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Research article

Polyethylene Glycol-Coated Collagen Patch (Hemopatchtm) Versus Axillary Drainage. In Patients Undergoing Axillary Lymphadenectomy: Interim Analysis of a Multicentre, Prospective, Randomized and Controlled Studys

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Abstract

Purpose: To compare HemopatchTM versus axillary drainage in patients undergoing axillary lymphadenectomy. Additionally, potential predictors of clinical outcomes were also evaluated. Methods: Multicentre, prospective and randomized study conducted on adult women diagnosed with breast cancer. Patients were randomly assigned (1:1) to underwent surgery with either patch or drainage. The primary end-points were the incidence rate of seroma and the needed-to-attend to the emergency-room for any event-related to the surgery. Results: One-hundred-and-eighty-two patients were included in the analysis, 94 (51.7%) in the patch- and 88 (48,3%) in the drainage-group. The incidence of seroma was significantly higher in the patch-group (53.2%; 95%confidence-interval [CI]: 38.9%-70.1%) than in the drainage-group (30.2%, 95%CI: 20.2%-44.4%); p=0.0196. Conversely, the incidence of emergency-department visits was significantly higher in the drainage group (28.4%; 95%CI: 18.4%-41.9%) than in the patch group (8.5%, 95%CI: 3.7%-16.8%), p=0.0016. The number of outpatients visits necessary to control the seroma was significantly greater in the drainage than in the patch group; Hodges-Lehmann median difference: 2.0 visits; 95%CI: 1.0-2.0 visits, p<0.0001. Factor predictor of seroma in the multivariate analysis was patch (OR: 2.90; 95%CI: 1.50-5.63). Patch was associated with a lower-risk of attending to the emergency-room (OR: 0.20; 95%CI: 0.08-0.50, p=0.0005); whereas previous axillary-surgery was associated with a greater-risk (OR: 5.78; 95%CI: 1.64-20.42, p=0.0065). Conclusions: HemopatchTM did not significantly reduce the incidence rate of seroma. Nevertheless, its use has been associated with a lower number of postoperative-visits and a lower number of visits to the emergency department, which, therefore, may be helpful for reducing costs.

Keywords: Seroma; drainage; patch, breast cancer; axillary lymphadenectomy

Introduction

Over the last 30 years, significant changes have been introduced in the surgical management of breast cancer [1,2]. Currently, since most patients with breast cancer are diagnosed in the early stages of the disease [3], conservative surgery has become the treatment of choice [1,2].

Similarly, there have been significant changes in the management of the axilla in the last decade [1]. It is known that the presence of lymph node metastases is an important prognostic factor in breast cancer, influencing surgical, neoadjuvant and adjuvant treatment [4].

In those patients in whom it has not been possible to show the presence of breast cancer in the radiological examination or who have not manifested symptoms, their evaluation is fundamentally carried out by means of the selective sentinel lymph node biopsy (SLNB) [5]. In many patients with clinically negative nodes, SLNB has replaced routine axillary lymph node dissection (ALND), mainly because ALND is overly aggressive [6,7]. However, there are clinical situations in which ALND is indicated [7].

Traditionally all patients proceeded to ALND irrespective of nodal status [6], although the current trend is to perform increasingly conservative surgical approaches to the axilla [1,2,6,7]. However, the optimal management of the axilla has not been fully elucidated [8].

Despite all these facts, ALND is a surgical procedure usually performed as part of the surgical management of breast cancer, particularly in those cases in which there is axillary disease [9]. It provides accurate prognostic information essential for systemic treatment planning, better local control of the disease; and its use has been associated with greater survival [8,9].

ALND is associated with significant morbidity, including bleeding, postoperative infection, temporarily decreased range of motion of the shoulder, hematoma, lymphorrhagia requiring delayed drain removal, seroma, etc. Among them, seroma below skin flaps is the most common complication of breast cancer surgery, occurring in 15–81% of patients after node dissection [9-12]. Although it does not represent a complication that entails important morbidity, its onset can increase the incidence of postoperative complications, including delayed wound healing, infections, and a delay in the start of adjuvant treatment [9-12].

Different strategies have been tried to reduce the seroma, such as the use of suction drains [13]; physiotherapy [14,15]; meticulous closure of the axillary fossa with stitches [14,15]; early mobilization of the shoulder above 90º in the first week [16]; use of pharmacological aids such as haemostatic biological adhesives [17-19]; etc. However, to this day, drainage is considered the only valid method to reduce and treat seroma formation [14, 15]; although it is not free of complications. Drainage leads to discomfort, pain, and functional limitation of the arm, and its prolonged maintenance may be a cause of infection [15].

Due to this, alternatives are still being sought that reduce the complications associated with the use of drains. The polyethylene glycol (PEG)-coated patch HemopatchTM has been associated with positive outcomes in different surgical procedures [20,21].

The Spanish REDHEMOPACH was created with the purpose to examine, from a sample of Spanish breast cancer centres, a comprehensive dataset which includes patient characteristics, intraoperative variables, and postoperative management of breast cancer patients undergoing ALND with the PEG-coated patch HemopatchTM.

The aim of this paper was to perform an interim analysis of the REDHEMOPACH data base. This analysis was mainly focused on comparing the incidence rate of seroma between the PEG-coated patch versus (vs) axillary drainage in patients who underwent ALND. This study also evaluated the need to attendance to emergency room for any event-related to the surgery in both groups. In addition, our study also aimed to estimate and test factors for their association with the primary endpoints. Among them, we have paid special attention to the relationship between obesity and the incidence of seroma.

Methods

Study design and participants

Multicentre, prospective and randomized study conducted on adult women diagnosed with breast cancer, scheduled for conservative surgery, who underwent ALND.

The study protocol was approved by the Ethics Committee of the University Clinical Hospital of Valencia (Register number: REDHEMOPACH V.6; 29 de Julio 2020). Written informed consent was obtained in all the patients before the study. The ethical principles outlined in the Declaration of Helsinki and Good Clinical Practice were followed. The study was registered in ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT04487561).

Inclusion/exclusion criteria

Patients included in the study were women aged ≥18 years; diagnosed with breast cancer; who were scheduled for surgical treatment including conservative surgery and ALND; and willingness to comply with the investigators and protocol indications. Patients with selective sentinel node biopsy negative, subsidiary mastectomy patients and those who did not sign informed consent for axillary lymphadenectomy were excluded of the study.

Study groups

Patients were randomly assigned (1:1) to one of the study groups

Patch group

Before surgical closure of the axillary incision, the PEG-coated patch HemopatchTM (Sealing Hemostat, Baxter AG, Vienna, Austria) was placed. The Patch was placed in contact with the surgical bleb (white side). Sodium bicarbonate solution (concentration 1M) at room temperature was used in conjunction with patch application. A gentle and uniform pressure for 2 minutes using a dry gauze was performed and thereafter the incision was sutured by using the usual technique.

Drainage group

A 12G Redon drain was placed before surgical closure of the axillary incision. The 12G suction-drain tube was placed on the surgical bed. Subsequently, the skin was closed and the drainage

was connected to a redon-type suction bottle. The drainage was maintained, beyond the first 24 hours, if the volume drained was > 30 mL.

In both groups, an external compressive bandage was applied, which was maintained for ≤24 hours.

Study visits

Follow-up visits were scheduled at day-1 and day 7 (±1). The patients continued with follow-up visits every 7 days (±1) until the seroma was resolved.

Outcomes

The primary end-points were the incidence rate of seroma and the need-to-attend to the emergency room for any event-related to the surgery.

The secondary endpoints included the total volume of the seroma and the incidence of adverse events.

Additionally, a combined secondary objective has been selected that takes into account the incidence of seroma and having attended to the emergency department. According to this criterion, the following assumptions have been defined: (1) Complete success, defined as those cases in which the presence of seroma was not evidenced and they did not attend to the emergency room; (2) Qualified success, defined as those cases that, presenting seroma, did not need to go to the emergency room; and (3) Failure, as those cases with seroma who went to the emergency room. Patients who attended to the emergency department for any reason related to surgery, even if they had not developed a seroma, were also considered failures.

Definitions

Seroma was defined as a palpable, uninfected, and clear fluid collection (≥20 mL) under the wound (in the dead space of the axilla). Seroma must require aspiration due to either high output or after removal of the drain, which can delay wound healing and increase the risk of wound infection.

According to the World Health Organization (WHO) classification, body mass index (BMI) was categorized into six groups: underweight (<18.5 Kg/m2), normal weight (18.5 Kg/m2–24.9 Kg/m2), pre-obesity (25.0 Kg/m2–29.9 Kg/m2), obesity class I (30.0 Kg/m2–34.9 Kg/m2), obesity class II (35.0 Kg/m2–39.9 Kg/m2) and obesity class III (≥40 Kg/m2) [22]. Considering the low number of underweight and obese patients in our study, the sample was stratified into normal weight (defined as BMI <25 Kg/m2), pre-obesity (defined as BMI ≥25 Kg/m2 to <30 Kg/m2), and obese (defined as BMI≥30 Kg/m2).

Statistical analysis

A standard statistical analysis was performed using MedCalc® Statistical Software version 20.033 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022).

Sample size calculation was based on the assumption that a 18% difference in seroma incidence rate between the study groups was clinically relevant (two tailed test). Approxi mately 111 patients for each group were required, given an α of 0.05 and a 1-β of 0.80. A statistical power of 80% was chosen to decrease the risk of a false negative result. According to our experience (unpublished data) the incidence rate of seroma in the patch group would be 29% and according to a Cochrane Database systematic review [13], the incidence rate of seroma in conservative surgery with drainage would be 47%.

Of the 222 patients planned to be included, this interim analysis evaluated the data from 182 patients, 94 patients in the patch group and 88 subjects in the drainage one.

Descriptive statistics number (percentage), mean and standard deviation (SD), mean and 95% confidence interval (95% CI), mean and standard error (SE), median and interquartile range (IqR) or median (95% CI) were used, as appropriate.

Data were tested for normal distribution using a D'Agostino-Pearson test.

The two-tailed unpaired Student's t-test or the Mann-Whitney U test were used as appropriate to compare means between treatment groups for quantitative variables at baseline.

A logistic regression model was used to estimate and test factors for their association with seroma incidence and the need to attend to the emergency department. A backward strategy was adopted, with a statistically significant cut-off for variable screening of 0.05. Factors associated with progression in the univariate analysis at p≤0.1 were included in the multivariate analysis.

Regarding the role of obesity, two different analyses have been carried out. In the first one, the groups have been divided into normal weight (BMI<25Kg/m2); pre-obesity (BMI ≥25 Kg/m2 to <30 Kg/m2) and obese (BMI≥30 Kg/m2). In the second analysis, the groups were stratified into Non-obese (BMI<30 Kg/m2) and obese (BMI≥30 Kg/m2).

Categorical variables were compared using chi-square test and Fisher's exact test, as required. P value of less than 0.05 was considered significant.

Results

This interim analysis included 185 patients. Three patients were removed from the analysis because it was necessary to perform a mastectomy. A total of 182 patients were included in the analysis 94 (51.7%) patients in the patch group and 88 (48,3%) in the drainage one.

Table 1 shows the main baseline demographic and clinical characteristics of the study sample. With the exception of the presence of positive sentinel node, which was significantly higher in the patch group (p=0.0327), no significant differences were observed in any of the preoperative variables between the two groups.

Regarding the characteristics of the surgical procedure, no differences were observed between both groups (Table 2). The median number of patches used during the procedure was 1.0 (IqR: 1.0 to 1.0) patches, with 71 patients (76.3%) undergoing surgery with only one patch.

The incidence of seroma was significantly higher in the patch (incidence rate: 53.2%; 95% CI: 39.5% to 70.1%) than in the drain group (incidence rate: 30.2%, 95% CI: 20.2% to 44.4 %); incidence rate difference 22.5%; 95% CI: 3.6% to 41.4%, p=0.0196 (Table 3). In contrast, the incidence of emergency

department visits was significantly higher in the drainage (incidence rate: 28.4%; 95% CI: 18.4% to 41.9%) than in the patch group (incidence rate: 8.5%, 95% CI: 3.7% to 16.8%), incidence rate difference: 19.9%; 95% CI: 7.5% to 32.3%, p=0.0016 (Table 3).

The time elapsed between surgery and the first seroma puncture was longer in the patch group (Hodges-Lehmann median difference: 3.0 days; 95% CI: 0.0 to 5.0 days), although it was not statistically significant (p=0.0589).

The number of outpatients visits necessary to control the seroma was significantly greater in the drainage (median: 4.0 visits, IqR: 3.0 to 5.0 visits) than in the patch group (median: 2.0 visits; IqR: 1.0 to 3.0 visits); Hodges-Lehmann median difference: 2.0 visits; 95% CI: 1.0 to 2.0 visits, p<0.0001.

The overall success rate was significantly greater in the patch group than in the drainage one, although this difference was mainly due to the qualified success (Table 3).

There were no significant differences in the incidence rate of postoperative complications between the patch (6.4%, 95% CI: 2.3% to 13.9%) and the drainage (1.1%; 95% CI: 0.02% to 6.3%) groups, p=0.1192.

Factors that were significant predictors of seroma incidence in the univariate analysis included group assignment [Odds ratio (OR): 2.57; 95CI: 1.40 to 4.72; p=0.0024] and presence of preoperative comorbidities (OR: 1.96; 95% C: 1.05 to 3.66, p=0.0359).

Table 1. Baseline demographic and clinical characteristics of the study populations

	Overall (n=182)	**Patch (n=94)**	**Drainage (n=88)**	**p**
Age, years Mean (SD) Median (IqR)	57.0 (12.7) 56.5 (47.0 to 67.0)	56.1 (12.8) 55.0 (46.0 to 64.0)	58.0 (12.5) 57.0 (49.5 to 67.5)	0.3218[a]
BMI, Kg/m^{2†} Mean (SD) Median (IqR)	27.3 (6.3) 26.2 (23.1 to 30.0)	27.2 (6.9) 25.8 (23.0 to 29.0)	28.0 (5.7) 27.4 (23.7 to 30.4)	0.3842[a]
BMI, Kg/m^2, n (%) Normal weight Pre-obesity Obese	64 (36.0) 68 (38.2) 46 (25.8)	40 (42.6) 33 (35.1) 21 (22.3)	24 (28.6) 35 (41.7) 25 (29.8)	0.0675[b]
Comorbidities, n (%) Yes No	60 (33.0) 122 (67.0)	29 (30.9) 65 (69.1)	31 (35.2) 57 (64.8)	0.6362[c]
DM, n (%) Yes No	20 (11.0) 161 (89.0)	6 (6.4) 88 (93.6)	14 (16.1) 73 (83.9)	0.0559[c]
Previous axillary surgery, n (%) Yes No	14 (7.7) 168 (92.3)	7 (7.4) 87 (92.6)	7 (8.0) 81 (92.0)	1.0000[c]
Preoperative phenotype, n (%) Luminal A Luminal B Triple-negative HER2	55 (31.1) 78 (44.1) 32 (18.1) 12 (6.8)	28 (30.4) 38 (41.3) 21 (22.8) 5 (5.4)	27 (31.8) 40 (47.1) 11 (12.9) 7 (8.2)	0.6692[b]
PSN, n (%) Yes No	114 (62.6) 68 (37.4)	66 (70.2) 28 (29.8)	48 (54.5) 40 (45.5)	0.0327[c]
Neoadjuvant therapy, n (%) Yes No	102 (56.4) 79 (43.6)	55 (59.1) 38 (40.9)	47 (53.4) 41 (46.6)	0.4569[c]
ASA, N (%) ASA I ASA II ASA II	39 (21.5) 107 (59.1) 35 (19.3)	19 (20.2) 54 (57.4) 21 (22.3)	20 (23.0) 53 (60.9) 14 (16.1)	0.3425[b]

[a]Two-tailed unpaired Student's t-test
[b]Chi-squared for trend test
[c]Fisher exact test
[†]Data were missed in 7 patients.
[*]Ligasure® (Medtronic, Minneapolis, MN, USA).
[**]Harmonic® (Ethicon Endo Surgery, Albuquerque, NM, USA)
SD: Standard deviation; IqR: Interquartile range; BMI: Body mass index; HER2: human epidermal growth factor receptor 2; PSN: Positive sentinel node; ASA: American Society of Anaesthesiologist Physical Status Classification System.

Table 2. Clinical characteristics of the surgical procedure

	Overall (n=182)	Patch (n=94)	Drainage (n=88)	p
TAI, n (%)				
TPM	84 (46.8)	41 (43.6)	43 (48.9)	
PPM	89 (48.9)	46 (48.9)	43 (48.9)	0.1714[a]
U-shaped	4 (2.2)	3 (3.2)	1 (1.1)	
Others	5 (2.5)	4 (4.3)	1 (1.1)	
Single breast and axillary incision, n (%)				
Yes	24 (13.3)	12 (12.8)	12 (13.2)	1.0000[b]
No	157 (86.7)	82 (87.2)	75 (86.2)	
Ligasure®, n (%)*				
Yes	61 (33.5)	33 (35.1)	28 (31.8)	0.7535[b]
No	121 (66.5)	61 (64.9)	60 (68.2)	
Harmonic®, n (%)**				
Yes	98 (54.1)	49 (52.7)	49 (55.1)	0.7657[b]
No	83 (45.9)	44 (47.3)	39 (44.3)	
Number of patches, n (%)				
1	71 (76.3)	71 (76.3)	Not Applicable	N.A.
2	20 (21.5)	20 (21.5)		
3	2 (2.2)	2 (2.2)		
Removed lymph nodes				
Mean (SD)	16.2 (6.1)	16.3 (6.0)	16.2 (6.2)	0.8995[c]
Median (IqR)	15.0 (12.0 to 19.3)	15.0 (13.0 to 20.0)	15.0 (12.0 to 19.0)	
Positive lymph nodes				
Mean (SD)	3.0 (3.7)	3.3 (3.7)	2.8 (3.6)	0.3786[c]
Median (IqR)	2.0 (1.0 to 4.0)	2.0 (1.0 to 5.0)	2.0 (1.0 to 4.0)	
Intraoperative complications, n (%)				
Yes	2 (1.1)	1 (1.1)	1 (1.1)	1.0000[b]
No	180 (98.9)	93 (98.9)	87 (98.9)	

[a]Chi-squared for trend test.
[b]Fisher exact test.
[c]Two-tailed unpaired Student's t-test
Ligasure® (Medtronic, Minneapolis, MN, USA).
Harmonic® (Ethicon Endo Surgery, Albuquerque, NM, USA)
TAI: Type of axillary incision; TPM: Transverse to pectoralis major; PPM: Parallel to pectoralis major; NA: Not applicable; SD: Standard deviation; IqR: Interquartile range.

While factors significantly associated with the need to attend to the emergency room in the univariate analysis were previous axillary surgery (OR: 5.78; 95% CI: 1.64 to 20.42, p=0.0065) and the group assignment (OR: 0.23; 95%CI: 0.10 to 0.55, p=0.0009) (Table 4).

Table 4 gives the results of the multivariate analysis. Patch group assignment increased the OR for seroma by 2.9 folds (OR: 2.90; 95% CI: 1.50 to 5.63) after adjustment for relevant factors. The patch reduced the probability of attending to the emergency room by 80% (OR: 0.20; 95% CI: 0.08 to 0.50, p=0.0005) after controlling for other predictors. Finally, having undergone a previous axillary intervention increased the probability of attending to the emergency room by 5.8 folds (OR: 5.78; 95% CI: 1.64 to 20.42, p=0.0065) after adjustment for relevant factors.

Discussion

The incidence of seroma is probably one of the most frequent complications following breast cancer surgery [9-12]. Although its appearance does not represent a life-threatening condition, it accounts for prolonged patient discomfort which translates as pain, delayed wound healing, skin flap necrosis, repeated visits to outpatient clinics, and surgical-site infection [9-12].

The effectiveness of different strategies aimed at preventing or reducing the incidence of seroma has been previously analysed

Table 3. Overview of the incidence of postoperative outcomes in the Intent-to-treat study population

	Overall (182)	Patch (94)	Drainage (88)	p
Seroma, n (%)				
Yes	77 (42.3)	50 (53.2)	27 (30.7)	0.0196[a]
Day of seroma onset				
Mean (SD)	11.6 (5.4)	11.1 (5.8)	12.8 (4.0)	0.0589[b]
Median (IqR)	11.0 (8.00 to 15.0)	10.0 (7.00 to 14.5)	14.5 (10.0 to 15.0)	
Patients requiring seroma puncture, n (%)				
Yes	61 (33.3)	44 (48.4)	17 (20.0)	0.0001[c]
No	115 (65.3)	47 (51.6)	68 (80.0)	
Number of punctures[1]				
Mean (SD)	3.1 (3.1)	2.9 (2.1)	3.4 (4.9)	0.6909[b]
Median (IqR)	2.0 (1.0 to 4.0)	2.0 (1.0 to 4.0)	2.0 (1.0 to 4.0)	
Seroma volume, mL				
Mean (SD)	459.4 (518.2)	405.1 (338.3)	603.1 (824.0)	0.7885[b]
Median (IqR)	267.5 (140.0 to 660.0)	275.0 (150.0 to 660.0)	260.0 (75.3 to 782.5)	
Attendance to emergency room, n (%)*				
Yes	33 (18.1)	8 (8.5)	25 (28.4)	0.0016[a]
Reason, n (%)[‡]				
Seroma	11 (33.3)	7 (87.5)	4 (16.0)	
Redon	21 (63.6)	0 (0.0)	21 (84.0)	0.0053[d]
Pain	1 (3.0)	1 (12.5)	0 (0.0)	
Postoperative combined criterion, n (%)				
Success	149 (81.9)	86 (91.5)	63 (71.6)	0.0425[a]
Qualified success[#]	59 (32.4)	42 (44.7)	17 (19.3)	0.0027[a]
Complete success[#]	90 (49.5)	44 (46.8)	46 (52.3)	0.6004[a]
Number of outpatient visits†				
Mean (SD)	3.3 (2.5)	2.6 (2.1)	4.0 (2.7)	<0.0001[b]
Median (IqR)	3.0 (1.0 to 4.0)	2.0 (1.0 to 3.0)	4.0 (3.0 to 5.0)	
Complication related to drainage, n (%)				
Yes	24 (25.5)	0 (0.0)	24 (29.6)	0.0342[c]
No	70 (74.5)	13 (100.0)	57 (70.4)	
Type of Complication**				
Bleeding	0 (0.0)			
Drain pipe extrusion	15 (53.6)	Not Applicable		N.A.
Infection	6 (21.4)			
Pain	3 (10.7)			
Decubitus ulcer	4 (14.3)			
Axillary wound dehiscence, n (%)				
Yes	3 (1.6)	3 (3.2)	0 (0.0)	0.2467[c]
No	179 (98.4)	91 (96.8)	88 (100.0)	
Axillary wound infection, n (%)				
Yes	4 (2.2)	2 (2.1)	2 (2.3)	1.0000[c]
No	178 (97.8)	92 (97.9)	86 (97.7)	
Number of Redon bottles				
Mean (SD)	2.6 (1.5)	Not Applicable	2.6 (1.5)	N.A.
Median (IqR)	2.0 (1.0 to 4.0)		2.0 (1.0 to 4.0)	

[a]Chi-squared test
[b]Mann-Whitney U test
[c]Fisher exact test.
[d]Chi-squared test for trend
[1]Among patients who needed seroma puncture
*If the patient needed to go to the emergency department for any event related to the surgery.
‡Reason for attending to the emergency room.
⁂Among success subjects.
†Number of outpatients visits necessary to control the seroma
**Type of complication related to the drainage. Patients may have had more than one complication. The percentages were calculated according to the patients who had complications
NA: Not applicable; SD: Standard deviation; IqR: Interquartile range.

Table 4. Univariate and multivariate analysis of the 182 patients included in the study to evaluate the potential factors for seroma and whether the patient went to the emergency room. Factors associated with success in the univariate analysis at $p < 0.1$ were included in the multivariate analysis

Variable	Seroma				Need to attend to emergency room			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age*								
> 55 years	1.55 (0.86 to 2.80)	0.1496			1.52 (0.70 to 3.27)	0.2872		
BMI								
Ref normal weight								
Pre-obesity	1.36 (0.68 to 2.72)	0.3799			1.37 (0.56 to 3.38)	0.4936		
Obese	2.00 (0.93 to 4.29)	0.1090	1.90 (0.81 to 4.44)	0.1	1.61 (0.61 to 4.25)	0.3353		
BMI								
Ref no obese								
Obese	1.71 (0.87 to 3.35)	0.0359			1.37 (0.59 to 3.14)	0.5637		
Comorbidities								
Ref No								
Yes	1.96 (1.05 to 3.66)	0.0958	1.59 (0.76 to 3.31)	0.2	1.65 (0.76 to 3.57)	0.2042		
DM								
Ref No								
Yes	2.24 (0.87 to 5.78)	0.0958	1.96 (0.63 to 6.04)	0.2	2.14 (0.76 to 6.07)	0.1516		
Previous axillary surgery								
Ref No								
Yes	1.40 (0.47 to 4.18)	0.5458			5.46 (1.77 to 16.87)	0.0032	5.78 (1.64 to 20.42)	0.0065
Preoperative phenotype								
Ref Luminal A								
Luminal B	1.51 (0.76 to 3.02)	0.2427			0.60 (0.26 to 1.38	0.2301		
Triple-negative	1.86 (0.78 to 4.45)	0.1644			0.43 (0.13 to 1.42)	0.1662		
HER2	1.33 (0.38 to 4.70)	0.6614			0.27 (0.03 to 2.29)	0.2316		
PSN								
Reference No								
Yes	2.16 (1.15 to 4.07)	0.0169	1.93 (0.99 to 3.75)	0.0533	0.77 (0.36 to 1.669	0.5072		
Neoadjuvant therapy								
Ref No								
Yes	0.99 (0.55 to 1.78)	0.9629			0.59 (0.28 to 1.279	0.1783		

ASA								
Ref ASA I								
ASA II	1.40 (0.66 to 2.98)	0.3813			2.07 (0.66 to 6.48)	0.2120		
ASA III	1.75 (0.69 to 4.44)	9.2354			3.12 (0.87 to 11.22)	0.822	3.31 (0.83 to 13.28)	0.0911
Study group								
Ref Drainage								
Patch	2.57 (1.40 to 4.72)	0.0024	2.90 (1.50 to 5.63)	0.0016	0.23 (0.10 to 0.55)	0.0009	0.20 (0.08 to 0.50)	0.0005
Ligasure®								
Ref No								
Yes	1.13 (0.61 to 2.10)	0.7048			1.37 (0.63 to 2.98)	0.4303		
Harmonic®								
Ref No								
Yes	0.80 (0.44 to 1.44)	0.4590			1.04 (0.49 to 2.21)	0.9290		
Removed lymph nodes*								
> 15	1.19 (0.66 to 2.14)	0.5704			1.80 (0.84 to 3.87)	0.1301		
Positive lymph nodes*								
> 2	0.89 (0.49 to 1.64)	0.7124			1.47 (0.68 to 3.14)	0.3253		

*Reference group ≤ Median.
Ligasure® (Medtronic, Minneapolis, MN, USA).
Harmonic® (Ethicon Endo Surgery, Albuquerque, NM, USA)
BMI: Body mass index; DM: Diabetes mellitus; HER2: human epidermal growth factor receptor 2; PSN: Positive sentinel node; ASA: American Society of Anesthesiologist Physical Status Classification System.

in different clinical studies [13-19].

According to the results of our study, the incidence of seroma in the overall study population was 42.3% (95% CI: 33.4% to 52.9%), with a significantly greater incidence in the patch than in the drainage group (incidence rate difference 22.5%; 95% CI: 3.6% to 41.4%, p=0.0196).

To the best of our knowledge, this is the first prospective, randomized and controlled study evaluating the effect of the PEG-coated patch on preventing the incidence of seroma.

The effectiveness of the use of sealant agents to prevent the incidence of seromas after axillary lymphadenectomy has not been clearly established. Differences in the methodology of the studies, as well as the clinical diversity of the patients analysed, makes it difficult to draw conclusions [19,20,23,24].

Many different factors, including patient demographic and clinical characteristics (age, BMI, diabetes mellitus, etc.); tumour-specific characteristics (tumour staging or grading, or presence of positive sentinel node; treatment-related (neoadjuvant chemotherapy, previous axillary surgery, etc.) have been evaluated regarding their association with seroma incidence [25-27]. However, only a few of these factors seem to have a significant effect on seroma production [25].

Body weight [19,28] and BMI [23,25-28] have been associated with increased seroma formation. However, in the current study obesity was not significantly associated with the incidence of seroma.

Although in our study, the presence of preoperative comorbidities was associated with a greater probability of seroma in the univariate analysis, this result was not confirmed in the multivariate analysis.

These results are in agreement with those reported by Ohlinger et al [29], although other authors have shown opposite results [27].

In our study, neither the use of Ligasure® nor the use of Harmonic® have been associated with a lower probability of seroma. These results are in agreement with those published previously by Gambardella et al [30], who suggested that these devices did not have any significant impact on seroma formation.

Regarding the cumulative total lymph volume collected, this study did not find significant differences between the patch and drainage groups. However, the incidence rate ratio of patients with a seroma volume ≥1000 mL was 3.97 (95% CI: 0.45 to 47.54) time-fold greater in the drainage group, although it was not statistically significant (p=0.1025).

In our study, patients assigned to the patch group had a significantly lower need to attend to the emergency room compared to the drainage group. In fact, the patch reduced the probability of attending to the emergency room, for any event related to the surgery, by 80%. Moreover, the use of HemopatchTM, in patients who underwent breast cancer surgery, reduced significantly the number of outpatients visits necessary to control the seroma. Fewer postoperative consultations may indicate that seroma is more easily controlled in the patch group. Additionally, the lower rate of large-volume seromas in the patch group speaks in favour of this hypothesis.

However, additional analyses will be necessary at the end of the study to confirm this hypothesis. Although it was not assessed in the current study, reducing the need to attend to the emergency room and fewer outpatient visits necessary to control the seroma would

intuitively result in a smoother patient postoperative journey and increase overall satisfaction. Additionally, this may contribute to reducing significantly the costs, not only to the patient/family, but also to the Health Systems.

It is important to mention that the results of the current paper are a reflection of an interim analysis, which has not included the total sample planned at the beginning. Therefore, the final results and conclusions of our clinical trial may vary once the final analysis has been carried out.

Conclusions

In patients who underwent axillary lymphadenectomy, the PEG-coated patch HemopatchTM did not significantly reduce the incidence rate of seroma. Nevertheless, its use has been associated with a lower number of postoperative outpatient visits and a lower number of visits to the emergency department, which, therefore, may be helpful for reducing costs.

Because breast cancer is one of the most prevalent malignancies in women, a large number of axillary lymphadenectomies are performed every year. Therefore, it is crucial to have high-quality scientific evidence regarding the best practice management of these patients.

We have to wait for the final analysis of the results to establish the true value of using the PEG-coated patch in our clinical practice. In addition, the cost analysis may provide information on the cost-effectiveness of the procedure.

Abbreviations

ALND: Axillary lymph node dissection; BMI: Body mass index; CI: Confidence interval; G: Gauge; IqR: Interquartile range; OR: Odds ratio; PEG: Polyethylene glycol; SD: Standard deviation; SE: Standard error; SLNB: Selective sentinel lymph node biopsy; WHO: World Health Organization.

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Conflicts of Interest

None of the co-authors have any conflict of interest to declare.

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