

The Difference of Interleukin-6 Level and Seroma Volume Between Quilting and Conventional Suture After Modified Radical Mastectomy

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ABSTRACT

Background: Modified radical mastectomy is the standard surgical therapy for locally advanced breast cancer (LABC). Seroma as the most common complication after MRM has many morbidities. Quilting suture after MRM to prevent dead space consistently decreased seroma formation on many studies. However, it is not widely applied in Indonesia. Interleukin-6 (IL-6) on the other hand has also been known to affect seroma production. However, the correlation between these two has not been well studied. **Objective:** To know the difference of IL-6 level and seroma volume between quilting and conventional suture after MRM in LABC. **Methods:** This study is a randomized controlled trial conducted from April to July 2022 with permuted block randomization which allocated samples that suited the inclusion and exclusion criteria into intervention group (quilting suture) and control group (conventional suture). **Results:** The average difference of total seroma volume between the two groups were 399.25 mL ($p=0.000$). The average difference of Interleukin-6 level between the two groups was 3160.75 mL ($p=0.000$). The result of linear regression shows that the total time needed for wound closure ($p=0.029$; 95%CI: 183.291 - 592.605) and the quilting technique ($p=0.018$; 95%CI: 1727.971 - 8101.730) were two variables that affected the level of IL-6 in the seroma and were statistically significant. Adjusted R^2 value was 0.118 indicating the effect of the two variables on the change of seroma volume was 11.8%. **Conclusion:** Quilting suture significantly reduced the total volume of seroma as well as the IL-6 level in the seroma after MRM in LABC. IL-6 level was also significantly affected by the duration needed for wound closure.

Keywords: modified radical mastectomy; quilting suture; interleukin-6; seroma

INTRODUCTION

Locally Advanced Breast Cancer (LABC) based on the U.S. National Comprehensive Cancer Network is defined as the most advanced breast cancer that fulfills the criteria of stage III breast cancer: 1) tumor with the size of >5cm with regional lymphadenopathy (N1-3), 2) tumor of any size with direct extension to the chest wall, skin or both (including ulcer or satellite nodule) aside from regional lymphadenopathy, 3) regional lymphadenopathy (clinically fixed axillary lymph nodes or internal mammary, supraclavicular or infraclavicular lymph nodes) aside from tumor stage. [1]. New incidence of LABC were 300-450 thousands cases per year. In Indonesia, the prevalence was 50% while in Bali it reached the number of 76.3% of all breast cancer cases [2].

LABC is divided into the operable and inoperable group depending on the ability to gain negative margins on the histopathology examination after the initial surgical approach.

In operable cancer, Modified Radical Mastectomy (MRM) has been the standard surgical therapy of LABC which involves total removal of the breast and most or all of the ipsilateral axillary lymph nodes [3]. MRM is a surgical removal of all breast tissue along with the tumor, nipple areola complex, skin above the tumor and pectoral fascia and level I-II axillary dissection, with lower local recurrence [4].

There are some complications that can be caused by MRM surgery. The most common one is the formation of postoperative seroma with an incidence of 15.5-90%. Seroma is a collection of subcutaneous serous fluid containing blood plasma and or lymph fluid that can be located under the skin flap or in dead space in the axillary area. Seroma can develop into clinically significant seroma (CSS) which is a risk factor for infection in the operating area because it forms an entry point for microorganisms.

Seroma in most cases is not a life-threatening complication, however it has serious morbidities associated with other complications such as skin flap necrosis, pain, infection, delayed wound healing, predisposition to sepsis and lymphedema. Seroma may also stretch the skin causing discomfort to the patient. All these conditions will increase the length of stay and slow down the healing process of post-MRM patients [5].

There have been many studies conducted related to the prevention of post-MRM seroma formation. Closure of the dead space with the use of skin flap fixation is concluded as one of the most effective techniques with consistent results. This technique minimized lymphatic drainage and serum leakage, held the skin flap securely in the chest wall structure and allowed for faster secretion of discharge/seroma [6]. Despite all the findings above, the majority of surgeons in Indonesia tend to use the conventional suture technique with two-drain insertion although the quilting suture with one-drain insertion showed a better outcome with minimal complications. Studies related to quilting technique are still rare in Indonesia.

The formation of seroma on the other hand is also known to be influenced by other factors other than the type of surgery, namely postoperative proinflammatory cytokines that is Interleukin-6 (IL-6) [7]. IL-6 detected on the wound or wound fluid has the potential as a marker of tissue damage [8]. However, there is no study identified the clear correlation between the post-MRM technique to the seroma production and IL-6 level.

RESEARCH METHODS

This study was a pure experimental study with single-blinded randomized controlled trial (RCT) design with post-test only. Each eligible subject was randomized so that they had the same opportunity to be selected into the intervention group (quilting suture technique) and control group (conventional suture technique). Each subject did not know the post-MRM suture technique used, but the researcher who was directly involved in it knew every given intervention. Each subject in the two groups was then followed-up 24 hours after MRM when the seroma samples were taken for the measurement of interleukin-6 levels.

Follow-up of the seroma volume was continued every 24 hours until drain removal or when seroma production was <50cc/24 hours to obtain total seroma volume. This research has received an ethical suitability letter from the Research Ethics Committee of Faculty of Medicine, Udayana University / Prof. Dr. IGNG Ngoerah General Hospital to ensure the ethical suitability of the research. This study was conducted in Prof. Dr. IGNG Ngoerah Denpasar General Hospital between November 2021 to July 2022, specifically in Oncology Surgery division. Samples were taken with consecutive random sampling with permuted block randomization technique with the consideration that each subject will have the same opportunity to be selected into the intervention or control group and at all times will ensure comparability between the two groups in terms of numbers.

RESULTS

A total of 39 samples were used in this study, 19 samples in the non-quilting group and 20 samples in the quilting group. The mean age of the non-quilting group was 50.63 ± 10.38 years and in the quilting group was 52.90 ± 10.57 years. The entire sample was in stage III according to the AJCC. In terms of subtypes, the non-quilting group was dominated by Her-2 subtype (31.6%) while the quilting group was dominated by Luminal B subtype (45%). Most of the samples in both groups had negative lymphovascular invasion (LVI) status (non-quilting group 13 (68.4%); quilting group 12 (60%)) while tumor-infiltrating lymphocyte (TIL) was mostly mild positive (non-quilting group 12 (63, 2%); quilting group 12 (60%)). There were no hematomas and surgical wound infections found in both groups. In the non-quilting group, the mean blood loss during surgery was 56.32 ± 13.83 mL while in the quilting group it was 54.50 ± 9.98 mL. The mean time of surgical wound closure in the non-quilting group was 30.89 ± 3.81 minutes and in the quilting group was 47.80 ± 3.49 minutes. The average duration to drain removal in the non-quilting group was 7.21 ± 0.92 days while in the quilting group was 4.90 ± 0.72 days. The average length of stay in the non-quilting group was 2.32 ± 0.58 days and in the quilting group was 2.10 ± 0.45 days. In the comparative analysis, only the time need for wound closure and duration to drain removal variables showed significant results ($p < 0.001$).

TABLE 1: Characteristics of respondents and the comparison between the non-quilting (conventional) suture and quilting suture groups.

Variables	Non-Quilting Group (N: 19)		Quilting Group (N:20)		p-value
	Frequency	Mean \pm SD	Frequency	Mean \pm SD	
AGE		50.63 ± 10.38 years		52.90 ± 10.57 years	0.503
Diabetes Mellitus	19 (100%)		20 (100%)		N/A
Hyper-tension	19 (100%)		20 (100%)		N/A
Subtype					
Luminal A	5 (26.3%)		3 (15%)		0.452
Luminal B	4 (21.1%)		9 (45%)		
Her-2	6 (31.6%)		5 (25%)		
TNBC	4 (21.1%)		3 (15%)		

Variables	Non-Quilting Group (N: 19)		Quilting Group (N:20)		p-value
	Frequency	Mean ±SD	Frequency	Mean ± SD	
LVI					
Negative	13 (68.4%)		12 (60%)		0.584
Positive	6 (31.6%)		8 (40%)		
TIL					
Negative			5 (25%)		0.233
Mildly Positive	3 (15.8%)		12 (60%)		
Moderately Positive	12 (63.2%)		1 (5%)		
Strongly Positive	4 (21.1%)		2 (10%)		
Needs for Seroma Aspiration					
Negative	14 (73.7%)		19 (95%)		0.91
Positive	5 (26.3%)		1 (5%)		
Limited Abduction					
negative	17 (89.5%)		19 (95%)		0.605
positive	5 (26.3%)		1 (5%)		
Hematoma					
Negative	19 (100%)		20 (100%)		N/A
Surgical Site Infection					
Negative	19 (100%)		20 (100%)		N/A
Intra-operative Blood Loss		56.32±13.83 mL		54.50±9.98 mL	0.604
Duration for Wound Closure after MRM		30.89±3.81 minutes		47.80±3.49 minutes	0.000
Time to Drain Removal		7.21±0.92 days		4.90±0.72 days	0.000
Length of Stay		2.32±0.58 days		2.10±0.45 days	0.205

The correlation between quilting technique and seroma production was analyzed with bivariate analysis. Unpaired t-test analysis was performed because the independent variable (technique) was categorical and the seroma variable was numerical. Bivariate analysis

showed that the mean total seroma production in the non-quilting group was 726.63±151.51 mL while in the quilting group was 315.40±112.12 ml. The mean difference was 399.25 mL which was statistically significant (p=0.000).

TABLE 2: Bivariate analysis result.

Variable	Non-quilting Mean± SD	Quilting Mean± SD	Mean difference	p-value
Total seroma	726.63 ±151.51 ml	315.40±112.12 ml	399.25	0.000

The correlation between quilting technique and seroma IL-6 level was analyzed in two stages. In bivariate analysis, unpaired t-test analysis was performed because the independent variable (technique) was categorical and the IL-6 variable was numerical.

Bivariate analysis found that the mean seroma IL-6 level in the non-quilting group was 4935.37±6103.79 pg/mL, while in the quilting group was 1723.90±445.943 pg/mL. The mean difference was 3160.75 mL, which was statistically significant (p=0.028).

TABLE 3: Bivariate Analysis.

Variable	Non-quilting Mean± SD	Quilting Mean± SD	Mean difference	p-value
IL-6 seroma	4935.37± 6103.79 pg/mL	1723.90± 445.943 ml	3160.75	0.028

Then, to see the independent effect of the quilting technique, a multivariate analysis was performed. Linear regression analysis was used because the target variable (IL-6 seroma level) was numerical. The results of linear regression showed that the time needed for wound closure (p=0.029; 95% CI: 183.291 - 592.605) and surgical technique used (quilting

suture) (p=0.018; 95% CI: 1727.971- -8101.730) were two variables that significantly affected IL-6 levels in the seroma. Adjusted R2 value obtained was 0.118 which indicated that the effect of these two variables on the change of seroma volume was 11.8% and the rest was influenced by other variables which were not studied in this research.

TABLE 4: Multivariate Analysis.

Variable	B	Standard error	P	95%CI
Time for wound closure	204.657	191.097	0.029	183.291- 592.605
Quilting technique	-4458.620	4073.355	0.018	1727.971-8101.730

DISCUSSION

This study showed that age, tumor subtype, lympho-vascular invasion, tumor-infiltrating lymphocyte status, postoperative complications, the need for seroma aspiration and length of hospital stay were not significantly different between the two groups. On the other hand, the total seroma volume, the time needed for surgical wound closure and the duration needed for drain removal were found to be significantly different in the quilting suture group compared to the conventional group after modified radical mastectomy (MRM). The quilting group had a mean seroma volume of 315.40 ± 112.12 mL, while the conventional group had a mean seroma volume of 726.63 ± 151.51 mL, which was statistically significant ($p = 0.000$). To these days, research that specifically discusses the comparison of seroma volume between the two techniques is still very limited. The results of this study are supported by a retrospective multicentre study conducted by Van Bastelaar which involved 180 patients who underwent mastectomy with or without axillary clearance. The results showed that there was less clinically proven seroma formation in patients with flap fixation group (35.9% vs. 59.1%, $p = 0.002$). More patients underwent seroma aspiration in the control group (15.2% vs. 43.2%, $p < 0.001$). The results of this study found that there was a significant difference in the number of seroma aspirates in the two groups and showed a higher number of seroma aspirations per patient in the control group ($p < 0.001$) [9].

The findings of this study are also in line with a systematic review conducted by van Bastelaar and van Roozendaal who found a decrease in seroma formation as well as complications caused by seroma in patients using the quilting technique compared to conventional technique [9]. In addition, a previous study by Myint also showed a decrease in the percentage of seroma formation after modified radical mastectomy. As much as 30% of the total patients experienced seroma formation in the control group compared to 14.3% in the intervention group ($p = 0.041$). Lower number of aspiration was found in the quilting suture (1.919 ± 0.801 vs. 2.806 ± 0.285 ; $p = 0.043$) [10]. A decrease in the incidence of seroma was also observed in a study by Wolden reporting an incidence of 80.5% compared to 22.5% in patients with quilting suture technique ($p < 0.01$). Several studies suggest the formation of seroma after mastectomy is determined by the amount of dead space that can be filled with fluid. Therefore, skin flap fixation using quilting technique gives advantage on preventing seroma production for it minimizes the dead space formed after breast removal [11].

Another study by Gonzales and Hashemi reported that the only statistically significant factor influencing seroma formation was the type of surgery.

The study showed that seroma rates were found to be higher on MRM compared to wide local excision and axillary dissection (BCS) [12,13]. Extensive dissection on mastectomy and axillary lymphadenectomy will damage several blood and lymphatic vessels, followed by the discharge of blood and lymphatic fluid from a large surface area which will further increase the potential for seroma formation [14]. Accumulation of seroma will lift the flap from the chest wall and axilla by inhibiting its attachment to the underlying tissue. Therefore, seroma will have an impact on a significant increase in morbidity such as wound hematoma, delayed wound healing, wound infection, wound dehiscence, prolonged hospitalization, delayed recovery as well as the initiation of adjuvant therapy [15].

The findings of this study also showed a shorter duration to drain removal in the quilting suture group with 1 drainage (axillary drainage) (4.90 ± 0.72 days) compared to the conventional group which used 2 drainages (tumor bed or pectoral drainage and axillary drainage) (7.21 ± 0.92 days). The difference was statistically significant ($p = 0.000$). This result was beneficial because early drain removal proved to have a good impact on post-MRM patients. Based on the research from Ramadanus, faster drainage release on the first day was not associated with seroma production within 7 days after discharge (62.5% vs 60%) and total seroma production ($p = 0.437$) but provided better quality of life based on the symptom scale ($p = 0.002$) [16].

These findings are also directly proportional to the study conducted by Wolde involving 176 patients who underwent mastectomy with axillary lymph node dissection. The control group ($n = 87$) consisted of patients who underwent surgery followed by low vacuum drainage in the axilla. A total of 89 consecutive patients underwent surgery with the quilting suture technique on the skin flap. The results showed that fewer patients in the quilting group had clinically significant seroma (22.5% vs 80.5%, $p = 0.000$). The group experiencing seroma had a fewer number of aspirations (2.4 vs. 4.86, $p = 0.015$), as well as a lower incidence of surgical site infection (10% vs. 31%, $p = 0.001$) in the quilting group [11].

A retrospective observational study ($n = 119$) was conducted by Ouldamer in patients undergoing mastectomy with or without axillary clearance using the quilting technique. The results showed a significant reduction of clinically evident seroma in the quilting group (17% vs. 51.7%, $p < 0.001$). Length of hospital stay was significantly shorter in the quilting group (4.24 days vs. 5.43 days, $p < 0.0001$) [17].

Our study found consistent results regarding shorter length of stay in the quilting group (2.0 +/- 0.45 days vs. 2.32 +/- 0.58 days) although it was not statistically significant ($p = 0.205$). This may be due to the fact that in the postoperative period in the previous studies, clinical observations were carried out in the hospital from the day when the surgery was performed until the day when the drain was removed. In contrast to our study in which if there were no significant complaints or complications occurred after surgery and axillary drainage was found to be functional, patients were allowed for discharge with axillary drainage still in place on the second postoperative day. The observation was later done by the patient every 24 hours until drain removal.

Another study conducted by Khater involved 120 patients who underwent modified radical mastectomy. In the first group, quilting suture was applied using 2/0 Vicryl suture and in the second group mastectomy was performed without quilting suture (drain-only group). Based on the volume of aspirated seroma, the study obtained a significantly higher number of aspirates in the drain-only group (4.7 vs 2.1, $p < 0.001$). The results also showed that seroma was found in 20% of patients undergoing quilting and in 78.3% of patients in the drainage-only group ($p < 0.001$) [18].

Several other researches also studied about the prevention of post-mastectomy seroma formation using skin flap fixation to minimize lymph fluid and serum leakage, secure skin flaps to chest wall structures, eliminate dead space, and allow faster discharge of secretions. Many types of methods such as the use of different suction drainage, shoulder joint immobilization, fibrin sealants, thrombin sealants and quilting sutures have been investigated to promote primary healing and minimize seroma formation. Some studies used quilting sutures along with pectoral drainage to reduce the chance of seroma formation, some studies used quilting sutures with axillary drainage only to minimize seroma formation, while some even used no drainage at all. The number of drainage tubes, the administration of neoadjuvant chemotherapy and the use of fibrin sealant as well as the number of lymph nodes removed were not proven to have a significant effect on seroma formation consistently in four different studies [19].

In general, modified radical mastectomy increased IL-6 levels systemically ($p < 0.001$) as reported by Matsumoto in 2018. The elevated concentration of IL-6 was also found locally in the patient's seroma. The increased concentrations of IL-6 were known to be associated with surgery and trauma, also correlated with the severity of the injury resulting from the procedures. Elevated IL-6 after pathological conditions is associated with poor prognosis or treatment failure [20].

This study found a significant difference between the levels of IL-6 in the seroma of the quilting suture group compared to the conventional group. Patients who received quilting suture had a mean seroma IL-6 level of 1723.90 ± 445.943 pg/mL and conventional

suturing group had an average IL-6 level of 4935.37 ± 6103.79 pg/mL. This finding was supported by the previous research concluded that quilting suture technique provided better primary healing and minimize seroma formation in post-mastectomy patients. Seroma is an increase in serous fluid in response to fibrinolytic activity and an inflammatory reaction. Previous studies reported post-MRM seroma had increased levels of IL-6, tissue inhibitor of metalloproteinase (TIMP-1) and tumor growth factor- β (TGF- β) as a response to inflammation and an attempt to promote wound healing. Another study also supported the findings above by showing that cumulative seroma production of 750 mL had significantly higher IL-6 levels ($p = 0.001$) as well as IL-8 levels ($p = 0.0001$) (Szecsi et al, 2012). One study also reported an average IL-6 level after MRM of $1,416 \pm 214$, $2,484 \pm 441$ and $1,664 \pm 310$ pg/mL each using a scalpel, electrocautery and ultrasonic dissector, respectively [21].

The high concentration of IL-6 after modified radical mastectomy is considered to be an important mediator of the acute phase response involving inflammatory components including pro-inflammatory cytokines that play a role in wound healing. IL-6 as an anti-inflammatory cytokine also has a relationship with the process of tumor development and malignancy and may contribute to inflammation-associated tumorigenesis. IL-6 signalling can also modulate T cell resistance to apoptosis. IL-6 secretion in the tumour microenvironment on one hand will play a role in immune defence to attack tumours but on the other hand may promote tumour cell proliferation during activation of signal transducers and transcriptional activators (STAT 3). Increased IL-6 in carcinogenesis can cause tumor progression by increasing the ability of angiogenesis, migration, invasion and proliferation thereby increasing recurrence, while low levels of IL-6 cytokines are associated with the effectiveness of the therapeutic response [22].

Higher levels of IL-6 in patients with conventional suture compared to flap fixation group were reported in a previous study by van Bastelaar in 2019 [9]. However, the decrease was not significant compared to the group with conventional suturing techniques with flap fixation-suture and flap fixation glue (54.21 ± 48.59 vs. 47.71 ± 29.59 vs. 44.58 ± 27.83 ; $p = 0.785$). It was also shown that an increase in IL-6 concentration was significantly associated with a decrease in seroma formation after 3 months after MRM (OR 0.952; 95% CI 0.90-0.99; $p = 0.027$). However, body mass index (BMI) and weight of the resected specimens were also associated with increased levels of IL-6 in the seroma of post-mastectomy patients ($p = 0.001$ and $p = 0.003$ respectively). Our study found that with the intervention or relatively greater trauma resulting from the quilting suture technique compared to the conventional one, IL-6 levels were significantly higher in the conventional suturing group or the control group and were significantly associated with total seroma volume ($p = 0.018$).

This result was in line with the theory that flap fixation would reduce the inflammatory process by minimizing lymphatic and serum leakage allowing seroma secretion/discharge which was a product of the inflammatory process that disturbed the wound healing process. The significance of the association between IL-6 and seroma production is important considering that seroma is the most common complication (up to 90% of the total post-MRM complications) with many negative clinical impacts including discomfort, surgical site infection, delayed wound healing, repeated aspiration and visits as well as increased costs for hospital visits.

CONCLUSION

Based on the result of the research, it can be concluded that quilting suture technique significantly reduced the total seroma volume and Interleukin-6 level in the seroma after modified radical mastectomy in locally advanced breast cancer. The concentration of IL-6 was also significantly affected by the duration needed for wound closure.

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