

Strategies for Preventing Seroma in Patients Undergoing Breast Cancer Surgical Treatment: Systematic Literature Review

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Estratégias para Prevenção do Seroma em Pacientes Submetidos ao Tratamento Cirúrgico do Câncer de Mama: Revisão Sistemática da Literatura

Estrategias para la Prevención del Seroma en Pacientes Sometidas a Tratamiento Quirúrgico por Cáncer de Mama: Revisión Sistemática de la Literatura

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ABSTRACT

Introduction: Seroma is the most common scar complication in the postoperative period of breast cancer, which impacts patients' quality of life and can lead to repeated punctures, new surgical procedures and delays in adjuvant treatment. **Objective:** Systematic review of the scientific literature on the procedures used to prevent seroma in patients undergoing surgical treatment for breast cancer, addressing their advantages and disadvantages. **Method:** Cochrane Collaboration-based methodology, including articles from clinical trials and observational studies. To identify relevant studies, the following databases were searched: MEDLINE via PubMed, PEDro, Cochrane Library and LILACS. The search was carried out from October 2022 to January 2023. The methodological quality of clinical trials was assessed using the PEDro scale and the Newcastle-Ottawa scale for observational studies. **Results:** 405 articles were identified and, after evaluation, 24 articles were included for analysis. There are several approaches that could minimize the incidence of seroma, as the use of a drain, obliteration of dead space, instruments used for tissue dissection and techniques that could control the inflammatory process. **Conclusion:** The seroma prevention strategies used in the studies minimized the incidence of seroma, with the exception of talc and iodine, however, the studies that focused on the obliteration of dead space, whether with quilting suture or sealant, showed more significant statistical results, suggesting that they are promising for seroma prevention.

Key words: Breast Neoplasms/surgery; Seroma/prevention & control; Review.

RESUMO

Introdução: O seroma é a complicação cicatricial mais incidente no pós-operatório do câncer de mama que impacta a qualidade de vida dos pacientes, podendo levar à necessidade de punções repetidas, novos procedimentos cirúrgicos e a atrasos no tratamento adjuvante. **Objetivo:** Revisão sistemática da literatura científica sobre os procedimentos utilizados para prevenção do seroma em pacientes submetidos ao tratamento cirúrgico do câncer de mama, abordando suas vantagens e desvantagens. **Método:** Utilizou-se o método da Colaboração Cochrane, sendo incluídos artigos de ensaios clínicos e estudos observacionais. Para identificar estudos relevantes, pesquisaram-se as seguintes bases de dados: MEDLINE via PubMed, PEDro, *Cochrane Library* e LILACS. A busca foi realizada nos períodos de outubro de 2022 a janeiro de 2023. A qualidade metodológica dos ensaios clínicos foi avaliada pela escala PEDro e a dos estudos observacionais, pela escala de Newcastle-Ottawa. **Resultados:** Foram identificados 405 artigos e, após avaliação, incluídos 24 para serem analisados. Existem várias abordagens que poderiam minimizar a incidência de seroma, como o uso de dreno, obliteração do espaço morto, os instrumentos utilizados para a dissecação tecidual e as técnicas que poderiam controlar o processo inflamatório. **Conclusão:** As estratégias de prevenção do seroma utilizadas nos estudos incluídos minimizaram sua incidência, com exceção do talco e do iodo, entretanto, os estudos que tiveram como objetivo a obliteração do espaço morto, seja com sutura *quilting* ou selante, mostraram resultados estatísticos mais significantes, sugerindo serem promissores para a prevenção do seroma. **Palavras-chave:** Neoplasias da Mama/cirurgia; Seroma/prevenção & controle; Revisão.

RESUMEN

Introducción: El seroma es la complicación cicatricial más común en el posoperatorio del cáncer de mama, lo que impacta la calidad de vida de las pacientes y puede llevar a la necesidad de repetidas punciones, nuevos procedimientos quirúrgicos y retrasos en el tratamiento adyuvante. **Objetivo:** Revisión sistemática de la literatura científica sobre los procedimientos utilizados para prevenir el seroma en pacientes sometidas a tratamiento quirúrgico por cáncer de mama, abordando sus ventajas y desventajas. **Método:** Se basó en la Colaboración Cochrane, incluyendo artículos de ensayos clínicos y estudios observacionales. Para identificar estudios relevantes, se realizaron búsquedas en las siguientes bases de datos: MEDLINE vía PubMed, PEDro, *Cochrane Library* y LILACS. La búsqueda se realizó desde octubre de 2022 hasta enero de 2023. La calidad metodológica de los ensayos clínicos se evaluó mediante la escala PEDro y la de los estudios observacionales, mediante la escala Newcastle-Ottawa. **Resultados:** Se identificaron 405 artículos y, luego de la evaluación, se incluyeron para el análisis 24 artículos. Existen varios enfoques que podrían minimizar la incidencia del seroma, como el uso de un drenaje, la obliteración del espacio muerto, instrumentos utilizados para la disección de tejidos y técnicas que podrían controlar el proceso inflamatorio. **Conclusión:** Las estrategias de prevención del seroma utilizadas en los estudios incluídos minimizaron la incidencia de este, con excepción del talco y yodo, sin embargo, los estudios que se centraron en la obliteración del espacio muerto, ya sea con sutura *quilting* o sellador, mostraron resultados estadísticos más significativos, lo que sugiere que son prometedores para la prevención del seroma. **Palabras clave:** Neoplasias de la Mama/cirugía; Seroma/prevenición & control; Revisión.

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INTRODUCTION

Breast cancer is the most frequent neoplasm in the female gender, excluding non-melanoma skin tumors, and one of the main causes of death among women around the world^{1,2}. In Brazil, estimates predict 73,610 new breast cancer cases for each year of the 2023-2025 period. Surgery is still the main treatment⁴ with healing potential, which can involve a resection that conserves the breast, or a mastectomy⁵, which entails postoperative complications, such as seroma⁶.

Seroma, defined as an abnormal serous fluid collection that develops under the skin flaps, is one of the most frequent complications derived from breast cancer surgery, occurring in up to 96% of patients⁷. This complication may impact the patient's quality of life, leading to repeated punctures, new procedures and delays in the adjuvant treatment^{8,9}. Therefore, preventing it is essential.

Although there are a variety of techniques described to reduce seroma formation, the use of a drain during the surgery is considered the gold standard to avoid this complication¹⁰. However, this can cause pain, increase the hospitalization period or reduce a patient's quality of life¹¹.

Based on these considerations, the present study aims to perform a scientific literature review on the procedures used to prevent seroma in patients undergoing surgical treatment for breast cancer, addressing their advantages and disadvantages.

METHOD

Cochrane Collaboration-based methodology systematic review submitted to the PROSPERO¹² (International Prospective Register of Systematic Reviews) register base, under number CRD42024506834.

This systematic review was conducted following the PICO Strategy. P: patients (men and/or women) with breast cancer submitted to surgery; I: seroma prevention strategies; C: comparing different prevention approaches; O: existing approaches to prevent postoperative seroma. The review began by formulating the following research questions: "what procedures for preventing seroma are most used in patients submitted to breast cancer surgical treatment?" and "what are the advantages and disadvantages associated to these procedures?"

To identify relevant studies, the following databases were searched: PubMed, Physiotherapy Evidence Database (PEDro), Cochrane Library and *Literatura Latino-Americana e do Caribe em Ciências da Saúde* (LILACS). The main researcher was responsible for searching and selecting the articles included in this review, while other two researchers verified the decisions made. Divergence

cases among researchers were settled through evaluation by another researcher. The search was carried out from October 2022 to January 2023.

The PubMed search strategies followed the Medical Subject Headings (MeSH), using the descriptor: seroma. The subheadings "prevention and control", "surgery and therapy" were used, restricted to the main MeSH topic. This same strategy was used in the Cochrane Library, however, only the "prevention & control" subheading were used, as the "surgery and therapy" subheading is not available in the Cochrane Library. In the PEDro e LILACS databases, simple searches were performed since the MeSH search was not possible, using the "seroma" and "breast cancer" descriptors, with the use of Boolean operator AND.

The selected articles met the following inclusion criteria: clinical trials and cohort studies in English and Portuguese, published between 2012 and 2022, about preventing seroma in breast cancer. Articles with animal model, about seroma treatment, seroma in reconstructions and refractory seroma, as well as protocols, studies about incidence and associated factors, documents not available in full, conference proceedings, letters to the editor, course completion works, literature review and clinical trials with a score ≤ 6 in the PEDro¹³ scale were excluded.

At first, titles and abstracts were analyzed, followed by a full reading of the potentially eligible publications. The main information from each article were inserted in a specific spreadsheet for data extraction, which included reference (author and year of publication), type of study, sample size, intervention type, time of follow-up, results, and conclusions. After collecting the information, the methodological quality of the clinical trials was analyzed using the PEDro scale, composed of 11 assessment criteria. Each satisfactorily met criterion received 1 point, except the first item, totaling 10 points¹³.

For the observational studies, the Newcastle-Ottawa scale was used, which assesses three dimensions: the selection of the study groups, the comparability of the groups, and the outcome of interest. Each dimension has items with answer options to which stars are attributed. The study groups selection has four items, the outcome has three, with each one able to receive one star, while comparability has one item, being able to receive up to two stars. The use of this scale, however, did not implicate in article exclusion, as this instrument is not developed for assessing methodological quality¹⁴.

RESULTS

A total of 405 articles were identified, 245 of which were excluded after applying the eligibility criteria. After



close analysis (Figure 1) and qualitative assessment of the clinical trials (Chart 1), 24 articles were included in this review.

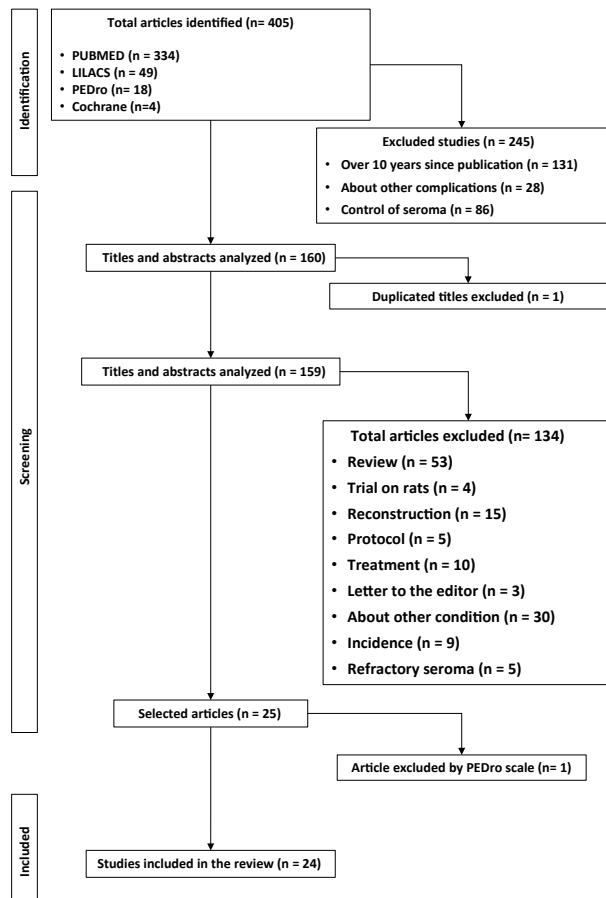


Figure 1. Flowchart showing the selection process of the articles included in this review.

Source: adapted from PRISMA 2020¹⁵

After complete readings of the observational studies included in this review, the methodological quality assessment was performed. All 11 articles were considered to have good methodological quality as they obtained a ≥ 7 score (Chart 2).

Of the 24 articles, five used sealants, five applied some kind of medicine, seven employed sutures for fixing the flap, two used some kind of surgical instrument for tissue dissection, one studied thoracic paravertebral nerve block, and four compared multiple approaches (Table 1).

DISCUSSION

According to the analyzed studies, all authors, regardless of the employed techniques, reported that patients submitted to axillary lymphadenectomy (AL) have a high risk of developing seroma compared to those who only performed sentinel lymph node biopsy (SLNB).

In addition to that, factors such as body mass index (BMI), tumor size, postoperative time and number of lymph nodes removed are associated to seroma development. However, it is hard to determine the superiority of a technique over another, since the incidence of seroma varies according to the definition adopted by each study researcher.

One strategy for preventing seroma formation involves the obliteration of dead space, which can be achieved through the following approaches: external pressure or flap fixation through suture. In the study conducted by Seenivasagam et al.¹⁶, the comparison between these techniques and the conventional method showed a significantly lower incidence of seroma in the group that used sutures with flap fixation (quilting). These findings are in line with the ones by ten Wolde et al.³⁰, Ouldamer et al.³¹, Mazouni et al.³², Myint et al.²⁵ and van Zeelst et al.³⁹, who also observed a reduction upon employing the quilting suture. Huang et al.³⁸, however, found that the incidence of seroma was similar in the three groups (quilting suture + drain removal between 5-9 days, conventional suture + drain removal between 13-15 days, conventional suture + drain removal between 20-22 days) (9.5% vs. 7.9%) vs. 5.3%; $p = 0.437/p = 0.780$).

Moreover, this technique contributes to reducing draining time, minimizes wound complications, decreases the need for fluid aspirations and apparently doesn't impact movements on the upper limb ipsilateral to surgery^{30-32,39}. However, it is worth mentioning that this approach demands approximately 10 minutes of additional time, as shown by Mazouni et al.³², Myint et al.²⁵ and van Zeelst et al.³⁹ (78 minutes vs. 85 minutes; 111.44±7.048 min vs. 124.5±6.39 min, 77.8 min vs. 68.5 min, respectively). Mazouni et al.³², however, did not identify a statistical significance in the average duration of the surgical procedure among the groups submitted to quilting and non-quilting suture ($p = 0.12$).

Concerns associated to the use of quilting suture include pain increase and tissue appearance. Ouldamer et al.³¹ showed a lower rate of patients feeling pain in the quilting suture cohort compared to the conventional suture (61% vs. 30%, $p < 0.001$). According to Myint et al.²⁵, however, no difference in the amount of pain killers used among the groups was observed (96±12.086 mg in the conventional and 94.7±10.996 mg in the quilting suture $p = 0.5067$). These results are in line with the study by van Zeelst et al.³⁹, in which no increase in pain killers use was found in both cohorts (61% vs. 30%, $p < 0.001$).

Regarding tissue quality, Ouldamer et al.³¹ refuted the initial hypothesis that the wound closure technique would not influence tissue quality. The authors found a significant improvement in the quilting group, resulting

Chart 1. Methodological quality assessment of clinical trials after synthesis of reviewed articles

Autor	1*	2	3	4	5	6	7	8	9	10	11	Score
Seenivasagam et al. ¹⁶	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	8/10
de Rooij et al. ¹⁷	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9/10
Benevento et al. ¹⁸	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	9/10
Kus et al. ¹⁹	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10/10
Baker e Piper ²⁰	Y	N	N	Y	N	N	N	Y	Y	Y	N	5/10**
Vasileiadou et al. ²¹	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	7/10
Pinero-Madrona et al. ²²	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10/10
Boeer et al. ²³	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	9/10
Garza-Gangemi et al. ²⁴	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9/10
Myint et al. ²⁵	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10/10
Qvamme et al. ²⁶	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10/10
Zhao et al. ²⁷	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	7/10
Yang et al. ²⁸	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9/10
Khan ²⁹	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	7/10

Captions: Y = Yes; N = No

(*) Although considered in the assessment, it was not included in the studies' final score.

(**) Excluded for not obtaining a ≤ 6 score in the criteria addition.

Chart 2. Methodological quality assessment of observational studies after synthesis of reviewed articles

Author	Selection			Comparability	Exposure			Score
ten Wolde et al. ³⁰	*	*	*	**	*	*	*	8/9
Ouldamer et al. ³¹	*	*	*	**	*	*	*	8/9
Mazouni et al. ³²	*		*	**	*	*	*	7/9
Selvendran et al. ³³	*	*	*	**	*	*	*	8/9
Kong et al. ³⁴	*	*	*	**	*	*	*	8/9
van Bastelaar et al. ³⁵	*	*	*	**	*	*	*	8/9
Conversano et al. ³⁶	*		*	**	*	*	*	7/9
van Bastelaar et al. ³⁷	*	*	*	**	*	*	*	8/9
Huang et al. ³⁸	*		*	**	*	*	*	7/9
van Zeelst et al. ³⁹	*	*	*	**	*	*	*	8/9
Gambardella et al. ⁴⁰	*	*	*	**	*	*	*	8/9

in better cosmetic results, fewer healing complications and better patient satisfaction. Myint et al.²⁷ also investigated the tissue aspect, observing the ripples on the skin due to the suture stitches, which disappeared on the seventh postoperative day.

Another strategy for obliterating dead space involves the use of sealant, acting to seal the lymphatic and blood vessels, preventing the buildup of liquid and promoting tissue adherence, thus eliminating dead space. In this review, all the articles used different sealants, which impaired direct comparisons. However, both Benevento et al.¹⁸ and Conversano et al.³⁶ used the same sealant. The sealant in question presents low concentration of thrombin in comparison to other similar products,

resulting in a polymerization of about 60 seconds, promoting extended time for tissue manipulation and application of sutures before polymerization.

Benevento et al.¹⁸ showed a significant statistical difference in the amount of drained serum output, reduced time for drain removal, shorter hospitalization time and lower incidence of seroma during 4 follow up weeks. Conversano et al.³⁶ reinforces almost all these findings, however, it is an observational study with a greater sampling, with no evidence to sustain the reduction in seroma formation with the use of sealant, though its use was safe and needed no drain.

The approach reported by Pinero-Madrona et al.²² showed a lower incidence of seroma in the intervention

Table 1. Synthesis of the reviewed articles on seroma prevention techniques

Author	Type of study	Number of participants	Technique	Seroma definition	Methodology	Results
Seenivasagam et al. ¹⁶	Clinical trial	150	Standard dressing, pressure dressing, and quilting suture	Palpation	Women – MRM or conservative surgery. Six groups: three main groups, each with two subgroups (group I – control, standard dressing; group II – external pressure dressing; group III – quilting suture) Subgroups A – drain removal after 7 days Subgroups B – drain removal after 20-30 ml/24h output	Incidence of seroma: significantly lower in groups III and II ($p = 0.003/p = 0.58$). Drain removal: increased incidence of seroma in subgroup A (28.4%) when compared to subgroup B (21.3%) ($p = 0.34$) Daily and cumulative production of drain: reduced in group III Drain duration: significantly decreased in groups III and II ($p = 0.001/p = 0.03$). Wound complications: more frequent in group II (34% vs. 31.3%; $p = 0.27$)
ten Wolde et al. ³⁰	Cohort	176	Quilting suture	Aspiration	Patients – MA and/or AL Two groups: conventional suture and quilting suture	Quilting group: lower incidence of seroma (80.5% vs. 22.5%; $p < 0.001$), lower average number of aspirations (4.86 ± 4.28 vs. 2.40 ± 1.98 ; $p = 0.015$) and lower average volume aspirated (1660.90 ± 2322.97 vs. 611.25 ± 754.43 ; $p = 0.050$) SSI: Significantly lower in the quilting suture cohort (31.0% vs. 11.2%; $p = 0.001$)
Mazouni et al. ³²	Cohort	82	Quilting suture	Aspiration	Women – MA, with or without AL Two groups: conventional suture and quilting suture Drain removal: < 50 ml/24h	Incidence of seroma: Lower in the quilting group (34.1% vs. 58.5%, $p = 0.03$), but with no statistical significance for the average number of aspirations needed ($p = 0.07$) Average drained volume: lower in the quilting group on the first day (107.1 ml vs. 156.5 ml; $p = 0.02$) and on the second day (108.4 ml vs. 162.8 ml; $p = 0.01$) SSI: lower in the quilting group (14 vs. 24 cases, $p = 0.03$) No difference was observed in the incidence of postoperative pain
Ouldamer et al. ³¹	Cohort	119	Quilting suture	Not informed	Women – MA Two types of wound closing: conventional + drain and quilting suture with no drain Drain removal: < 50 ml/24h, not surpassing 5 days of PO	Occurrence of seroma type 2 or 3 and global incidence of seroma: lower in the quilting group (21.7% vs. 6.8%; OR = 0.26; CI: 0.08-0.86; $p = 0.03$) and (17.0% vs. 51.7%; OR = 0.19; CI: 0.08-0.45; $p = 0.001$) Tissue appearance: significantly better results in the quilting group ($p = 0.003$)
van Bastelaar et al. ³⁵	Cohort	180	Quilting suture	Palpation and aspiration	Patients – MA, MA + SLNB Two groups: historical control group – conventional suture; quilting suture group	Incidence of seroma and seroma aspiration: significantly lower in the quilting group (35.9% vs. 59.1%; $p = 0.002$), (14/92 vs. 38/88 patients, $p < 0.001$) Number of aspirations: Significantly lower in the quilting group ($p < 0.001$) SSI: No significant difference observed ($p = 0.33$)

to be continued



Table 1. continuation

Author	Type of study	Number of participants	Technique	Seroma definition	Methodology	Results
Myint et al. ²⁵	Clinical trial	140	Quilting suture	Palpation, ultrasound, and aspiration.	Women – MRM Two groups: quilting suture + one drain or conventional suture + two drains Drain removal: < 30 ml/24h	Average surgery time: significant difference among groups ($p = 0.0001$) Incidence of seroma ($p = 0.041$), average aspiration frequency ($p = 0.043$) and average aspirated volume ($p = 0.00015$): significantly higher than in the conventional group Average drainage in the first 72 hours ($p = 0.731$), full drain output ($p = 0.941$), draining time ($p = 0.447$) and shoulder movements limitation during PO ($p = 0.3979$): no significant differences among the groups
Huang et al. ³⁸	Cohort	388	Quilting suture	Not informed	Women – MA + SLNB or AL Three groups: group 1: quilting suture and drain removal within 5-9 PO days; group 2: conventional suture and drain removal within 13-15 PO days; group 3: conventional suture and drain removal within 20-22 PO days	Incidence of seroma: similarities among groups SSI ($p = 0.251$), inadequate wound healing ($p = 0.580$) and PO hospitalization time ($p = 0.609$): no significant differences among the groups. Quilting group: lower drain volume in comparison to conventional groups (374.9 vs. 439.1 vs. 461.4 ml; $p < 0.001$). Eighteen patients in groups 2 and 3 with level 2 and 3 seroma reported discomfort, wishing to prolong draining time in the wound location to avoid/reduce level 2 and 3 seroma
van Zeelst et al. ³⁹	Combined cohort	255	Quilting suture	Aspiration	Women – MA and/or AL CWZ Hospital: Quilting suture without PO drain RH Hospital: Conventional closure + drain	Average surgery time: higher in the quilting cohort Seroma formation: less frequent in the quilting cohort for both analyses, with lower rates in the prospective group (6.9% vs. 59.3%) and in the combined group (12.9% vs. 62.3%) SSI: significantly lower in the quilting cohort (5.0% vs. 14.0%; $p = 0.013$) Trend of increase in bleeding complications in the non-quilting cohort in the prospective group (14.8% vs. 0%/ $p = 0.031$) Wound healing issues: less reported in the quilting cohort in both analyses Use of painkillers: no increase in both cohorts
Benevento et al. ¹⁸	Clinical trial	60	Sealant	Ultrasound	Women – MRM and QU + AL Two groups: control group – drain; and intervention group – sealant + drain Drain removal: not surpass 30 ml/24h output	Total amount of drained fluid: significantly lower in the intervention group (94.3 ± 22.4 vs. 176 ± 24.6 ml, $p < 0.001$) Average drain removal time and PO hospitalization: significantly lower in the intervention group ($p = 0.002$; $p = 0.001$, respectively) Seroma formation: no significant difference among the groups Average aspirated volume: lower in the intervention group (70 ml), solved in 5 days; in the control group, the volume was of 135 ml solved in average 12 days

to be continued



Table 1. continuation

Author	Type of study	Number of participants	Technique	Seroma definition	Methodology	Results
Pinero-Madrona et al. ²²	Clinical trial	94	Sealant	Palpation and aspiration	Two groups: control group: standard AL; intervention group: collagen sponge coated with human coagulation factors Drain removal: < 50 ml	Control group: 46.8% of patients developed seroma, significantly lower in the intervention group (15.9%/p = 0.002) No problems were observed in the functionality of the arm ipsilateral to surgery, and no adverse events were observed. Early removal of the drain in the intervention group, but with no significant difference (p = 0.244) Global drain output in the first 3 days: lower in the intervention group, but with no significant difference (p = 0.253)
Boeer et al. ²³	Clinical trial	14	Sealant	Palpation and ultrasound.	Two groups: control group – with drains; intervention group – sealant + no drains Drain removed: < 30 ml/24h in two consecutive days	The control group had approximately 12% more fluid in the wound (578 ml vs. 514 ml, p = 0.779) 100% of the intervention group patients developed seroma, needing puncture aspiration 63% of patients in the control group developed seroma. Wound complications: 25% of patients in the group had complications, while the control group showed no healing issues Average hospitalization duration: shorter in the intervention group (3.5 days, SD 0.8 vs. 5.2 days, SD 3.3; p = 0.662) and the number of non-planned outpatient visits increased (3.9, SD 3.1 vs. 1.3, SD 1.6, p = 0.121) Sleep disorder and shoulder mobility: lower in the intervention group
Conversano et al. ³⁶	Cohort	149	Sealant	Not informed	Women – AL, with or without conservative surgery Two groups: control group: conventional suture + drain; intervention group: quilting suture + sealant + external compression, no drain used Drain removal: <50 ml/24h	Average hospitalization: significantly lower in the intervention group (2.6 vs. 4.7; p < 0.001) After hospital discharge, 32.2% of patients were submitted to seroma puncture with no significant difference observed in the incidence of seroma among the groups (30.6% vs. 33%/p = 0.77) Wound complications: 6.1% (intervention) and 14.0% (control)/ (p = 0.16) Average cost of hospitalization: € 5,730 (CI = 95%/€ 5,349 and € 6,111) in the control group and € 3,376 (CI = 95% / € 3,111 and € 3,642) in the intervention group

to be continued



Table 1. continuation

Author	Type of study	Number of participants	Technique	Seroma definition	Methodology	Results
Vasileiadou et al. ²¹	Clinical trial	128	Sealant	Not informed	Women – MRM or QU + AL Two groups: Control group – only drain. Intervention group – sealant + drain Drain removal: 30 ml/day	Duration (2.51 ± 0.89 days vs. 3.63 ± 1.62 days), drain volume (155.77 ± 103.35 vs. 457.81 ± 435.51) aspirated seroma volume (25.46 ± 27.14 vs. 94.69 ± 109.26): significantly ($p = 0.000$) lower in the intervention groups
van Bastelaar et al. ³⁷	Cohort	230	Quilting suture, sealant and drain	Palpation and aspiration	Women – MA with or without SLNB and MRM Three groups: Suture + drain group; sealant + drain group; just drain group Drains removed: < 50 ml/24h. After 7 days, all drains were removed	Comorbidities: significantly less than the suture group compared to the sealant group (2.8 vs. 3.8 ($p = 0.007$)) General complications: significant statistical difference between the sealant group (58%) and the suture group (39%) ($p = 0.03$). Seroma aspiration: 15.2% in the suture group, 14% in the sealant group and 59.1% in the drain group ($p < 0.001$) Seroma aspiration in the suture group and the sealant group with no significant difference ($p = 0.85$) Number of seroma aspirations per patient: significantly reduced in both groups of flap fixation ($p < 0.001$) SSI: no significant differences among groups Aspirations: significantly reduced in patients submitted to MA + SLNB ($p = 0.001$) or MRM ($p = 0.04$) and who had flap fixation
de Rooij et al. ¹⁷	Clinical trial	339	Quilting suture, sealant and drain	Aspiration	Patients – MA or MRM. Three groups: group I – conventional wound closure; group II – suture; group III – sealant Drain removal – MRM: < 50 ml/24h or after a maximum of 5 days MA: < 50 ml/24h or after a maximum of 48 hours	Compared to group I, less patients were submitted to seroma aspiration when the flap fixation was applied with suture and sealant (17.5% vs. 7.3%) vs. 10.8%, respectively). PO drain output total volume: no significant differences among groups (group I 316.2 ± 302.9 ml vs. group II 246.0 ± 285.1 ml vs. group III 256.3 ± 285.6 ml; $p = 0.151$) More outpatient appointments: group I patients showed up more in comparison to the other groups (standard – 47.3% vs. suture – 32.1% vs. sealant – 36.9%)
Kus et al. ¹⁹	Clinical trial	40	Thoracic paravertebral block	Aspiration	Women – MRM Two groups: intervention group – TPB; control group – no intervention	Reduction of seroma incidence in the TPB group. Average seroma volume 24 hours after surgery: 112.5 ± 53.3 ml in the control group and 74.5 ± 47.4 ml in the intervention group ($p = 0.022$) NRS score: similar in both groups Average morphine consumption: lower in the TPB group

to be continued



Table 1. continuation

Author	Type of study	Number of participants	Technique	Seroma definition	Methodology	Results
Yang et al. ²⁸	Clinical trial	111	Medication	Ultrasound	Women – MRM or QU + AL Two groups: Intervention group – 100 ml of OK-432 + drain; control group – just drain Drain removal: < 80 ml	Average total drained volume: 325.22 ± 67.23 ml in the intervention group and 362.07 ± 75.98 ml in the control group ($p = 0.008$) Draining duration: significantly shorter in the intervention group ($p = 0.003$) Puncture aspiration: significantly fewer ($p = 0.001$) in the intervention group
Qvamme et al. ²⁶	Clinical trial	212	Medication	Aspiration	Women – MA + SLNB or MRM Two groups: control group – placebo; intervention group – 80 mg methylprednisolone Drain removal: intervention group – first day of PO, regardless of the drained volume and medication applied	Compared to the placebo group, methylprednisolone reduced the incidence of seroma in MA + SNLB (46% vs. 78% / $p < 0.001$), but had no effect on MRM (95% vs. 94%/ $p = 0$) After MA+ SNLB, there was a seroma formation duration reduction ($p = 0.008$), number of aspirations ($p < 0.001$), average seroma volume ($p < 0.001$), cumulative total seroma volume ($p < 0.001$) and cumulative seroma volume in the first 10 days and 30 days ($p < 0.001$). However, in the MRM in which the medication was used, seroma formation duration was greater in comparison to the placebo Wound complication rates: no difference
Kong et al. ³⁴	Cohort	80	Medication	Not informed	Two groups: group A – intervention, 30 ml OK-432 in the wound through the drain Group B – control, drain removed when the fluid did not surpass 30 ml/24h	OK-432 could reduce incidence of seroma (30% vs. 5%; $p < 0.01$), and seroma volume (75.83 ± 36.05 ml vs. 15.00 ± 7.07 ml; $p = 0.040$) Total volume drained: significantly lower in the intervention group (706.78 ± 343.93 ml vs. 977.65 ± 441.83; $p = 0.030$) Draining duration: statistical differences among groups ($p < 0.01$) Differences in aspiration punctures reduction (3.75 ± 1.29 vs. 1.50 ± 0.71; $p = 0.036$) and healing time (28.00 ± 11.50 days vs. 16.00 ± 3.00 days; $p < 0.01$)
Zhao et al. ²⁷	Clinical trial	224	Medication	Ultrasound	Three groups: control group – conventional closure; Sapylin group: 100 ml locally for 30 min; Avitene group: 50 mg applied on the axillary wound surface Drain removal: < 30 ml for two consecutive days	Average drain duration time: Sapylin group – 7.97 ± 0.41 days; Avitene group – 8.68 ± 0.39 days; control group: 11.64 ± 0.65 days. Significantly lower in both treated groups ($p < 0.001$) Average total drained volume: Significantly lower in the Sapylin group compared to the control group (430.49 - 34.42 ml, vs. 602.74 - 48.54 ml, respectively; $p = 0.003$) No significant difference among the average drained volume in the treated groups. Seroma removal: Sapylin (5/78) and Avitene (5/68) needed less removals in comparison to the control group (14/78) Complications: significantly less in the Sapylin than in the control group ($p = 0.043$)

to be continued



Table 1. continuation

Author	Type of study	Number of participants	Technique	Seroma definition	Methodology	Results
Khan ²⁹	Clinical trial	65	Medication	Palpation, aspiration, and ultrasound	Patients – MRM Two groups: group A – conventional closure Group B – 120 mg Depo-medrol 1 hour before surgery Drain removal: < 30 ml/24h	Depo-medrol reduced total seroma incidence in the seventh PO day. Significant decrease of serum output in group B (755.4 ± 65 vs. 928.3 ± 102.5; <i>p</i> < 0.005) Draining duration: significantly lower in group B (6.5 ± 1.6 vs. 10.2 ± 2.2/ <i>p</i> < 0.005) Wound infection: slightly greater in group B
Garza-Gangemi et al. ²⁴	Clinical trial	80	Talc, iodine and drain	Palpation	Women – MRM Three groups: group A – control; group B – talc; and group C – iodine Drain removal: < 25 ml/24h	Seroma formation frequency: 21.2% and no statistical difference among the control groups and talc (23.3 vs. 19.4%; <i>p</i> = 0.70) Number of aspirations: no difference among groups (<i>p</i> = 0.87) Drained volume per aspiration: lower in the talc group compared to the control group (88.2 ± 73 vs. 158.3 ± 90.5; <i>p</i> = 0.17) The iodine group used more pain killers (74 vs. 60% and 40%), and there were no differences among the talc and control groups (<i>p</i> = 0.38). Total of days and pectoral drainage volume: control group – 8 ± 4.5 days/388 ± 302.3 ml; talc – 7.5 ± 7 days/404 ± 528.3 ml; iodine – 10 ± 5 days/620.3 ± 315.2 ml Total of days and axillary drainage volume: control group – 12.5 ± 6.5 days/847 ± 353.58 ml; talc – 11.3 ± 6.1 days/640 ± 1,031 ml; iodine – 18.5 ± 5.3 days/1,421.7 ± 625.4 ml
Selvendran et al. ³³	Cohort	94	Harmonic scalpel and conventional diathermy	Not informed	Women – submitted to one of the three surgical interventions: MRM, wide local excision + AL or just AL if they had SLNB + Two drains inserted in the patients who underwent MRM; one drain in the ones who underwent wide local excision with AL. Thoracic wall drain: removed after 24 hours Axillary drain: kept for 3 and 4 days or over if the production was > 30 and 50 ml/day	General average operation time: No statistical difference between HS and CD (MRM – <i>p</i> = 0.064; MA – <i>p</i> = 0.887). Average seroma volume in two days: 205 ml HS and 227.5 ml CD (<i>p</i> = 0.0913) Surgery duration of over 2.5 hours impacted the significant increase in seroma formation (<i>p</i> < 0.001) in comparison to 2 hours Patients who performed MRM had an increase in seroma volume (<i>p</i> < 0.05)
Gambardella et al. ⁴⁰	Cohort	100	Harmonic scalpel (HS), LigaSure (LS), Thunderbeat (TB), and electrocautery (EC)	Ultrasound	Women – MA, QU or AL Divided in four groups: EC, HS, LS, and TB Drain removal: < 30 ml/day	Surgical procedure duration: lower in the EC group (137.5 minutes for MRM, 88 minutes for QU + AL) compared to the other groups Significant statistical difference (<i>p</i> < 0.01) between EC and TB groups in relation to intraoperative blood loss Drained volume: significantly lower in the TB group (<i>p</i> = 0.002) compared to EC group Seroma formation rate: lower in the TB group (16%) compared to other groups (EC 64%; HS 24%; LS 44%)

Captions: MA = mastectomy; MRM = modified radical mastectomy; AL = axillary lymphadenectomy; SSI = surgical site infection; SLNB = sentinel lymph node biopsy; CWZ = Canisius Wilhelmina Hospital; RH = Rijnstate Hospital; SD = standard deviation; CI = confidence interval; OR = odds ratio; TPB = thoracic paravertebral block; NRS = numeric rating scale; EC = electrocautery; HS = harmonic scalpel; LS = LigaSure; TB = Thunderbeat; QU = quadrantectomy; CD = conventional diathermy; PO = postoperative.



group. Though the difference was not statistically significant, the patients in this group had an early drain removal and a lower serum output in the first three days. The authors suggested this technique can be considered.

Vasileiadou et al.²¹ investigated the adhesive effects of Glubran Cyanoacrylate, which has hemostatic, sealant, and adhesive properties. The group that used the adhesive showed a significant reduction in the amount and duration of draining, as well as in the total amount of seroma collected. This is due to the adhesive's quick polymerization, forming an elastic film with high resistance to traction and firm adherence to the tissue where it is applied. This approach is considered safe, easy to apply, and effective in preventing seroma formation, being a viable recommendation for high-risk patients.

The study by Boer et al.²³ investigated the use of a lysine-urethane-based adhesive with no drainage associated in comparison to a conventional closure technique with drain. Though the study has been closed prematurely due to sample issues, the findings were relevant. The patients who used drain reported more pain in the insertion, affecting sleep and limiting movement on the upper limb ipsilateral to surgery. This highlights the negative impact of the drain in the quality of life.

Van Bastelaar et al.³⁷ showed that the use of sealant had similar results to the quilting suture, suggesting that both techniques reduce the dead space by sealing skin flaps to the pectoral muscle, possibly decreasing lymphatic leaking and liquid build up. However, de Rooij et al.¹⁷ did not show significant differences among the groups (conventional closure (CON); suture (FFS); and sealant (FFG)) regarding drain liquid output, postoperative pain, functionality of the upper limb ipsilateral to surgery, tissue aspect, and postoperative infection. When comparing the used techniques, patients submitted to flap fixation techniques were submitted to fewer aspirations (CON 17.5% vs. FFS 7.3%) vs. FFG 10.8%; $p = 0.057$). However, no significant differences in seroma aspiration were observed in the flap fixation techniques ($p = 0.371$). It is worth highlighting that this difference was significant in the CON and FFS groups ($p = 0.025$).

Moreover, in the study by de Rooij et al.¹⁷, the CON group had more patients who visited the hospital than the ones submitted to suture or sealant. Though they have not reached statistical significance, these data are relevant, since patients with this kind of wound closure may generate more hospital expenses. The authors suggest that flap fixation with suture is the most recommended technique, as it results in fewer additional outpatient appointments in the postoperative period and requires fewer seroma aspirations compared to CON and FFG.

Several techniques based on distinct physiological theories have been tested to minimize seroma occurrence after breast cancer surgery. One article included in this review used thoracic paravertebral block (TPB), while other five articles tested some medication.

TPB may be effective in reducing seroma, since, in this approach, the sympathetic nerves are also blocked, causing venous relaxation and post-capillary resistance reduction, potentially contributing to decrease seroma occurrence. This technique is widely used as the gold standard for providing analgesia to patients submitted to breast cancer treatment surgery¹⁹.

Kus et al.¹⁹ evaluated the effect of TPB in preventing seroma and highlighted a reduction of 34.0% in its formation in comparison to the control group ($p < 0.05$). In addition, it was also effective in the postoperative analgesia in patients submitted to modified radical mastectomy (MRM). Although the pain score 24 hours after the surgery was similar in both groups ($p = 0.367$), the average consumption of morphine was significantly lower in the TPB group (5.6±4 mg in the TPB group and 16.6±6.9 mg in the control group/ $p < 0.001$). However, more studies are needed to evaluate the results of these approaches on the long-term.

Another approach based on physiological theories is the use of OK-432 (Sapylin), a lyophilized streptococcal preparation from a low-virulence strain of *Streptococcus pyogenes* incubated with penicillin^{28,27,34}. In the study by Yang et al.²⁸, a lower incidence of palpable seroma was observed when OK-432 was used during the operation (10 vs. 28/ $p = 0.001$). The intervention group had fewer seroma aspirations than the control group, and the use of this medication promoted a small advantage in reducing the average duration (4.52±1.09 days vs. 5.16±1.31 days; $p = 0.003$) and total drained volume (67.23 ml vs. 75.98 ml).

These findings are in line with the ones by Kong et al.³⁴. However, though the authors used the same medication, they applied it differently. Kong et al.³⁶ applied the medication to the wound after three days through the suction drain. Some patients presented fever as a side effect, attributed to the local inflammatory response, inducing cytokine production. At the same time, these cytokines contributed to tissue repairing, leading to sclerosis and limiting lymphatic leaking. Both studies emphasized that the use of OK-432 is safe, effective, and a viable option to reduce seroma.

Zhao et al.²⁷ compared the efficacy and safety of OK-432 (Sapylin) and Avitene in reducing seroma formation. Avitene is an absorbable hemostatic material composed mainly of bovine skin collagen which, upon contact with blood, triggers platelet aggregation, resulting in the



rapid formation of clots. The authors demonstrated that both Sapylin and Avitene can significantly reduce drain use duration. However, regarding total drained volume reduction, the Sapylin effect seems superior to the Avitene ($p = 0.285$). It is worth mentioning that Sapylin requires additional penicillin immersion time (30 minutes), which can be contraindicated for some patients, making it less widely used than Avitene in clinical practice.

The use of steroids can reduce seroma formation by attenuating the post-surgical trauma inflammatory response. Qvamme et al.²⁶ administered methylprednisolone in the postoperative period and observed a greater incidence of seroma in women submitted to MRM, confirming the tendency of greater seroma incidence in extensive surgeries. Moreover, the medication significantly reduced ($p < 0.001$) the seroma formation in women submitted to MA + SLNB compared to the placebo group, in addition to decreasing the cumulative seroma volume in the first 10 to 30 days after surgery ($p < 0.001$). However, this treatment did not influence seroma formation after MRM, on the contrary, it increased the seroma duration compared to the placebo (56 *vs.* 38 days, respectively; $p = 0.003$), suggesting the surgical trauma derived from MRM can be much more extensive to be effectively controlled by just one dose of steroid.

On the other hand, Khan²⁹ administered 120 mg of Depo-medrol steroid and observed a statistically significant reduction in total drain draining and in draining days ($p < 0.005$). There was also a decrease in total seroma incidence in the seventh postoperative day when compared to the control group (18% *vs.* 6%). These results have the potential to improve the quality of life of patients, reducing the total drain time and the need for analgesia. However, it is worth noting that the incidence of infection was slightly greater in the intervention group than in the control group (9.0% *vs.* 3.0%, respectively). The administration of antibiotics before and after surgery can mitigate this adverse effect. It is also relevant to consider that the drain itself can be an infection source.

Garza-Gangemi et al.²⁴ assessed the safety and efficacy of using talc (group B) and iodine (group C), compared to the standard treatment (group A). The iodine intervention had to be discontinued due to adverse effects. Regarding seroma formation, number of aspirations, use of postoperative pain killers, volume and draining days, no significant statistical differences were found between groups A and B ($p = 0.70$; $p = 0.87$; $p = 0.38$; $p = 0.35$; $p = 0.10$, respectively). Though the number of aspirations drained per patient was lower in the talc group compared to the control group, there was no statistical significance ($p = 0.17$). The application of talc was considered safe

in the short-term, but there was not enough evidence to support its use in preventing seroma.

The surgical techniques may affect the incidence of seroma, given that one of the hypotheses for its formation is cell damage and incomplete destruction of lymphatic vessels and ducts during dissection^{41,42}. Selvendran et al.³³ compared the harmonic scalpel to the conventional diathermy minimizing seroma formation. Though the harmonic scalpel may reduce the buildup of seroma due to a smaller thermal lesion, there was no significant statistical differences regarding surgery time, seroma volume and complications, indicating that the harmonic scalpel is not superior to the conventional diathermy.

Gambardella et al.⁴⁰ compared harmonic scalpels, LigaSure and Thunderbeat with electrocautery to investigate their efficacy in seroma formation and surgical results. The electrocautery is easy to manipulate but can increase the risk of seroma due to high temperatures. LigaSure offers hemostasis by pressure and electrothermal energy, while Thunderbeat uses ultrasonic bipolar energy for a quick tissue cut and vessel seal. The results highlighted that Thunderbeat was superior in reducing intraoperative blood loss, postoperative draining, and incidence of seroma compared to other devices ($p < 0.05$; $p = 0.004$, respectively). According to Gambardella et al.⁴⁰, more studies are needed to fully understand the advantages of this instrument.

CONCLUSION

Several techniques are used to prevent seroma formation after surgeries, but the extension of the surgical trauma is correlated to this complication. The seroma prevention strategies used in the analyzed studies minimized the incidence of seroma, except for talc and iodine; however, the studies that focused on the obliteration of dead space, whether with quilting suture or sealant, showed more significant statistical results, suggesting that they are promising for seroma prevention. Nonetheless, the lack of a defined standard for diagnosing seroma among the studies prevents a direct comparison between methods, which makes it complex to determine its efficacy.

CONTRIBUTIONS

All the authors have substantially contributed to the study design, acquisition, analysis and interpretation of the data, wording, and critical review. They approved the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interest to declare.



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