an informed written consent was obtained.

Approval by the ethical committee for research in Tanta Faculty of medicine was obtained before initiating this study.

Conflict of interest

Authors have declared that no conflict of interests exists.

Reference

1. Lukong KE, Ogunbolude Y, Kamdem JP: Breast cancer in Africa: Prevalence, treatment options, herbal medicines, and socioeconomic determinants. ***Breast Cancer Research and Treatment.*** 2017; 166(2): 351-65.

2. Conversano A, Mazouni C, Thomin A, et al: Use of low-thrombin fibrin sealant glue after axillary lymphadenectomy for breast cancer to reduce hospital length and seroma. ***Clinical Breast Cancer.*** 2017; 17(4): 293-7.

3. Benevento R, Santoriello A, Pellino G, et al: The effects of low-thrombin fibrin sealant on wound serous drainage, seroma formation and length of postoperative stay in patients undergoing axillary node dissection for breast cancer. A randomized controlled trial. ***International Journal of Surgery.*** 2014; 12(11): 1210-1215.

4. H Turner EJ, Benson JR, Winters ZE: Techniques in the prevention and management of seromas after breast surgery. ***Future Oncology.*** 2014;10(6):1049-63.

5. Hart AM, Duggal C, Pinell-White X, et al: A prospective randomized trial of the efficacy of fibrin glue, triamcinolone acetonide, and quilting sutures in seroma prevention after latissimus dorsi breast reconstruction. ***Plastic and Reconstructive Surgery.*** 2017; 139(4): 854e-863e.

6. De Luca A, Tripodi D, Frusone F, et al: Retrospective evaluation of the effectiveness of a synthetic glue and a fibrin-based sealant for the prevention of seroma following axillary dissection in breast cancer patients. ***Frontiers in Oncology.*** 2020; 10.

7. Eichler C, Fischer P, Sauerwald A, et al: Flap adhesion and effect on postoperative complication rates using Tissuglu® in mastectomy patients. ***Breast Cancer.*** 2016; 23(3): 486-90.

8. Docimo G, Limongelli P, Conzo G, et al. Axillary lymphadenectomy for breast cancer in elderly patients and fibrin glue. ***BMC Surgery.*** 2013; 13(2): 1-5.

9. Van Bastelaar J, Granzier R, van Roozendaal L, et al: A multi-center, double blind randomized controlled trial evaluating flap fixation after mastectomy using sutures or tissue glue versus conventional closure: Protocol for the seroma reduction after mastectomy (SAM) trial. ***BMC Cancer.*** 2018; 18(1): 1-8.

10. Sajid MS, Hutson K, Kalra L, et al: The role of fibrin glue instillation under skin flaps in the prevention of seroma formation and related morbidities following breast and axillary surgery for breast cancer: A meta-analysis. ***Journal of Surgical Oncology.*** 2012; 106(6): 783-95.

11. Van Bastelaar J, Theunissen LL, Snoeijs MG, et al: Flap fixation using tissue glue or sutures appears to reduce seroma aspiration after mastectomy for breast cancer. ***Clinical Breast Cancer.*** 2017; 17(4): 316-21.

12. Christodoulakis M, Sanidas E, De Bree E, et al: Axillary lymphadenectomy for breast cancer–the influence of shoulder mobilisation on lymphatic drainage. ***European Journal of Surgical Oncology (EJSO)***. 2003; 29(4): 303-5.

13. Moore M, Burak JR WE, Nelson E, et al: Fibrin sealant reduces the duration and amount of fluid1 drainage after axillary dissection: A randomized prospective clinical trial. ***Journal of the American College of Surgeons.*** 2001; 192(5): 591-9.

14. Moore MM, Nguyen DH, Spotnitz WD: Fibrin sealant reduces serous drainage and allows for earlier drain removal after axillary dissection: A randomized prospective trial. ***The American Surgeon.*** 1997: 63(1); 97-102.

15. Miri Bonjar MR, Maghsoudi H, Samnia R, et al: Efficacy of fibrin glue on seroma formation after breast surgery. ***International Journal of Breast Cancer.*** 2012.

16. Fawzy A, Gaber A: Role of fibrin glue in seroma reduction after modified radical mastectomy. ***International Surgery Journal***. 2017: 4(7); 2103-9.

17. Ayoade BA, Tade AO, Salami BA: Clinical features and pattern of presentation of breast diseases in surgical outpatient clinic of a suburban tertiary hospital in South-West Nigeria. ***Nigerian Journal of Surgery.*** 2012; 18(1).

18. 18) Mann RM, Hoogeveen YL, Blickman JG, et al: MRI compared to conventional diagnostic work-up in the detection and evaluation of invasive lobular carcinoma of the breast: A review of existing literature. ***Breast Cancer Research and Treatment.*** 2008; 107(1): 1-4.

19. Cipolla C, Fricano S, Vieni S, et al: Does the use of fibrin glue prevent seroma formation after axillary lymphadenectomy for breast cancer? A prospective randomized trial in 159 patients. ***Journal of Surgical Oncology.*** 2010: 101(7); 600-3.

20. Zieliński J, Jaworski R, Irga N, et al: Analysis of selected factors influencing seroma formation in breast cancer patients undergoing mastectomy. ***Archives of Medical Science.*** 2013; 9(1): 86-92.

21. Azhar Y, Maududy Ai, Dalimoenthe Nz: Role of autologous fibrin glue (AFG) to reduce drainage volume after modified radical mastectomy for breast cancer. ***Indonesian Journal of Cancer.*** 2021: 15(4): 173-177.

22. Gilly FN, Francois Y, Sayag-Beaujard AC, et al: Prevention of lymphorrhea by means of fibrin glue after axillary lymphadenectomy in breast cancer: Prospective randomized trial. ***European Surgical Research.*** 1998: 30(6); 439-43.

23. Langer S, Guenther JM and DiFronzo LA: Does fibrin sealant reduce drain output and allow earlier removal of drainage catheters in women undergoing operation for breast cancer?. ***The American Surgeon.*** 2003: 69(1); 77.

24. Fu MR, Guth AA, Cleland CM, et al: The effects of symptomatic seroma on lymphedema symptoms following breast cancer treatment. ***Lymphology.*** 2011; 44(3): 134-43.

25. Burak Jr WE, Goodman PS, Young DC, et al: Seroma formation following axillary dissection for breast cancer: Risk factors and lack of influence of bovine thrombin. ***Journal of Surgical Oncology.*** 1997: 64(1); 27-31.

26. Vaxman F, Kolbe A, Stricher F, et al: Does fibrin glue improve drainage after axillary lymph node dissection? Prospective and randomized study in humans. ***European Surgical Research.*** 1995: 27(5); 346-52.

27. Dinsmore RC, Harris JA and Gustafson RJ. Effect of fibrin glue on lymphatic drainage after modified radical mastectomy: A prospective randomized trial. ***The American Surgeon.*** 2000; 66(10): 982.