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Original Article

Lymphatic Ligation versus Conventional Axillary Lymph Node Dissection in Breast Cancer Patients: A Randomized Control Trial

Nawin Kuntaraksa, MD*

**Department of Surgery, Surin Hospital, Surin, Thailand*

Abstract

Background and Objective: **Seroma was a common complication of breast cancer surgery. It is a source of significant morbidity that led to delay adjuvant treatment. The primary objective was to evaluate seroma formation in a comparison between the lymphatic ligation technique and conventional axillary lymph node dissection.The secondary objective was to evaluate the factors affecting seroma formation.**

Materials and Methods: **A randomized control trial was conducted between January 2014 and November 2017.Sixty eight consecutive patients underwent mastectomy with axillary lymph node dissection by one experienced surgeon. The patients were randomly assigned to Group1 (lymphatic ligation) (n=34) and Group 2 (conventional surgery) (n=35).**

Results: **18 patients developed seroma (26.09%) with 8 (23.53%) patients were in the lymphatic ligation group and 10(28.57%) patients were in the conventional group. No statistical significance was found in seroma formation ($p = 0.633$), drain duration ($p = 0.238$) or total drain volume ($p = 0.330$) between the two groups. Lymphatic ligation was statistically and significantly correlated with longer operative time ($p = 0.002$). Age, BMI, total drain volume and drain dislodgement were significant factors influencing seroma formation ($p = 0.005$, $p = 0.002$, $p = 0.008$, $p = 0.015$, respectively). Multivariate analysis showed age and BMI were significant factors influencing seroma formation ($p = 0.008$, $p = 0.025$, respectively).**

Conclusion: **The lymphatic ligation technique could not reduce the incidence of seroma formation. Age, BMI were the factors influencing seroma formation in the patients undergoing mastectomy with axillary lymph node dissection.**

Keywords: Breast cancer, axillary dissection, seroma, lymphatic ligation

Correspondence address: *Nawin Kuntaraksa, Department of Surgery, Surin Hospital, Surin 32000, Thailand; Telephone: +66 8 1572 1527; Email: knawin21@gmail.com*

Introduction

Seroma is a common complication of breast cancer surgery occurring in 3-85 percent[1,2] of breast cancer patients after breast or axillary surgery. Seroma can also interfere with healing, increase morbidity and discomfort and lead to delayed adjuvant treatment.

Several surgical techniques have been reported to reduce seroma formation[3-8]. Khan S, et al.[4] reported low incidence of seroma and drain volume when harmonic scalpel was used. Harmonic scalpel dissection yields better outcomes compared to electrocautery. Flap coverage in dead space has shown a significant decrease in seroma formation[5,6]. Fibrin glue can reduce axillary lymphatic drainage but cannot reduce seroma formation[7]. Gong Y, et al.[8] reported axillary dissection by lymph vessel ligation and dead space closure as an effective approach to reducing the incidence of seroma formation.

The authors hypothesized that seroma was most likely to originate from lymph. The primary objective of this study was to evaluate seroma formation, drain duration and total drain volume compared between the lymphatic ligation technique and conventional axillary lymph node dissection in breast cancer patients. The secondary objective was to evaluate the factors affecting seroma formation.

Methods

A randomized control trial was conducted between January 2014 and November 2017. Ethical approval was granted by the Ethics Committee. All patients were scheduled for modified radical mastectomy or mastectomy with sentinel lymph node biopsy. Negative sentinel lymph node biopsy patients were excluded from the study. The inclusion and discontinuation criteria are shown in Table 1. Sample size was calculated from formula.

Informed consent was obtained from all eligible patients. The patients undergoing modified radical mastectomy were randomized preoperatively. Patients undergoing sentinel lymph node biopsies were randomized after positive pathologic reporting (using randomly ordered sealed envelopes). The patients were randomly assigned to either lymphatic ligation (Group 1) or conventional surgery (Group 2). All patients received antibiotic prophylaxis. After the pathologic reporting, axillary lymph node dissection was performed in the positive sentinel lymph node patients. Axillary dissection was done up to level 2 in all cases. In some patients, axillary dissection was done up to level 3 due to suspected level 3 of lymph node metastasis. In the lymphatic ligation group, blue stain lymphatic channels are identified and ligated, all of the tissues that had been connected from the axillary vein bundle to the specimen were ligated with No. 3-0 silk (Figure 1).

The thoracodorsal nerve, long thoracic nerve and some branches of the intercostobrachial nerve were identified and preserved. Electrocauterization was used to control bleeding. An active suction drain (Redivac Drain No. 10-12) was placed at the pectoralis

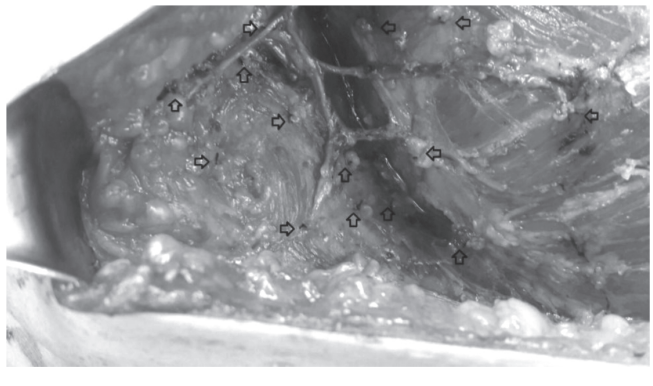

Figure 1 Axillary lymph node dissection by the lymphatic ligation technique (Arrow = ligation point)

Table 1 Shows the Inclusion and Discontinuation Criteria

Inclusion Criteria	Discontinuation Criteria
1. Breast cancer patients undergoing modified radical mastectomy	1. Major complication during surgery (accidental axillary vessel tearing, etc.)
2. Breast cancer patients undergoing mastectomy with sentinel lymph node biopsy	2. Refusal to continue in the study
3. Females older than 15 years	3. Incomplete data
	4. Loss during follow-up

muscle and in the axillary area (2 points). The drain was connected to a 600-ml suction bottle. The daily drain output was measured and recorded by the research team. The drain was removed when output was less than 30 ml for at least two consecutive days. The patients were discharged once at least one of the drains had been removed. The patients were instructed to monitor and observe the drain while they were at home. The daily drain output was recorded in a record sheet and the bottles were marked by the patients.The patients were scheduled for follow-up at one week after discharge and then weekly until the drain was removed. During the follow-up period, data collection was performed by the physician. Seroma was defined as a fluid collection by palpation on clinical examination. Needle aspiration was performed in patients with symptomatic seroma. All patients received adjuvant treatment if indicated by an oncologist. Follow-up appointments were made to monitor for early complications until three months after the operation.

Statistical Analysis

The studies were performed with STATA (Version 14) and data on characteristics were compared by using *t*-test. The Mann-Whitney U test was used to assess the statistically significant variances between the two groups. Chi-square and Fisher exact tests were applied to analyze the categorical variables. Logistic regression analysis was used to analyze the factors influencing seroma formation.

Results

A total of 87 patients with breast cancer were included; 19 patients with negative sentinel lymph node biopsies were excluded from the study, thereby leaving 68 consecutive patients undergoing mastectomy with axillary lymph node dissection by one experienced surgeon (50 modified radical mastectomy, 20 positive sentinel lymph node biopsy). There were two patients who had bilateral breast cancer had been treated on each side with the lymphatic ligation and conventional techniques. One patient was discontinued from the study due to accidental axillary vein tearing during the operation (Flow chart 1). The patients were randomly assigned to lymphatic ligation (n=34) and conventional surgery (n=35). No statistically significant differences were found between the two groups in terms of age,

Table 2 Demographic Data of the Patients

Data	Lymphatic ligation (n = 34)	Conventional (n = 35)	*p*-value
Age (years), mean (SD)	52.08 (11.58)	51.62 (10.70)	0.864
BMI* (kg/m^2), mean (SD)	22.89 (3.62)	22.94 (3.88)	0.953
Tumor size (cm), median (IQR)	4 (2.1, 6)	3 (2.5, 4.2)	0.258
Number of positive nodes, median (IQR)	2 (0, 8)	2 (1, 8)	0.917
Number of resected lymph nodes, median (IQR)	18.5 (15, 22)	17 (14, 20)	0.260
Neoadjuvant chemotherapy, n (%)	8 (23.53)	11 (31.43)	0.463
Operative time (min), mean (SD)	132.67 (19.28)	117.54 (19.68)	0.002
Blood loss (ml), median (IQR)	50 (30, 80)	40 (30, 55)	0.206
Drain dislodgement, n (%)	2 (5.88)	3 (8.57)	0.999
Total drain volume (10^2 ml), median (IQR)	7.85 (4.60, 16.38)	10.20 (6.60, 15.70)	0.330
Drain duration (days), median (IQR)	11 (7, 20)	15 (11, 19)	0.238
Seroma, n (%)	8 (23.53)	10 (28.57)	0.633
Complications, n (%)	4 (11.76)	3 (8.57)	0.710
Lymphedema	1 (2.94)	2 (5.71)	
Surgical site infection	1 (2.94)	0	
Wound dehiscence	1 (2.94)	0	
Superficial skin necrosis	0	1 (2.86)	
Dead during follow-up	1 (2.94)	0	

*BMI - body mass index

Flow chart 1 Flow Diagram of Participants

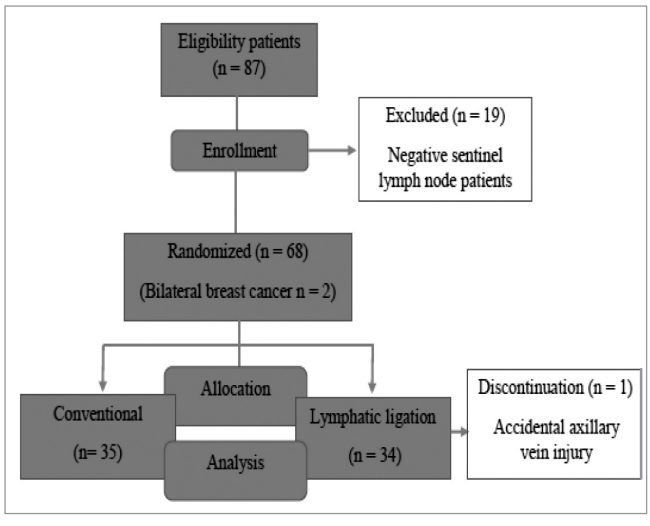

Figure 2

BMI, tumor size, number of positive nodes, number of resected lymph nodes, neoadjuvant chemotherapy, blood loss, drain dislodgement and complications. Longer operative time, however, showed statistically significant effects in lymphatic ligation (p = 0.002) (Table 2).

Seroma formation was developed in 18 (26.09%) operated breasts, including, 8 (23.53%) in the lymphatic ligation group and 10 (28.57%) in the conventional group (p = 0.633).

The drain duration in the lymphatic ligation group was lower than that of the conventional group (11 vs. 15 days), but with no statistically significant difference (p = 0.238). The total drain volume in the lymphatic ligation group was lower than that of the conventional group (785 vs. 1,020 ml), but with no

Table 3 Factors Affecting Seroma Formation

Data	Seroma (n=18)	Non-Seroma (n=51)	*p*-value	Univariate OR (95%CI)	Univariate *p*-value	Multivariate OR (95%CI)	Multivariate *p*-value
Age (years), mean (SD)	58.00 (2.01)	49.68 (11.11)	0.005	1.079 (1.02-1.14)	0.010	1.087 (1.02-1.15)	0.008
Ligation technique, n (%)							
No	10 (55.56)	25 (49.02)	0.633	1			
Yes	8 (44.44)	26 (50.98)		0.769 (0.26-2.26)	0.634		
Conventional technique, n (%)							
No	8 (44.44)	26 (50.98)	0.633	1	0.634		
Yes	10 (55.56)	25 (49.02)		1.300 (0.44-3.82)			
BMI* (kg/m^2), mean(SD)	24.63 (3.43)	22.31 (3.67)	0.002	1.207 (1.02-1.42)	0.028	1.234 (1.02-1.48)	0.025
Tumor size (cm), median(IQR)	3.5 (2.5, 5.4)	3 (2.5, 5)	0.716	1.044 (0.85-1.27)	0.670		
Number of positive node, median (IQR)	2 (1, 11)	2 (1, 7)	0.430	1.035 (0.96-1.11)	0.340		
Number of resected lymph node, median (IQR)	17 (13, 20)	18 (15, 21)	0.435	0.972 (0.89-1.05)	0.482		
Neoadjuvant chemotherapy, n(%)							
No	15 (83.33)	35 (68.63)	0.230	1			
Yes	3 (16.67)	16 (31.37)		0.437 (0.11-1.72)	0.238		
Operative time (min), mean (SD)	127.88 (15.38)	123.98 (22.43)	0.496	1.009 (0.98-1.03)	0.491		
Blood loss (ml), median (IQR)	50 (30, 80)	50 (30, 60)	0.540	1.000 (0.99-1.00)	0.922		
Total drain volume (10^2 ml), median (IQR)	14.55 (7.50, 22.40)	7.60 (5.10,13.20)	0.008	1.088 (1.01-1.16)	0.015		
Drain duration (days), median (IQR)	16 (12, 21)	15 (7, 19)	0.055	1.059 (0.98-1.13)	0.098		
Drain dislodgement, n(%)							
No	14 (77.78)	50 (98.04)	0.015	1			
Yes	4 (22.22)	1 (1.96)		14.285 (1.47-138.28)	0.022		

*BMI - body mass index

statistically significant difference ($p = 0.330$). The operative time in the lymphatic ligation group was longer than that of the conventional group with statistical significance (132.67 vs. 117.54 min, $p = 0.002$). Complications occurred in 7 patients, including 3 cases of lymphedema, 1 surgical site infection, 1 wound dehiscence and 1 superficial skin necrosis. One patient developed severe sepsis and died within two months after the operation due to the complications of adjuvant chemotherapy.

According to the findings of this study, the ages of the patients in the seroma group were significantly higher than those of the non-seroma group (58 vs. 49.68 years, $p = 0.005$). The BMI values in the seroma group were significantly higher than those in the non-seroma group (24.63 vs. 22.31 kg/m^2, $p = 0.002$). Total drain volume in the seroma group was significantly higher than that of the non-seroma group (1,455 vs 760 ml, $p = 0.008$). In the group of patients who had drain dislodgement before their follow-up appointments, 80 percent developed seroma. It can be concluded, therefore, that drain dislodgement before follow-up appointment was one factor that significantly affected seroma formation ($p = 0.015$). Multivariate analysis showed age and BMI were significance factors influencing seroma formation ($p = 0.008$, $p = 0.025$ respectively) (Table 3).

Discussion

According to the findings, seroma can interfere with the healing process, prolong treatment, increase patient discomfort, and delay adjuvant treatment. Lymph leakage is also believed to be an important factor in seroma formation[9-12].

Hashemi E, et al.[13] found type of surgery to be a predicting factor for seroma formation in breast cancer patients. Seroma formation in the modified radical mastectomy group was higher than that of the breast conserving therapy group (39 vs. 23%, $p = 0.04$). These findings are comparable to those of the study of Gonzalez EA, et al,[14] who found seroma formation in a modified radical mastectomy group to be significantly higher than a breast conserving therapy group (19.9 vs. 9.2%, $p = 0.01$).

The randomized clinical study of Gong Y, et al.[8] showed that lymph vessel ligation and dead space closure could significantly reduce the incidence of seroma formation after modified radical mastectomy. Some studies have reported flap fixation aimed at reducing dead space to show a significant decrease in seroma formation[5,6] . The results of this study indicate that the lymphatic ligation technique was unable to reduce seroma formation when compared to conventional axillary lymph node dissection in breast cancer patients.

In assessing the severity of seroma, which is defined as Grade 1 if asymptomatic, Grade 2 if symptomatic (medical intervention or simple aspiration indicated) and Grade 3 if intervention radiology or operative intervention is indicated[6,15]. According to this definition, all seroma formations in this study were categorized as Grade 2. However, Grade 1 was occasionally underestimated as having no impact on clinical care.

The incidence of seroma formation in this study was 26.09 percent, which makes it comparable to other literature.[1,2] The primary outcome of this study shows that the lymphatic ligation technique could not reduce seroma formation, drain duration and total drain volume when compared to conventional axillary lymph node dissection in breast cancer patients. Although there were no differences in complications between the two groups, the operative time in the ligation group was significantly longer. Total drain volume and drain duration were lower in the ligation group, but the difference was not statistically significant. Small sample size might have been a limitation in this study.

The literature[5,6,7] supported the dead space closure technique (sutured subcutaneous skin to underlying muscle) in terms of its ability to reduce the incidence of seroma formation.

The secondary outcome in this study showed that age and BMI were key factors influencing seroma formation. In contrast, Woodworth PA, et al.[16] reported that age and BMI had no impact on seroma formation. Woodworth PA, et al. further reported that surgical drains that remained in place longer represented the only factor affecting seroma formation. However, the study of Woodworth PA, et al. was a retrospective review, and many studies have shown that high body weight and BMI are the factors influencing seroma formation[17-19]. Zielinski J, et al.[20] reported that patients older than 60 years or those with BMI exceeding 30 were key factors in seroma formation. Zielinski J, et al. asserted that obese people had larger surgical incisions,

which implies greater likelihood and higher numbers of lymphatic vessels potentially damaged.

Conclusions

The lymphatic ligation technique could not reduce the incidence of seroma, total drain volume and drain duration when compared to conventional axillary lymph node dissection in breast cancer patients. The complications were no different between the two groups. Operative time was significantly longer in the lymphatic ligation group. Age and BMI were important factors influencing seroma formation in breast cancer patients undergoing mastectomy with axillary lymph node dissection.

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บทคัดย่อ **การผ่าตัดเลาะต่อมน้ำเหลืองที่รักแร้โดยวิธีผูกหลอดน้ำเหลืองเทียบกับการผ่าตัดแบบดั้งเดิมในผู้ป่วยมะเร็งเต้านม**

นาวิน ขันธรักษา, พ.บ.

โรงพยาบาลสุรินทร์

วัตถุประสงค์: 1. ศึกษาอัตราการเกิดภาวะน้ำเหลืองคั่งภายหลังผ่าตัดเทียบระหว่างการผ่าตัดโดยวิธีผูกหลอดน้ำเหลืองกับการผ่าตัดเลาะต่อมน้ำเหลืองบริเวณรักแร้แบบดั้งเดิม 2. ศึกษาปัจจัยที่มีผลต่อการเกิดภาวะน้ำเหลืองคั่งภายหลังการผ่าตัด

วิธีการศึกษา: ทำการศึกษาแบบการทดลองแบบสุ่มและมีกลุ่มควบคุมตั้งแต่เดือนมกราคม 2557 ถึงเดือนพฤศจิกายน 2560 ผู้ป่วยมะเร็งเต้านมจำนวน 68 รายได้รับการผ่าตัดเต้านมร่วมกับผ่าตัดเลาะต่อมน้ำเหลืองบริเวณรักแร้โดยศัลยแพทย์ 1 คน โดยทำการเลือกผ่าตัดแบบสุ่ม จำแนกเป็นกลุ่มที่ 1 ผ่าตัดโดยวิธีผูกหลอดน้ำเหลือง จำนวน 34 ราย กลุ่มที่ 2 ผ่าตัดเลาะต่อมน้ำเหลืองแบบดั้งเดิมจำนวน 35 ราย

ผลการศึกษา: จากการศึกษาพบภาวะน้ำเหลืองคั่งภายหลังการผ่าตัดทั้งหมด 18 ราย (26.09%) โดย8 ราย (23.53%) เกิดในกลุ่มที่ทำการผ่าตัดโดยวิธีผูกหลอดน้ำเหลือง อีก10 ราย (28.57%) เกิดในกลุ่มที่ทำการผ่าตัดเลาะต่อมน้ำเหลืองแบบดั้งเดิม ซึ่งไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ (p = 0.633) สำหรับระยะเวลาการใส่สายระบายและจำนวนของเหลวทั้งหมดจากสายระบายไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติเช่นกัน (p = 0.238, p = 0.330 ตามลำดับ) พบว่าระยะเวลาที่ใช้ในการผ่าตัดในกลุ่มทำการผ่าตัดโดยวิธีผูกหลอดน้ำเหลืองมากกว่าอย่างมีนัยสำคัญทางสถิติ (p = 0.002) การศึกษาพบว่า อายุ ค่าดัชนีมวลกาย จำนวนของเหลวทั้งหมดจากสายระบายและสายระบายหลุดก่อนกำหนดเป็นปัจจัยที่มีผลต่อการเกิดภาวะน้ำเหลืองคั่งภายหลังการผ่าตัด (p = 0.005, p = 0.002, p = 0.008, p = 0.015 ตามลำดับ) ซึ่งเมื่อใช้การวิเคราะห์หลายตัวแปรพบว่าอายุ ค่าดัชนีมวลกายเป็นปัจจัยที่มีผลต่อการเกิดภาวะน้ำเหลืองคั่งภายหลังการผ่าตัด (p = 0.008, p = 0.025 ตามลำดับ)

สรุป: การผ่าตัดเลาะต่อมน้ำเหลืองบริเวณรักแร้โดยวิธีผูกหลอดน้ำเหลืองไม่สามารถลดอัตราการเกิดภาวะน้ำเหลืองคั่งภายหลังการผ่าตัดเมื่อเทียบกับการผ่าตัดเลาะต่อมน้ำเหลืองแบบดั้งเดิม อายุ ค่าดัชนีมวลกายเป็นปัจจัยที่มีผลต่อการเกิดภาวะน้ำเหลืองคั่งภายหลังการผ่าตัดเต้านมร่วมกับการผ่าตัดเลาะต่อมน้ำเหลืองบริเวณรักแร้