Evaluating HEmopatch® in Reducing Seroma-Related Complications following Axillary Lymph Node DIssection: A Pilot Study (HEIDI)

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Abstract

Purpose: Axillary lymph node dissection (ALND) is performed to treat locoregional metastatic disease in breast cancer and melanoma patients. However, it is notorious for its complications, most commonly seroma formation and its sequelae. Ample research has been done to evaluate seroma formation after ALND; these results, however, have not been conclusive. Hence, this pilot study aimed to evaluate a readily available haemostatic patch, Hemopatch®, to assess its effect on seroma formation following ALND. **Methods:** In this pilot study, a prospective cohort of 20 patients receiving Hemopatch® following ALND was compared to a retrospective cohort of patients who underwent ALND between 2014 and 2019. The primary outcome measure was the number of patients developing clinically significant seroma (CSS) after ALND. Additionally, the number of wound complications, subsequent interventions, additional outpatient clinic visits, and drain output was assessed. Differences between groups were deemed clinically relevant if the proportions differed >50% between groups. **Results:** In total, 20 prospective and 42 retrospective patients were included. In the Hemopatch® group, 30% of the patients developed CSS, compared to 43% in the control group. Three patients in both groups developed a surgical site infection . Thirty-five percent of patients in the Hemopatch® group required additional unscheduled visits versus 62% of patients in the control group. **Conclusion:** The application of Hemopatch® after ALND did not lead to a clinically relevant reduction of CSS and wound complications. However, fewer Hemopatch® patients required additional outpatient clinic visits. Due to the limited amount of participants, the true value of Hemopatch® in ALND remains unclear.

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Introduction

With the shift from axillary lymph node dissection (ALND) to sentinel lymph node biopsy as a staging procedure in breast cancer and melanoma patients, the physical and psychological morbidity has been reduced significantly. As a therapeutic procedure, ALND is still performed in a substantial number of patients as an effective treatment for locoregional metastatic disease, and these patients are exposed to the complications of ALND, such as neuropathy, impairment of shoulder movement, arm lymphedema, and most commonly seroma formation [1]. With an incidence of 15–81%, seroma formation after ALND is regularly considered to be an unavoidable nuisance rather than a complication. Seroma, however, is associated with an increased risk of delayed wound healing, infection, pain, and skin necrosis with a prolonged hos-

pital stay, increased number of outpatient visits, additional interventions (e.g., aspirations), and even delay of adjuvant treatments [2–4].

The aetiology of seroma is multifactorial; residual dead space and leakage of lymph fluid are considered to be the most important causes [4]. Individual patient characteristics such as a high body weight and body mass index (BMI) also seem to predispose to seroma formation [2]. Strategies to reduce seroma formation have focused on obliteration of the dead space and on improved sealing of lymphatic vessels. Obliteration of dead space with external compression dressings did not show any advantage over standard dressings [5, 6]. Closing the dead space with various suturing techniques reduced clinically significant seromas (CSSs) in mastectomy and modified radical mastectomy. Flap fixation in the axillary area could be effective after ALND as a standalone procedure. However, it potentially leads to problems regarding cosmesis and mobility of the arm [2, 6–8]. Different surgical devices aimed to improve sealing of lymphatic and blood vessels, for example, a bipolar vessel sealing system and ultrasonic scalpel have shown contradictory results regarding incidence of seroma formation after ALND and are not considered helpful [9–12]. Chemical substances that seal small blood vessels by triggering collagen and fibrinogen syntheses could also contribute to sealing of the lymphatic vessels. Fibrin glue-coated collagen patches and fibrin glue application to the wound area were tested in ALND patients with ambiguous results regarding seroma prevention [3, 4, 13–17]. None of these studies provided proof of a good strategy to reduce the incidence of seroma after axillary lymph node clearance.

The Hemopatch® (Baxter International, Deerfield, IL, USA) is a collagen pad derived from bovine dermis, coated with pentaerythritol polyethylene glycol ether tetrasuccinimidyl glutarate (NHS-PEG). In contact with blood or other body fluids, the NHS-PEG forms a hydrogel which enhances its adhering properties and seals the tissue surfaces. In addition, the collagen induces aggregation of platelets. The hypothesis is that Hemopatch® seals blood and lymphatic vessels, in consequence reducing the incidence of seroma and its clinical sequelae. Hence, this pilot study aimed to assess the value of a different haemostatic sealant, the Hemopatch®, in ALND to reduce the incidence of seroma and seroma-related complications.

Materials and Methods

Study Design and Participants

A prospective cohort was compared to a historical cohort. Since this was an explorative proof of principle study, the aim was to include a pragmatically selected number of 20 patients in the prospective Hemopatch® group. All patients were included and treated in the Zuyderland Medical Centre, The Netherlands. Inclusion criteria were age ≥18 years and an indication for ALND combined with surgery for melanoma or breast-conserving therapy for breast cancer or for secondary ALND. Patients with an indication for modified radical mastectomy, pregnant patients, and patients who were unable to comprehend the implications and extent of the study to give an informed consent were excluded. All patients in the Hemopatch® group were evaluated at the outpatient clinic at 7–10 days, 6 weeks, and 3 months after surgery. This prospective cohort was compared to all patients undergoing surgery between 2014 and 2018 who met the same in- and exclusion criteria. Data of the control group were retrospectively retrieved from the electronic patient record system at the Zuyderland Medical Centre.

This study was approved by the Institutional Ethics Research Committee (METC Zuyd, Zuyderland Medical Centre, The Netherlands, METCZ20190124) and was prospectively registered at ClinicalTrials.gov (Identifier: NCT04185480). Written informed consent was obtained from all prospective cohort patients. Informed consent from patients of the historical cohort was waived by the Institutional Ethics Research Committee.

Study Interventions

All patients underwent ALND as standard of care. In the prospective group, a Hemopatch® of 45 mm by 90 mm was applied to the wound surface. A second Hemopatch® was applied if the total wound surface could not be covered by one patch. Subsequently, gauzes drenched in sodium bicarbonate solution were gently pressed on the Hemopatch® for 2 min to enhance the adhesive effect of the Hemopatch®. Additionally, all prospective and retrospective patients received a low vacuum drain (Armstrong medical) before wound closure. This was removed when drain production was <50 mL/24 h or after 5 days, whichever occurred first, as per standard hospital protocol.

Outcomes

The primary endpoint was the proportion of patients who developed CSSs. CSS was defined as (1) seroma that required an invention because of a risk of wound healing problems (wound breakdown, seroma leakage, or necrosis), (2) large seromas causing discomfort or pain and requiring aspiration, (3) contaminated/infected seroma requiring aspiration and antibiotics, or (4) abscess or infected seroma requiring incision and drainage.

Secondary endpoints consisted of wound complications, including the number of surgical site infections (SSIs), wound dehiscence, and the presence of wound necrosis. In addition, interventions required for complications, number of outpatient clinic visits in the first 3 months after surgery, number of days before drain removal, and drain output (millilitres) were assessed.

Statistical Analysis

All statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, version 26, New York, USA). Since this is a pilot study, all statistical null-hypothesis testing was explorative. The interpretation of results was based on clinical relevance and not statistical significance. For this reason, no power calculation was performed prior to this study. Differences between groups were deemed clinically relevant if proportions decreased or increased by 50% between groups.

Baseline characteristics and outcome measurements were described as mean ± standard deviation or in case of severe skewness, as median and interquartile range for continuous variables. Categorial variables were reported as absolute numbers and percentages. Differences in baseline characteristics were tested using the independent samples t test or the Mann-Whitney U test for continuous variables, depending on distribution of measurements. Pearson's χ^2 test was used for categorial variables, and in case of an expected cell count

Table 1. Baseline characteristics

	Hemopatch® group (n = 20)	Control group (n = 42)	p value
Age, years	63±12	58±16	0.123
Female, n (%)	19 (95)	27 (64)	0.010
BMI, kg/m²	30.0±6.4	26.5±3.8	0.010
Neoadjuvant therapy, n (%)	5 (25)	10 (24)	1.000
Smoking, n (%)	0 (0.0)	6 (14)	0.164
Anticoagulant use, n (%)	3 (15)	8 (19)	1.000
Charlson Comorbidity Index	5 (3.3–5.8)	4 (2.0–6.0)	0.397
Indication, n (%)			
Primary ALND for melanoma	1 (5.0)	7 (17)	
Secondary ALND for melanoma	2 (10)	19 (45)	0.003
Primary ALND for breast cancer	13 (65)	15 (36)	
Secondary ALND for breast cancer	4 (20)	1 (2.4)	
Lymph nodes removed, N	18 (14–23)	16.5 (11.3–20)	0.445
Lymph nodes with tumour cells, n	2 (1–4)	1 (0–2)	0.002
Patients with matted nodes, n (%)	1 (5.0)	0 (0.0)	0.323
Adjuvant therapy, n (%)	19 (95)	22 (52)	0.001

Continues variables are noted as mean ± SD or median (IQR) in case of severe skewness. Categorial variables are noted as absolute values (percentages). BMI, body mass index; ALND, axillary lymph node dissection.

of <5, Fisher's exact test was used. Differences between proportions were computed including 95% confidence interval (CI).

For primary and categorial secondary outcomes, the relevance of variables was assessed using univariate logistic regression. Multivariable logistic regression was performed to estimate the odds for CSS, wound complications, undergoing interventions, and the need for extra visits. Values were adjusted for BMI, gender, neoadjuvant chemotherapy, and adjuvant chemo- and radiotherapy, since these were deemed clinically relevant based on clinical experience and literature. All p values were interpreted in accordance with the American Statistical Association Statement on p values [18].

Results

Between June 2020 and May 2021, 20 patients were included in the prospective Hemopatch® group, and 42 patients were included in the retrospective cohort between March 2014 and November 2018. All prospective patients received axillary treatment including Hemopatch®. Eleven patients received one Hemopatch® and 9 patients received two.

Baseline characteristics are shown in Table 1. A statistically significant difference between groups was observed in the number of female participants and mean BMI. Indication for ALND, number of lymph nodes with malignant cells, and number of patients receiving adjuvant therapy was also statistically significantly different between groups.

Clinically Significant Seroma

During the 3 months after surgery, seroma was diagnosed in half of the Hemopatch® group patients (n = 10)

and in two-thirds of the control group patients (n = 28). Criteria for CSS were met in 6 patients (30%) of the Hemopatch® group and 18 patients (43%) of the control group.

Secondary Outcomes

In both groups, 3 patients developed wound complications. Three Hemopatch® patients developed SSI, while 2 control patients developed an SSI and 1 control patient developed wound dehiscence. Interventions for seroma or wound complications in the Hemopatch® group and the control group were seroma aspirations (4 vs. 16), surgical drainage (4 vs. 3), wound debridement (1 vs. 0), oral antibiotics (6 vs. 10), intravenous antibiotics (3 vs. 3), and vacuum-assisted closure therapy (1 vs. 1), respectively. Postoperatively, patients from both groups returned for a median of three visits in 3 months. For Hemopatch® patients, a median of two unscheduled visits were observed compared to 2.5 visits in the control group. Thirty-five percent of the Hemopatch® patients required one or more unscheduled hospital visits, compared to 62% in the control group. Detailed information regarding drain output was only available in 5 patients in the control group. The number of days before drain removal was reported in 9 patients in the control group. Results are displayed in Table 2.

Regression Analysis

Univariate analysis showed that none of the included variables were statistically relevant to affect secondary outcomes. Outcomes of both univariate and multivari-

Table 2. Primary and secondary endpoints per group

	Hemopatch® group (n = 20)	Control group (n = 42)	Difference in proportions (95% CI)
Seroma, n (%)	10 (50)	28 (67)	−17 (−43 to +8.9)
CSS, n (%)	6 (30)	18 (43)	−13 (−39 to +13)
Median seroma aspirations (numbers)	1 (1- -)	1 (1–1.5)	
Mean seroma aspiration, mL	445±405	441±241	
Wound complications, n (%)			
Total	3 (15)	3 (7.1)	+7.9 (−7.8 to +24)
SSI	3 (15)	2 (4.8)	+10 (−4.3 to +25)
Dehiscence	0 (0.0)	1 (2.4)	−2.4 (−9.1 to +4.3)
Interventions, n (%)			
Aspiration	4 (20)	16 (38)	−18 (−43 to +6.9)
Surgical drainage	4 (20)	3 (7.1)	+13 (−3.9 to +30)
Wound debridement	1 (5.0)	0 (0.0)	+5.0 (−1.7 to +12)
Oral AB	6 (30)	10 (24)	+6.0 (−17 to +29)
Intravenous AB	3 (15)	3 (7.1)	+7.9 (−7.9 to +24)
VAC therapy	1 (5.0)	1 (2.4)	+2.6 (−6.8 to +12)
Postoperative visits, N	3 (3–4)	3 (1–4)	
Patients with unscheduled outpatient clinic visits, n (%)	7 (35)	26 (62)	−27 (−54 to 0.0)
Unscheduled visits, n	2 (1–5)	2.5 (1–3.25)	
Drain output, mL	510 (195–606)	40 (33–195)*	
Duration of drainage, days	5 (3.25–6)	2 (1–6)**	

Continues variables are noted as mean ± SD or median (IQR) in case of severe skewness. Categorial variables are noted as absolute values (percentages). * n = 5. ** n = 9. 95% CI, 95% confidence interval; VAC, vacuum-assisted closure; mL, millilitre; SSI, surgical site infection; AB, antibiotics.

Table 3. Adjusted and unadjusted odds ratios for CSS, wound complications, and interventions (adjusted for BMI, gender, and adjuvant therapy)

	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
CSS	1.75 (0.56–5.44)	0.334	1.64 (0.43–6.27)	0.467
Wound complications	0.44 (0.08–2.38)	0.338		Unable to estimate
Interventions	1.22 (0.42–3.56)	0.713	0.73 (0.20–2.67)	0.648
Unscheduled visits	3.02 (0.99–9.16)	0.051	3.89 (1.02–14.85)	0.047

Control versus Hemopatch® (reference).

able regression analysis are displayed in Table 3. Due to the limited number of events, it was not possible to estimate an adjusted OR for wound complications.

Patients with a Hemopatch® are less likely to develop CSS (adjusted OR 1.64 95% CI: 0.43–6.27). In contrast, wound complications are more likely to develop in the Hemopatch® group (OR 0.44 95% CI: 0.80–2.38). BMI, gender, and adjuvant therapy seem to affect the likelihood of requiring an intervention, adjusted OR 0.73 95% CI: 0.20–2.67 versus unadjusted OR 1.22 95% CI: 0.42–3.56. The logistic regression models were not statistically significant.

Discussion

This is a small exploratory comparative study on the use of Hemopatch® in ALND for breast cancer and melanoma. The use of Hemopatch® results in a modest decrease in CSS from 43% to 30% when compared to a historical cohort. This difference was not statistically significant nor clinically relevant. This is the first study to evaluate the effect of an NHS-PEG-coated patch in patients undergoing ALND. Previously, fibrin-coated patches were assessed, and results were variable. Gasparri et al. [19] performed a meta-analysis with results from multiple studies on the use of fibrinogen sealant patches after ALND as well as after inguinofemoral, ilioinguinal,

pelvic, and para-aortic lymph node dissections. This meta-analysis showed a significant reduction of symptomatic seroma formation and wound complications in patients receiving fibrinogen sealant patches after surgery. However, in this meta-analysis, all types of lymph node dissections were analysed collectively. The effect on ALND seems to be less pronounced in this heterogeneous group. Results for this procedure vary from a statistically significant and clinically relevant reduction of seroma formation to a non-significant increase in seroma incidence after patch application [13–15]. The effect of Hemopatch® application in this study seems to be comparable to most data on fibrin-coated patches.

In the present study, Hemopatch® patients had a 15% incidence of wound complications compared to 4.8% of patients in the control group. According to the previously stated definition, this difference should be considered clinically relevant. However, this difference was based on a low number of events and was not statistically significant. The number of SSIs in the Hemopatch® group is consistent with previously reported rates of 9–15% after ALND [20, 21]. Additionally, a number of studies on the use of Hemopatch® for a variety of indications did not show an increased risk for infections [22, 23]. Another study on the use of Hemopatch® as a dural sealant reported an SSI rate of 4.5% compared to 1.0–5.6% after dural closure without Hemopatch® [24]. Previous results on fibrin-coated patches in ALND patients showed comparable incidences of wound complications between control and treatment groups [4, 15, 25].

Treatment of complications was also compared between groups. The number of seroma aspirations was reduced from 38% to 20% after Hemopatch® application and tends to be clinically relevant. On contrary, more patients underwent surgical drainage and were treated with intravenous antibiotics after Hemopatch® application, even though absolute numbers are relatively low. These differences could also be partly explained by recent protocol updates. Previously, seroma aspirations were performed at surgeons' own discretion. However, during this trial, aspirations were only performed when seroma was associated with pain or infection or if wound healing was at risk.

The total number of postoperative visits was equal in both groups. However, the proportion of patients requiring unscheduled clinical visits to evaluate (suspected) complications was almost twice as high in the control group. This correlates with a higher CSS rate in this group, requiring rapid assessments in the outpatient clinic or emergency department. Another possible explanation for this difference between groups might be due to the study protocol, as Hemopatch® patients came in for three standard visits, compared to only one or two planned visits in the control group. Patients may tend to wait for assessment of CSS or wound complications when an appointment is already planned in the near future. This was more likely in the Hemopatch® group.

The main limitation of this study is the limited number of participants and the non-randomized design. Some statistical associations could not be estimated due to the lack of sufficient numbers of events, and power to detect clinically meaningful differences was low. This is confirmed by the broad CIs of all parameters, which do not exclude a clinically relevant 50% reduction. The differences in baseline characteristics between the two groups are related to the use of a historic control group. Both the indication for ALND and the use of immunotherapy in melanoma patients have changed considerably after a number of recent studies [26–28] resulting in a smaller proportion of melanoma patients, more female patients, and the use of adjuvant immunotherapy in the 2020–2021 Hemopatch® cohort.

Additionally, data such as volume and duration of drainage could not be retrieved accurately in the retrospective control group, and a comparison with the Hemopatch® group was therefore impossible. However, as this was an exploratory pilot study, it was considered more important to obtain an estimate of the size of the clinically relevant effect.

Conclusions

The application of Hemopatch® after ALND did not lead to a clinically relevant reduction of CSS and wound complications. Although not statistically significant, fewer Hemopatch® patients required seroma aspirations. Hemopatch® patients required significantly fewer unscheduled visits. Due to the limited number of participants in this feasibility study, the true value of the Hemopatch® remains unclear.

Statement of Ethics

This study is in accordance with the ethical standard of the Institutional Research Committee and with the 1964 Helsinki Declaration and its later amendments. This study was approved by the Institutional Ethics Research Committee (METC Zuyd, Zuyderland Medical Centre, The Netherlands, METCZ20190124) and was prospectively registered at ClinicalTrials.gov (Identifier: NCT04185480). Written informed consent was obtained from all prospective cohort patients. Informed consent from patients of the historical cohort was waived by the Institutional Ethics Research Committee.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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