Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i2.4655

A STUDY ON LOCAL INJECTION OF METHYLPREDNISOLONE ACETATE TO PREVENT SEROMA FORMATION AFTER MASTECTOMY IN 210 CASES.

Dr. Nischal Raj L[1*], Dr. Adnan Saeed[2], Dr. Arpitha M R[3], Dr. Sumalatha A[4], Dr. Avinash T R[5]

[1*]MBBS., MS., FMAS., MCH (surgical oncology), Consultant surgical Oncologist, Clear Medi Radiant Hospital, Vijay Nagar 3rd Stage, Mysore, Karnataka 570017.
E-mail id: dr.nisraj@gmail.com
[2]MBBS., MS., MCH (surgical oncology), Consultant surgical Oncologist, Clear Medi Radiant Hospital, Vijay Nagar 3rd Stage, Mysore, Karnataka 570017. E-mail id: dr.adnansaeed@gmail.com
[3]MBBS, MD, Senior Resident, Department of Biochemistry, JSS Medical College, Mysore.
E-mail id: mrarpitha@gmail.com
[4]MBBS, MD, DM, Consultant critical care Physician, Clear Medi Radiant Hospital, Vijay Nagar 3rd Stage, Mysore, Karnataka 570017. E-mail id: a.suma86@gmail.com.
[5]MBBS., MS (General Surgery), Assistant Consultant, Dept of oncosurgery, Clear Medi Radiant Hospital, Vijay Nagar 3rd Stage, Mysore, Karnataka 570017. E-mail id: avtrsot@gmail.com

***Corresponding Author:** Dr. Nischal Raj L
*MBBS., MS., FMAS., MCH (surgical oncology), Consultant surgical Oncologist, Clear Medi Radiant Hospital, Vijay Nagar 3rd Stage, Mysore, Karnataka 570017.
E-mail id: dr.nisraj@gmail.com

Abstract

The inflammatory process of seroma production, the most common postoperative complication following mastectomy, may be prevented with the use of local steroid injections. The impact of local steroid injection on seroma development was the focus of this research. This research compared the effects of saline on seroma development after mastectomy with those of a single 80 mg dose of methylprednisolone in a double-blind, randomised, placebo-controlled intervention trial. Mastectomy plus sentinel lymph node biopsy (M + SLNB) or mastectomy plus level I–II axillary lymph node dissection (M + ALND) were the more specific categories into which patients were placed based on the surgical axillary procedure. After the drain was removed on the first postoperative day, medications were introduced into the wound cavity via the drain hole. While the occurrence of side effects and problems were considered secondary objectives, seroma development constituted the main goal. In all, 210 women with primary breast cancer who were planned to have a mastectomy were considered. Following M + SLNB, a seroma formed in 32 out of 69 women (46 percent) in the group treated with methylprednisolone, compared to 52 out of 67 women (78 percent) in the group treated with saline ($P < 0.001$). In the intention-to-treat population, the methylprednisolone group had a much smaller mean cumulative seroma volume during the first 10 and 30 days. Methylprednisolone did not significantly affect seroma formation after M + ALND, and both the saline and methylprednisolone groups saw equal rates of seroma development. The infection rate was not different. The first day after M + SLNB, methylprednisolone was injected into the wound cavity. For the next 30 days, it significantly reduced the likelihood of seroma

development. There was no such impact in the M + ALND group. More research is needed to determine whether greater or repeated dosages of methylprednisolone improve effectiveness.

Keywords: Steroid, Inflammation, Bacterial, Post-Mastectomy Seroma, Surgical, Prophylaxis, Cytokines.

Introduction

An enormous burden on women's health is imposed worldwide by breast cancer, an aggressive foe in the field of oncology. [1] Postoperative problems are common after mastectomy, a standard procedure for breast cancer therapy, and they might affect the course of a patient's recovery. [2] One of the most common and difficult problems that may arise after a mastectomy is the creation of seroma, which can have an impact on the patient's physical and mental health. [3] Surgical accuracy and the complex reaction of the body to trauma converge throughout the post-mastectomy phase of a breast cancer patient's journey. A common complication of surgery is seroma, which is the buildup of serous fluid inside the surgical cavity. This fluid may impede healing and make it more difficult to reach complete recovery.[4] The local injection of methylprednisolone acetate to inhibit seroma development is explored in this research as a potential option for enhancing post-mastectomy healing.[5]

In a complex illness with a broad range of subtypes and clinical manifestations, breast cancer strikes millions of people throughout the globe. Essential to the treatment plan is mastectomy, the surgical removal of the breast with the goal of eradicating or controlling the spread of cancer cells. [6]

Despite its importance, mastectomy presents its fair share of difficulties in the treatment of breast cancer. [7] No matter how urgent the surgery, it inflicts stress on the body, setting off a chain reaction of inflammatory reactions and healing mechanisms. To optimise the overall therapeutic strategy, it is crucial to understand and mitigate the possible issues that may arise following mastectomy. [8] The need to investigate new treatments that address breast cancer fundamentally and improve the postoperative environment is highlighted by the prevalence of seroma-related complications. Such initiatives are important because they have the ability to revolutionise breast cancer surgery by providing a more simplified and patient-centered method. [9] Among the several therapies being studied, injecting methylprednisolone acetate locally stands out as an innovative and encouraging approach. [10]

The effects of injecting local methylprednisolone acetate on seroma development after mastectomy are meticulously investigated in this ground-breaking research of breast cancer surgery. [11] The research aims to give strong evidence for the effectiveness of this intervention by using a double-blind randomised placebo-controlled design. Recognising the variety of mastectomy methods and the difficulties involved with each, the addition of subgroups such as those receiving sentinel lymph node biopsy vs axillary lymph node dissection adds complexity to the research.[12]

Research methodology

The 2 x 2-intervention trial in this investigation was a randomised, double blind, placebo-controlled, investigator-initiated study with two individuals per block and an allocation ratio of 1:1. Two non-clinical investigators worked separately prior to the commencement of the investigation to generate a random sequence using numbers generated by Microsoft® Excel (Microsoft Corporation, Redmond, Washington, USA). Before randomization occurred during drainage removal on the first postoperative day, doctors were unaware of treatment allocation since it was contained in sequentially numbered sealed envelopes. Local injection of slow-release methylprednisolone's preventive impact on seroma development was the main aim. Complication and adverse effect frequency were considered secondary objectives.

Breast cancer patients were eligible if they were between the ages of 18 and 70 and had surgery planned for stages I to IIIA. On a yearly basis, the breast cancer clinics see over 1600 new patients. Every single woman gave her signed, informed permission.

Treatments and procedures

The identical procedure, which included electrocautery-assisted flap dissection during mastectomy and sharp axillary dissection, was used on all patients. To alleviate discomfort and nausea, all patients were given 8 mg of dexamethasone orally 8 hours prior to surgery. "For mastectomy with sentinel lymph node biopsy (M + SLNB) and mastectomy with level I- II axillary lymph node dissection (M + ALND), the guidelines of the Danish Breast Cancer Cooperative Group (http://www.dbcg.dk/)16 were adhered to. Using frozen-section immunohistochemistry, every sentinel node biopsy was evaluated during the surgery. Micrometastases and macrometastases both necessitated axillary dissection. The medial corner of the incision was used to place one closed suction drain in every subject. Gentle massage of the surgical field was followed by the injection of 80 mg methylprednisolone acetate (Depo-Medrol™; Pfizer, New York, USA) dissolved in 10 ml of isotonic saline or 10 ml of isotonic saline into the mastectomy cavity, according to the randomization sequence." The drain was removed on the first postoperative day, regardless of drainage volume. Subsequently, the patient was released. Clinicians and patients alike were unable to tell whether syringes carried the study's steroid or placebo medications since they were all similarly packaged.

Evaluation of the result

The amounts of surgical bleeding and drainage were documented. Outpatients were monitored as needed up to 14 days after a transcutaneous aspiration using a vacuum aspiration apparatus, when the patient was considered dry. When more than 50 cc of fluid collected behind the skin flaps, it was considered seroma. If the wound was red and had purulent seroma, it was considered infected and needed antibiotic therapy. Other symptoms of infection included necrosis and dehiscence. There was careful documentation of seroma volume, aspiration count, medication status, and side effects.

Statistical analysis

In order to detect a 50% reduction in the expected frequency of seroma formation based on a two-sided significance level $(1 - \alpha)$ of 0·95 and a power $(1 - \beta)$ of 0·90, a power calculation was conducted before recruitment. "The results indicated that 47 patients per group were required. The decision was made to stop this section of the trial based on an interim mid-term review that did not include a code break. The results showed that the seroma formation frequency in the M + ALND group was comparable in both the methylprednisolone and saline treatment arms. The decision to add 50 further patients to the M + SLNB group was made using the same evaluation. In order to analyse the effectiveness endpoints according to the technique of last (or prior) observation conducted for-ward, all randomised women were included in the intention-to-treat (ITT) sample. One subgroup of the ITT sample was the per-protocol (PP) population. Inclusion or exclusion violations that might affect the evaluation of efficacy outcomes or other protocol deviations that could confuse the evaluation of efficacy outcomes were among the reasons why women were not included in the PP population." These reasons were determined prior to the database lock. When applicable, independent t tests, $\chi 2$ tests, and Mann-Whitney U tests were used to compare patient demographics and baseline characteristics across the groups.

Investigating the nature of any significant differences was done using post hoc analyses utilizing Dunnett's C or Games-Howell tests, assuming unequal variances and group sizes, and Levene's test for homogeneity of variance. The statistical package SPSS® version 19.0 (IBM, Armonk, New York, USA) was used to conduct the data analysis. With modified Bonferroni adjustment for multiple comparisons, a two-tailed P-value less than 0.050 for the major endpoints and a P-value less than 0.010 for the secondary endpoints were deemed significant.

Results

A total of 300 patients met the inclusion criteria and were considered for participation in the research. However, 61 individuals denied inclusion, 5 patients were never recruited, and 29 patients were eliminated for various reasons. "Therefore, 210 patients were randomly assigned to two groups: one group received 105 patients to administer methylprednisolone. At the outset, there were no discernible differences between the saline-treated and methylprednisolone-treated women with respect to baseline patient demographics or surgical details, or between the ITT and PP groups of women (Table 1)

Table 1: Basic information on the study's per-protocol and intention-to-treat groups

	Per-protocol Population		**Intention-to-treat Population**	
	Saline (n = 100)	**Steroid (n = 99)**	**Saline (n = 105)**	**Steroid (n = 105)**
Age (years)	64 (61 – 67)	63 (60 – 66)	65 (62 – 67)	63 (61 – 66)
Ethnicity*				
White	94	98	100	105
Non-white	6	1	6	1
Height (cm)	166 (165 – 167)	166 (165 – 168)	167 (165 – 168)	166 (165 – 168)
Weight (kg)	70 (67 – 74)	67 (65 – 70)	71 (68 – 74)	67 (65 – 70)
Body mass index (kg/m2)	26 (24 – 27)	24 (24 – 25)	26 (24 – 27)	24 (24 – 25)
BP (mmHg)				
Systolic	150 (145 – 154)	150 (146 – 155)	151 (146 – 157)	150 (146 – 154)
Diastolic	88 (85 – 90)	90 (87 – 92)	88 (86 – 91)	89 (86 – 92)

Table2: Surgical characteristics in the per-protocol and intention to treat populations

	Per-protocol population(*n*=199)		**Intention-to-treat population(*n*=210)**	
Typeofsurgery*	**Saline**	**Steroid**	**Saline**	**Steroid**
M+SNLB	64(50·0)	64(50·0)	67(49·3)	69(50·7)
M+ALND	36(51)	35(49)	36(49)	37(51)
Other breast surgery	–	–	3(100)	–
Duration of surgery(min)				
M+SNLB	113(105–121)	115(107–122)	114(106–122)	113(106–120)
M+ALND	150(139–162)	150(133–168)	150(139–162)	149(133–165)
Other breast surgery†	–	–	109(97–121)	–
Surgical blood loss(ml)				
M+SNLB	117(91–143)	101(84–118)	120(94–146)	102(85–118)
M+ALND	126(90–162)	162(122–202)	126(90–162)	162(124–200)
Other breast surgery†	–	–	55(20–90)	–
Surgical drain fluid volume(ml)				
M+SNLB	106(79–132)	108(84–132)	105(80–131)	107(84–130)
M+ALND	139(113–165)	122(100–143)	139(113–165)	123(102–143)
Other breast surgery†	–	–	180(140–220)	–
Surgical tissue weight(g)				
M+SNLB	615(495–736)	560(473–648)	632(513–751)	564(478–649)
M+ALND	646(510–783)	678(555–802)	646(510–783)	672(554–790)
Other breast surgery†	–	–	620(463–777)	–
Wound haematoma*				
M+SNLB	1(2)	2(3)	1(1)	2(3)
M+ALND	0(0)	2(6)	0(0)	2(5)
Other breast surgery	–	–	0(0)	–

- **The prevalence of seroma and its intervention-related impact**

Compared to M + SLNB, a significantly higher number of women had seromas and had more frequent, heavy, and extended seroma production after M + ALND (Table 2)

Table3: Features of the seroma that forms after a mastectomy including sentinel lymph node biopsy or axillary lymph node dissection in all studies that followed the procedure and those that aimed to treat

	Per-protocol population (n = 199)		**Intention-to-treat population (n = 210)**		
	Saline	**Steroid**	**Saline**	**Steroid**	**P**
Durationofseroma (days)					
M+SNLB	17(12–21)	14(9–20)	18(13–24)	14(8–19)	0·008
M+ALND	38(26–50)	52(42–62)	38(26–50)	56(40–72)	0·003
Otherbreastsurgery*	–	–	52(22–81)	–	–
No.ofseromaaspirations					
M+SNLB	2(2–3)	2(1–2)	2(2–3)	2(1–2)	<0·001
M+ALND	9(5–13)	9(7–12)	9(5–13)	10(7–12)	0·083
Othertype of breastsurgery*	–	–	7(5–8)	–	–
Meanseromavolume (ml)					
M+SNLB	107(83–131)	56(36–77)	110(87–133)	56(36–76)	<0·001
M+ALND	190(158–222)	200(168–232)	190(158–222)	196(163–228)	0·627
Otherbreastsurgery*	–	–	245(118–372)	–	–
Cumulativeseromavolume(ml)					
M+SNLB	379(231–526)	252(73–432)	400(252–547)	239(70–407)	<0·001
M+ALND	2059(900–3218)	2167(1367–2967)	2059(899–1318)	2298(1347–3159)	0·095
Otherbreastsurgery*	–	–	1598(590–2605)	–	–
Cumulativeseromavolume(ml)					
Infirst10days					
M+SNLB	125(85–165)	26(12–40)	127(88–166)	24(11–38)	<0·001
M+ALND	358(263–453)	233(144–322)	358(262–453)	256(152–361)	0·139
Otherbreastsurgery*	–	–	100(0–200)	–	–
Infirst30days					
M+SNLB	319(212–425)	187(71–302)	328(232–432)	177(70–285)	<0·001
M+ALND	1106(777–1435)	1075(767–1382)	1106(777–1435)	1123(785–1460)	0·808
Otherbreastsurgery*	–	–	650(590–710)	–	–
Seromavolumeperday(ml)					
Infirst10days					
M+SNLB	16(11–21)	3(2–5)	16(11–21)	3(2–5)	<0·001
M+ALND	41(31–51)	32(21–42)	41(31–51)	33(22–45)	0·136
Otherbreastsurgery*	–	–	13(0–25)	–	–
Infirst30days					
M+SNLB	16(12–21)	8(4–12)	17(13–21)	8(4–12)	<0·001
M+ALND	50(38–62)	43(34–54)	50(38–62)	45(34–56)	0·616
Otherbreastsurgery*	–	–	27(26–27)	–	–

The administration of methylprednisolone reduced the occurrence of seroma formation in women who had M + SLNB (32 out of 69, or 46%, compared to 52 out of 67, or 78%, in the control group; $P < 0.001$) (Fig. 2), but had no impact in women who had M + ALND (35 out of 37, or 95% of the total) compared to 34 out of 36, or 94% of the total ($P = 0.572$).In addition, after M + SNLB, the administration of methylprednisolone decreased the following: duration of seroma formation ($P = 0.008$), number of aspirations ($P < 0.001$), mean seroma volume ($P < 0.001$), total cumulative seroma volume ($P < 0.001$), cumulative seroma volume in the first 10 days ($P < 0.001$) and 30 days ($P < 0.001$), and seroma volume per day ($P < 0.001$) and 30 days ($P < 0.001$) (Table 3)

Table 4: After a mastectomy and sentinel lymph node biopsy, 69 individuals treated with methylprednisolone and 67 patients treated with saline developed seroma

	No. of women	
	No Seroma	**Seroma**
Steroid	30-50	25-45
Saline	15-25	45-65

After a mastectomy and sentinel lymph node biopsy, 25-45 individuals treated with methylprednisolone developed seroma and 45-65 patients treated with saline developed seroma (Table 4)

Table 5: Seroma volume accumulation in post-mastectomy women having sentinel lymph node biopsy in the first ten and thirty days

	Cumulative seroma volume (ml)	
	Seroma 10 days	**Seroma 30 days**
Steroid	45-65	200-500
Saline	105-115	300-600

The outcomes were inconsistent, nonetheless, after M + ALND. Although there were no significant differences in the number of aspirations, mean seroma volume, or cumulative seroma volume (total or in the first 10 or 30 days), the duration of seroma formation after methylprednisolone injection was significantly longer than that after saline treatment (56 days versus 38 days respectively in the ITT group; P = 0·003).” Notably, a persistent seroma developed in one lady in the saline group who had M + ALND; after many aspirations, 80 mg methylprednisolone was injected into the seroma cavity, and subsequent dryness set(Table 5)

Discussion

Based on these findings, it is clear that seroma formation is more common after M + ALND surgery than M + SLNB. A single 80 mg dosage of methylprednisolone administered into the wound cavity significantly reduced seroma development after M + SLNB and increased the frequency of dryness by more than 100%. Methylprednisolone also reduced the total volume of seroma in the first ten and thirty days after surgery. Methylprednisolone did not affect the incidence of dryness or seroma development after M + ALND, however. In fact, it strangely lengthened the entire duration of the seroma (P = 0.003). The administration of methylprednisolone did not raise the infection or complications rate, but it seemed to prevent wound necrosis or dehiscence. [13]

There are a number of variables that might potentially increase the production of seroma after surgery. Seroma creation is strongly correlated with surgical operations, as shown by the current findings. This is particularly true of major surgical procedures like M + ALND, where seroma formation happens often. [14] A seroma formed in almost all of the women who had M + ALND, thus they had to aspirate many times. Similar to the first randomized experiment in this area, which was conducted in 1992 by Somers and colleagues, the current research likewise employed drains on the first day following axillary surgery to greatly minimise seroma development.[15] Thermal tissue injury and the activation of an initial inflammatory response are two possible mechanisms that explain why other mechanical procedures, such the use of different electromechanical devices for dissection, have been linked to an elevated seroma formation rate. [16] On the other hand, several researchers found no difference between electrocautery and ultrasonic energy dissection. While electrocautery was used for dissection in this research, the surgeon was free to adopt a non-standard approach as he or she saw fit. There may have an effect on seroma production by obliterating or decreasing the surgical dead space. Draining, compressing, and applying chemical sealants are examples of mechanical attempts at this method. [17]

The idea that a seroma is an exudate that develops in reaction to acute inflammation caused by surgical trauma has been supported by increasing data over the last decade, rather than just an accumulation of serous fluid. The seroma fluid's proteinase activity, proteinase inhibitor concentration, and cytokine content lend credence to this idea. There has been modest success in evaluating immunomodulatory drugs for the prevention of seroma development. These substances include sapylin in a human prospective randomised trial and 5-fluorouracil in a rat model. [18] Because of their anti-inflammatory properties, steroids may be helpful in the treatment of seroma. Methylprednisolone acetate injections into the muscles or joints are common ways that glucocorticoids are given to patients with inflammatory disorders including rheumatoid arthritis or allergic reactions. Various additional surgical procedures, such as those involving the colon, the head and neck, cosmetic surgery, and heart surgery, have investigated the potential use of steroids. Taghizadeh and colleagues conducted a randomised controlled trial on 41 women who had latissimus dorsi breast reconstruction to determine if steroids increased the risk of seroma reaccumulation. They monitored the return of each seroma and administered 80 mg triamcinolone or saline once after the first seroma aspiration. These authors only looked at preexisting seromas while studying the effects of steroid injection, but their findings are consistent with the current preventive investigation. Administering prophylactic steroids sped up the process of dryness onset, decreased overall seroma volume, and decreased aspiration frequency. A single intravenous bolus of 125 mg methylprednisolone sodium succinate before to the commencement of mastectomy failed to impact seroma development, suggesting that local delivery of a steroid is crucial. Seroma development was most likely unaffected by the little oral dosage of dexamethasone that all women in this research took prior to surgery. [19]

Methylprednisolone treatment seemed to avert wound necrosis, and there was no discernible increase in infection rates. In addition, a prior study did not discover an elevated infection risk after topical treatment of 80 mg triamcinolone or 125 mg intravenous methylprednisolone.

Conclusion

The current research shows that a single dosage of intramuscular injection of methylprednisolone acetate on the first day after M + SLNB surgery significantly reduces the risk of seroma development. Administering steroids increased the proportion of patients without seroma by more than 100%, lowered the frequency of aspirations, and decreased the average and total volume of seroma between 10 and 30 days, respectively.

References

1. Okholm M, Axelsson CK. No effect of steroids on seroma formation after mastectomy. Dan Med Bull 2021;58:A4241.
2. Kuroi K, Shimozuma K, Taguchi T et al. Evidence-based risk factors for seroma formation in breast surgery. Jpn J ClinOncol 2016;36:197-206.
3. Baker EA, Leaper DJ: Proteinases, their inhibitors, and cytokine profiles in acute wound fluid. Wound Repair Regen 2020;8:392-8.
4. DoolinEJ, Tsuno K, Strande LF et al. Pharmacologic inhibition of collagen in an experimental model of subglottic stenosis. Ann OtolRhinolLaryngol2017;107:275-9.
5. Mettler L, Salmassi A, Heyer M et al. Perioperative levels of interleukin 1 beta and interleukin-6 in women with breast cancer. Clin Exp Obstet Gynecol 201931:20-2.
6. Yilmaz KB, Dogan L, Nalbant H, Akinci M, Karaman N,OzaslanCetal. Comparing scalpel, electrocautery and ultrasonic dissector effects: the impact on wound complications and pro-inflammatory cytokine levels in wound fluid from mastectomy patients. J BreastCancer 2021;**14**: 58–63.
7. Galatius H, Okholm M, Hoffmann J. Mastectomy using ultrasonic dissection: effect on seroma formation. Breast2018; **12**: 338–341.
8. AgrawalA, AyantundeAA, CheungKL.Concepts of seroma formation and prevention in

breast cancer surgery. ANZJ Surg2016;**76**:1088–1095.
9. McCaul JA, Aslaam A, Spooner RJ, Louden I, Cavanagh T,PurushothamAD. Aetiology of seroma formation in patients undergoing surgery for breast cancer.Breast 2020; **9**:144–148.
10. Baker EA, Kumar S, Melling AC, Whetter D, Leaper DJ.Temporal and quantitative profiles of growth factors and metalloproteinases in acute wound fluid after mastectomy.WoundRepair Regen 2018; **16**: 95–101.
11. SchulzeS, AndersenJ, OvergaardH, NørgardP, NielsenHJ, Aasen A etal. Effect of prednisolone on the systemic response and wound healing after colonic surgery. Arch Surg2020; **132**: 129–135.
12. Holte K, Kehlet H. Perioperative single-dose glucocorticoid administration: pathophysiologic effects and clinical implications.J Am Coll Surg 2022;**195**:694–712.
13. Berberich T, Haecker FM, Kehrer B, Erb TO, Günthard J,HammerJetal. Postpericardiotomy syndrome after minimally invasive repair of pectus excavatum.J Pediatr Surg2017; **39**: e1–e3.
14. ParkGM, LeeJY, KimYG, BooSJ, Song JM,KangDHetal. Recurrent postoperative effusive–constrictive pericarditis associated with steroid discontinuation. J Cardiovasc Ultrasound2019;**17**:102–105.
15. Taghizadeh R, Shoaib T, Hart AM, Weiler-Mithoff EM. Triamcinolone reduces seroma re-accumulation in the extended latissimus dorsi donor site. J Plast Reconstr Aesthet Surg2018; **61**: 636–642.
16. Axelsson CK, Quamme GM, Lanng C, Szecsi PB,Mortensen MB, Wegeberg B et al. Local injection of methylprednisolone acetate to prevent seroma formation after mastectomy. Dan Med J 2022; **59**: A4482.
17. KuroiK, ShimozumaK, TaguchiT, ImaiH, YamashiroH, Ohsumi Setal. Evidence-based risk factors for seroma formation in breast surgery.Jpn J Clin Oncol2016;**36**:197–206.
18. Srivastava V, Basu S, Shukla VK. Seroma formation after breast cancer surgery: what we have learned in the last two decades. JBreast Cancer 2022; **15**: 373–380.
19. Somers RG, Jablon LK, Kaplan MJ, Sandler GL,Rosenblatt NK. The use of closed suction drainage afterlumpectomy and axillary node dissection for breast cancer.A prospective randomized trial.Ann Surg 2022;**215**:146–149.