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Reduction of lymphocele rate in patients undergoing sentinel node biopsy for melanoma by intraoperative placement of plant-based hemostatic powder: Results of a prospective trial

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ABSTRACT

Background: Lymphocele is a complication of sentinel node biopsy (SNB) for melanoma. Plant-based hemostatic powder (PBHP) may have a lymphostatic benefit. We studied whether PBHP placed intra-operatively could reduce lymphocele rates.
Methods: We performed an open label, prospective, IRB -approved, before- and-after, matched control trial of PBHP placed into the wound in patients undergoing SNB of groin or axillary nodes for melanoma staging. Patient/tumor features and lymphocele rates were compared by standard statistical tests.
Results: 66 control and 66 treatment (49 axillary and 17 groin in each arm) SNBs were performed in 61 and 55 patients, respectively, for a total 132 SNBs in 116 patients. Patient and tumor features were similar between groups. Nineteen lymphoceles occurred (14.4%); lymphocele rates were 22.2% (14/66) in the control group and 7.6% (5/66) in the treatment group ($p = 0.026$). The reduction in lymphocele rates between arms was greater for axillary than for groin sites (87.5% vs. 33%); the axillary reduction was statistically significant ($p = 0.030$).
Conclusions: Intra-operative placement of PBHP reduced the rate of lymphoceles in patients undergoing SNB for melanoma.

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Introduction

The sentinel node (SN) is the first draining node in a patient with cutaneous melanoma, and the presence of tumor in the sentinel node was found to be the most important predictor of recurrence and death and a major determinant of disease free survival in the first Multicenter Selective Lymphadenectomy Trial (MSLT-1).[1,2] Accordingly, per current National Comprehensive Cancer Center guidelines, SN biopsy (SNB) is standard of care for patients with intermediate thickness (T2-T3) and thick (T4) melanomas,[3] as well as some thin (T1) but higher risk tumors.[4]

Although a minor procedure, SNB (which is usually done under the same anesthetic as the wide local excision (WLE) of the primary tumor [5]) is not without complications. In the MSLT-1 trial complications occurred in 10% of sentinel node biopsies, and were most commonly fluid collections at the SNB site (5.5%), followed by infections (4.6%) and wound disruptions (1.2%).[6] Other reported complications include lymphedema, nerve injuries, and pain, and our group has more recently added the formation of axillary webs ("Mondor's disease") to the list.[7]

Post-operative fluid collections are defined by the composition of the fluid they contain, and therefore those that occur in the area of lymphatic nodal beds after node removal are most correctly described as "lymphoceles". The incidence of lymphoceles is variably reported in the literature from as low as 2%[8] to high as 24%,[9,10] and likely depends on such factors as how carefully they are looked for, patient BMI, the number of nodes removed, site of the SNB (lymphoceles rates are lowest in the neck and highest in the groin [9]), and whether a drain is placed (which is rarely done).

In a 2013 report from our group we noted a 15% overall lymphocele rate (9.9% in the axilla and 26.5% in the groin), with the lowest rates after use of a bipolar vessel sealer (Ligasure; Medtronic, Dublin, Ireland).[11] However, lymphocele remains a common complication of SNB for melanoma in ours and other practices, and we have sought other intraoperative methods to reduce its'

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occurrence. Prior studies, mostly from the urologic literature[12,13] suggest that absorbable, plant-based hemostatic powder (PBHP) may have a lymphostatic benefit. We therefore studied the possibility that PBHP placed intraoperatively into the SNB wound could reduce lymphocele rates.

Materials and methods

Patients in this study had histologically proven, clinically node negative melanoma of the extremities or trunk (clinical stages I-II) and were referred to our Melanoma Program at the Oregon Health & Science University (OHSU) for surgical staging procedures (WLE and SNB). Patients with head and neck melanoma (in whom the SN proved on lymphoscintigraphy to be in the neck) were excluded because of the known low lymphocele rate in that nodal site. Patients signed a consent form to have their data for this study prospectively recorded in our OHSU IRB-approved (eIRB # 00001108) Sentinel Lymph Node Working Group (SLNWG) database, which is part of the national SLNWG data consortium. All patients were consented for the study by the principal investigator (JTV). All procedures were performed by a single surgeon (JTV) and the data was entered and protected per IRB guidelines by a single Certified Tumor Registrar (JF).

We performed an open label, prospective, before-and-after, matched-control trial of PBHP placed into the wound before closure in patients undergoing SNB of groin or axillary nodes for melanoma staging. Patents entered into the trial prospectively had the PBHP placed, and each SNB site constituted a study event. These events defined the "treatment" (or "after") arm, which was compared to a "control" (or "before") arm consisting of the same number of events collated retrospectively from the SLNWG data in patients who did not receive BPHP, starting backwards from the trial start data and matching patients by site, so that there were the same number of groin and axillary sites in each arm. All lymphoceles and other post-operative complications were detected clinically, and lymphoceles were defined as a palpable mass in the SNB wound >1 cm and confirmed by ultrasound to be fluid filled by two investigators (EM and JTV) at the first or any subsequent post-operative visits. All patients had at least 1 month of follow-up.

All patients in the study underwent WLE and SNB under the same (usually general) anesthetic as an outpatient using the standard "dual dye" technique (1% lymphozurin blue [isosulfan blue, patent blue] dye and Tcn^{99}-sulfur colloid). All radiotracer was injected by the Nuclear Medicine staff in their department within 24 h of the operation, and all patients had a lymphoscintigram performed by standard technique using a gamma detector immediately after radiotracer injection, before the patient left the Nuclear Medicine Department. All blue dye was injected by the surgical staff (JTV or EM) after the patient was anesthetized and before sterile prepping and draping.

All SNs were removed using a bipolar vessel sealer, in keeping with our published experience.[11] Our most recent method of dye injection, lymphoscintigraphy, SNB, and pathologic analysis of the SNs has been previously described in detail[14] and was uniform throughout this study. No patients had frozen section examination of their nodes (and thus no further nodal operation beyond the SNB) or drain placement. All patients in the treatment arm had up to 3 g of PBHP (Arista Absorbable Hemostat; Bard, Murray Hill, N.J.) placed into the wound after achieving hemostasis with the electrocautery and before closure.

Patient/tumor features (including age, gender, BMI, site of the SNB, tumor thickness, and number of SNs removed) and complications (including lymphocele rates) were extracted from the SLNWG data base and compared between groups by Chi-square analysis for categorical variables (gender and total numbers of lymphoceles), T-test for continuous variables (age, BMI, Breslow thickness, number of nodes per SNB sites), and Fisher's Exact Test for small numbers (number of lymphoceles per site [groin vs, axilla], other complications), using an online calculator.[15] Data was extracted and analyzed by two individuals not involved in the clinical portion of the study (JL, JF).

Results

Sixty-six control and 66 treatment SNBs were performed in 61 and 55 patients, respectively, for a total 132 SNBs in 116 patients. Table 1 compares the patient and tumor features between the two study arms; in general, patient and tumor features were similar. There was trend toward more females in the treatment arm ($p = 0.06$), while mean patient age, BMI, and tumor Breslow thickness were not significantly different. For the entire control arm there were a significantly higher mean number of nodes and positive nodes removed from each SNB site ($p = 0.007$ and 0.02, respectively), but the mean number of nodes removed from the lymphocele sites was not different ($p = 0.48$), nor was the number of SNB sites with positive nodes different. As noted above under Materials and Methods, the SNB site mix (groin vs. axilla) was identical because the controls were matched for site.

Table 2 shows the complications by study arm. There were 9 lymphoceles in 98 axillary SNB sites, for an overall axillary lymphocele rate of 9%, while there were 10 lymphoceles in 34 groin SNB sites, for an overall groin lymphocele rate of 33%. Overall, there were 19 lymphoceles in 132 SNB sites, for an overall 14.4% lymphocele rate, in keeping with our previously published study,[11] and the mid-range of the published literature.[8–10] Lymphocele rates were 22.2% (14/66) in the control group and 7.6% (5/66) in the treatment group ($p = 0.026$). Excluding one patient in the treatment group who had chronic malnutrition and wound complications at all sites, the lymphocele rate in the treatment group was 6% (4/66; $p = 0.020$). The percent reduction in lymphocele rates between arms was greater for axillary than for groin sites (87.5% vs. 33%), and the reduction in lymphocele rates in the axilla was statistically significant ($p = 0.030$). Eighty percent (4/5) of the lymphoceles in the treatment arm were in the groin. Other complications, including cellulitis, wound disruptions, and axillary webs, were uncommon and the overall number of complications was not significantly different between groups ($p = 0.49$).

Table 1
Patient and tumor features.

Feature	Study Arm	Control Arm	p value[15]
No. of SNB sites	66	66	–
No. of patients	61	55	–
No. of axillary SNBs	49	49	–
No of groin SNBs	17	17	–
No. of Males	25	32	
No. of Females	36	23	$p = 0.06$[b]
Mean age (years)	59.4	58.7	$p = 0.7$[a]
Mean BMI	27.8	29.1	$p = 0.21$[a]
Mean Breslow thickness (mm)	2.4	2.85	$p = 0.45$[a]
Mean number of nodes/SNB	1.7	2.5	**$p = 0.007$**[a]
Mean # nodes/SNB sites with a lymphocele	1.6	2.0	$p = 0.48$[a]
Mean number of + nodes/SNB	1.0	1.3	$p = 0.02$[a]
No. + SNB sites	11	13	$p = 0.65$[a]

Abbreviations: No. = number; SNB = sentinel node biopsy; + = positive (tumor-containing).
BOLD = significant at 0.05.
[a] By T-test.
[b] By Chi-square test.

Table 2
Complications of SNB.

Complication	Study Arm	Control Arm	p value
Lymphocele	5	14	**p = 0.026**[a]
Groin	4	6	p = 0.71[b]
Axilla	1	8	**p = 0.030**[b]
Other			
Cellulitis	1	0	
Wound disruption	1	1	
Axillary web	1	4	
Hematoma	0	1	
Total	3	6	p = 0.49[b]

Abbreviations: No. = number; SNB = sentinel node biopsy.
BOLD = significant at 0.05.
[a] By Chi-square test.
[b] By Fisher's Exact Test.[15]

Discussion

SNB is pivotal in the management of clinically node negative melanomas but it is not without complications. Although lymphoceles usually resolve with observation or aspiration, the natural history is uncertain; they occasionally require surgical drainage and can become fairly troublesome to the patient and provider. Lymphocele formation is likely multifactorial, and causes cited include lymphatic disruption unrecognized through the typically small incisions used for SNB,[11] the local inflammatory response of surgical intervention, dead space created by the node removal, [16] fibrinolytic activity in lymph and serum,[17] and mobilization of the extremity after operation.[18] Because many of these factors cannot or should not be modified, our group has been interested in the intraoperative use of devices[11] and materials that may be lymphostatic.

All PBHPs are hemostatic, but some manufacturers claim that their agents have lymphostatic properties as well. Published data for this is sparse. The urologic literature contains two reports of the reduction of lymph collections after the placement of PBHP intraoperatively during robotic prostatectomy and pelvic node dissection[12] and renal transplantation.[13] A randomized controlled trial (RCT) of the same PBHP we used for our study (Arista), also placed into operative beds before closure (in this case after thyroidectomy with or without neck node dissection) is looking at drainage (presumably lymph) output, but this trial is ongoing[19] and there are no reported results.

We chose to study a particular PBHP (Arista) for a theoretical reason: it contains microporous polysaccharide hemospheres (MPHs). MPHs not only activate the coagulation cascade but they cause tissue desiccation,[19] which presumably seals capillaries and could theoretically also seal small lymph vessels left open by electrosurgical devices. Further, this particular PBHP has been shown to be fairly inert and well tolerated. Indeed, we saw only one wound infection, one axillary web, and one healing problem in the study arm, not significantly different than in the control arm (Table 2).

Our study demonstrated that 1) lymphoceles remain a common occurrence in SNB (the overall rate in the study was 14.4%), and 2) PBHP appeared to significantly reduce the rate of lymphoceles for the overall and axillary groups. The number of groin cases in our study was low and we may see a statistical improvement in that group as well with further study, although it is also clear that groin lymphoceles remain a challenge-they accounted for 80% (4/5) of the lymphoceles in the treatment arm.

This study had some limitations. First, the numbers were relatively small (132 SNB sites), which actually *increases* the risk of a type II error (failure to reject the null hypothesis) and-as noted above-likely contributed to the failure to see a statistically significant lymphocele reduction in the groin SNBs. Second, the mean number of nodes removed per SNB incision (a known risk for lymphocele)[11] was higher in the treatment arm, but this did not reach significance when we looked only at the SNB sites with lymphoceles.

Third, the study was not a RCT, and according to the Canadian Task Force on the Periodic Health Examination Levels of Evidence only a RTC can provide level I evidence. Our trial can therefore only provide level II.1 evidence to support the use of PBHP[20] for lymphocele reduction. However, because groin and axillary sites have different lymphocele rates we felt that it was important to match the control SNBs by site (Table 1), as patients were enrolled as they came to our practice, and a randomized study could therefore result in an uneven site mix between arms. Indeed, when we initially analyzed the data using a consecutive (convenience) sample of unmatched controls, the control arm had twice as many groin sites as the study arm, resulting in a very low p value, which we felt was due to this bias.

Fourth, we conducted our study as an open label trial, which can lead to Hawthorne effect (observer and performer bias toward the treatment arm). This decision was reinforced by the fact we could not obtain a placebo for the PBHP that did not contain plant-based powder, and we attempted to minimize observer bias by disconnecting the treatment from the data teams of the study. Besides this disconnection and the site matching, our study had another strength: lymphocele rates vary greatly between centers and surgeons,[8–10] so that the single surgeon design gave some consistency to surgical technique and the resultant lymphocele rates.

We did not do a formal cost analysis. We *can* evaluate charges: because the average patient charge for a 3 g container of Arista at our institution at the time of the study was $210, the study resulted in an increase in patient charges of $13,860 (66 × $210). Since the treatment arm had 9 less lymphoceles than the study arm, the charge of preventing 1 lymphocele in this study was $1540 (13,860/9). The treatment of lymphoceles increased costs but did not increase patient charges per se; we did not charge for the ultrasounds, drainage, or observation of lymphoceles.

As a result of this study we plan to continue to use of PBHP in our SNBs, and we are continuing to accrue data, especially for groin SNBs. At the same time, we recognize that groin lymphoceles may remain a difficult (and we believe, under-reported) issue and are looking into other ways to further reduce them.

Conclusions

Intra-operative placement of PBHP may be able to reduce the rate of lymphoceles in patients undergoing SNB for melanoma. The reduction we observed was greater for axillary sites; lymphoceles in groin sites remain a challenge, and further study is required.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2019.02.016.

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