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Prophylactic incisional negative pressure wound therapy shows promising results in prevention of wound complications following inguinal lymph node dissection for Melanoma: A retrospective case-control series

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Abstract *Background:* Inguinal lymphadenectomy (ILND) for melanoma is associated with a number of complications including seroma, surgical site infection (SSI), and lymphedema. Incisional negative pressure wound therapy (iNPWT) has shown promising results in preventing postoperative morbidity across a wide variety of surgical procedures, but these results are yet to be investigated in patients undergoing ILND for melanoma.
Methods: In this study, we reviewed the data of 55 melanoma patients treated with ILND between January 2015 and January 2017 at Odense University Hospital. Patients were followed up until April 2018 for the occurrence of seroma, SSI, and lymphedema. We used prophylactic iNPWT after ILND in 14 patients and compared their morbidity outcomes with the 41 patients receiving standard postoperative wound care in the same period.
Results: The iNPWT intervention significantly reduced seroma compared to the control group (28.6% vs. 90.3%, $p < 0.001$) and had a trending impact on wound infection (42.9% vs. 65.9%, $p = 0.13$). The effect was not significant for the prevention of lymphedema (35.7% vs. 51.2%, $p = 0.33$). Because the iNPWT group had relatively fewer incidences of seroma, SSI, and lymphedema, the iNPWT intervention was more cost-effective than conventional wound care (US$911.2 vs. US$2542.7, $p < 0.05$).

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Conclusion: The use of prophylactic iNPWT significantly reduced seroma formation following ILND. These promising results, however, need to be confirmed in a future prospective randomized trial.

Introduction

Inguinal lymph node dissection (ILND) is often indicated when treating malignant melanoma with a high tumor burden.[1,2] Postoperative complications following ILND are frequent as patients often develop seroma, surgical site infection (SSI), and/or lower limb lymphedema.[3,4] These debilitating short- and long-term complications are often associated with an impaired quality of life for the patients as well as time-consuming inpatient and outpatient visits, thereby increasing healthcare costs.[5,6]

Incisional negative pressure wound therapy (iNPWT) is a mechanical treatment modality that facilitates wound healing through vacuum-assisted closure. The iNPWT package consists of a portable single-use battery-powered device with longevity of up to 7 days and 2 wound dressings. The treatment reduced interstitial fluid, wound edge stress, and morbidity.[7-9] Prophylactic iNPWT for closed incisions reduced seroma and wound infection rates across other high-risk surgeries.[9] The safety and efficacy of iNPWT in cancer surgery are yet to be investigated thoroughly, and it is yet to be considered, whether iNPWT can reduce wound complications following ILND in patients with melanoma.

The aim of this study was to examine the effectiveness of a portable iNPWT in preventing seroma, SSI, and lymphedema after ILND in patients with malignant melanoma.

Methods

In this retrospective study, we extracted data from the charts of two patient cohorts, i.e., patients with metastatic melanoma treated with ILND with and without postoperative iNPWT. All patients underwent ILND between January 1, 2015, and December 31, 2016, at Odense University Hospital, Denmark, and postoperative complications were assessed retrospectively using electronic medical charts until March 31, 2018. We collected data of patient demographics, medical history, postoperative seroma, SSI, and lymphedema. Hypertension was recorded, if patients received one or more antihypertensive prescription drugs. Postoperative seroma was defined as inguinal transcutaneous fluid aspiration within the first 3 months after ILND. At our institution, seromas are generally drained based on a clinical decision to relieve patient discomfort. Only seromas with an aspirated volume of 30 mL or more were noted. Postoperative wound infection was defined as any prescription of antibiotics administered on infectious indications to the inguinal wound up to 3 months after ILND. Infections were treated with dicloxacillin or flucloxacillin based on a clinical decision and a new check-up was scheduled after 7 days. Lymphedema was defined, if patients had received physiotherapeutic lymphedema treatment to the correlating limb in the period between ILND and March 31, 2018. Regular dressing changes were not planned (e.g., every third day). Dressing changes would only be executed if the dressing would get permeated.

The healthcare costs related to the treatment of postoperative complications were estimated using repayment rates for the given treatment.[10] In Denmark, the government reimburses the hospitals for their medical care expenses. Therefore, specific codes and reimbursements costs were available for outpatient visits, seroma punctures, and physiotherapeutic lymphedema treatment. Reimbursement costs were converted from Danish krone to US dollars using a 0.15 conversion rate. No specific codes were available for wound infection and antibiotic prescriptions, and the costs related to these treatments are reimbursed as just an outpatient visit. Postoperative costs for all patients were calculated by multiplying the reimbursements costs for seroma (US$526.95), wound infection (US$283.65), and lymphedema treatments (US$283.65) with their respective incidences. For each patient, multiple seroma incidences were recorded, but there was only one incidence of wound infection and physiotherapeutic lymphedema treatment. For patients in the iNPWT group, we additionally added the price for one iNPWT device for all patients (US$123.75). Healthcare costs were compared between the iNPWT group and the control group.

Surgical technique

The ILNDs were performed as standard dissections. All lymph nodes and adipose tissue were removed inside the triangular region delineated by the sartorious and adductor longus muscle and inguinal ligament. The great saphenous vein was routinely sacrificed, and we did not use a Sartorius switch. At the end of the procedure, two suction drains were placed in the surgical cavity distally to inguinal wound. In the case of postoperative iNPWT treatment, the dressing was applied over the inguinal suture line immediately after wound closure (Figure 1). The iNPWT device exerted a continuous pressure of 125 mmHg.

Statistical methods

The baseline characteristics were described as mean ± standard derivation (SD) for continuous parametric variables, median (interquartile range (IQR)) for continuous nonparametric variables, and rounded frequencies (%) for categorical variables. STATA 14 (StataCorp. 2015. Stata Statistical Software: Release 14., College Station, TX: StataCorp LP) was used for the statistical analysis and conducted with a two-tailed significance level of 0.05 and reported with 95% CI when applicable. The

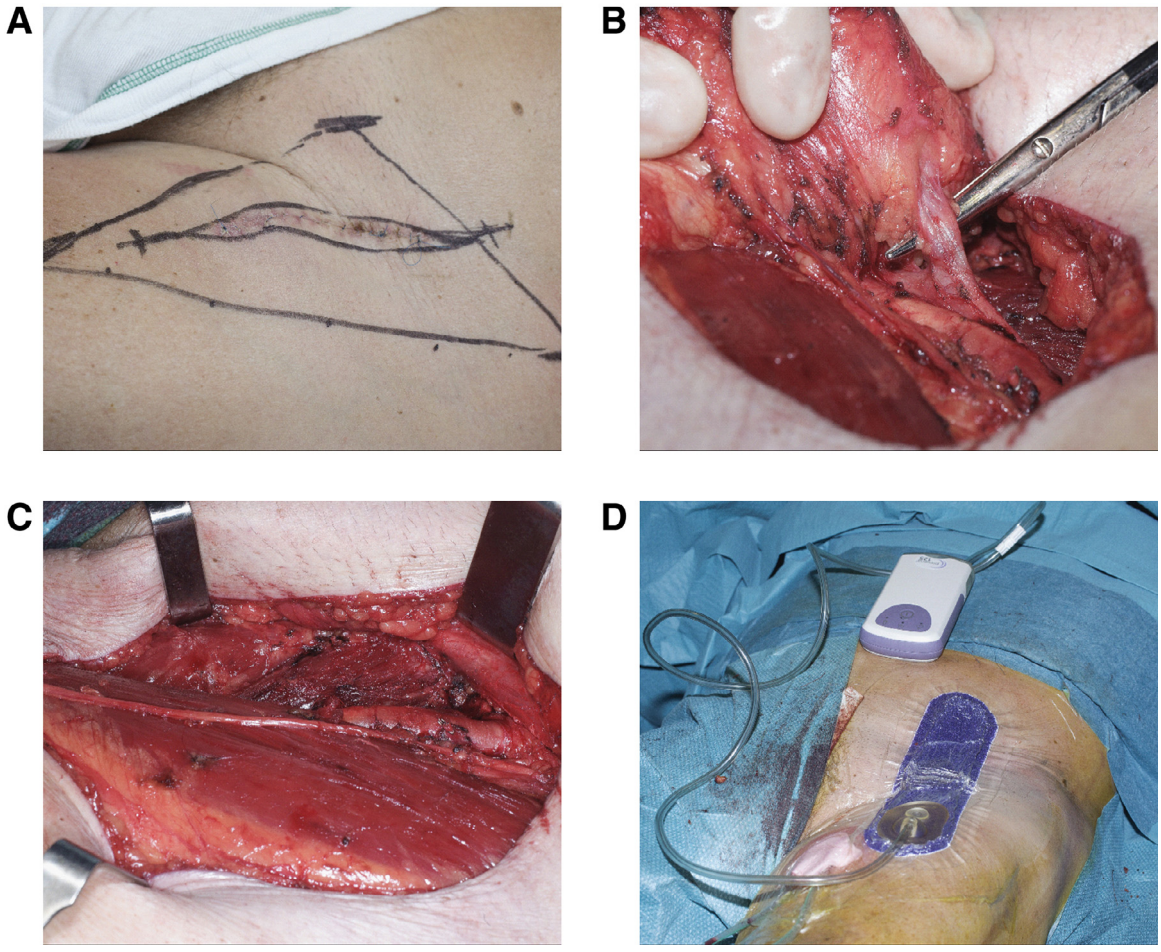

Figure 1 This figure shows the inguinal lymph node dissection with iNPWT application. (A) Preoperative marking of the inguinal triangular delineated by the sartorious and adductor longus muscle and inguinal ligament. Scar from sentinel lymph node biopsy in the center. (B) Identification and ligation of the great saphenous vein. (C) Inguinal area after removal of lymph nodes and adipose tissue and ligation of the great saphenous vein. Lateral cutaneous nerve is identified in the middle of the incision. (D) After wound closure, iNPWT was performed over the inguinal suture line. The device exerted negative pressure corresponding to 125 mmHg. Two suction drains were placed distally to the operated inguinal site.

baseline characteristics were compared between patients treated with conventional postoperative wound dressing and prophylactic iNPWT by unpaired *t*-test, chi-square test, or Mann–Whitney test depending on data type and distribution. The numbers needed to be analyzed were calculated as 1/(absolute risk reduction).

Results

We included 55 patients who received melanoma-related ILND between January 1, 2015, and December 31, 2016, at our institution. Following ILND, we treated 14 patients with iNPWT over the inguinal suture line for up to 7 days, and 41 patients received conventional wound care dressing (Micropore™ tape, 3M, Copenhagen, Denmark). ILND was performed for both macro- and micrometastatic melanoma. In micrometastatic subpopulations, 13 patients had a median melanoma thickness of 2.08 (1.94) mm in the iNPWT group and 35 patients had a median melanoma thickness of 2.08 (2.71) mm in the control group. There was no statistically significant difference in melanoma thickness between subpopulation groups undergoing ILND for micrometastatic disease ($p = 0.79$). Patients receiving iNPWT wore the dressing until discharge. Patients were discharged after removal of the last suction drain, ranging from the 5th to the 7th postoperative day. The mean number of days with iNPWT was 5.71 $\pm$ 0.40 days. The median number of follow-up for all patients was two years and 64 $\pm$ 273 days, and patient demographics were similar between treatment groups (Table 1). A seroma formation was treated at least once in 4 out of 14 patients (28.6%) in the iNPWT group and 37 out of 41 patients (90.3%) in the control group (Table 2). Patients who received prophylactic iNPWT were significantly less likely to develop treatment-necessitating seromas than the controls ($p < 0.001$) (Figure 2(A)). The color of aspirated seromas was described as straw yellow in the journals regardless of patients having signs of simultaneous wound infection or not. Additionally, patients in the iNPWT group had, on average, a lower number of treated seroma than patients in the control group (mean 1.1 vs. 4.2, $p < 0.001$) (Figure 3). A SSI was treated in 6 of 14 patients (42.9%) in

Table 1 This table shows the demographics of patients in the control and iNPWT groups. There were no significant differences in the demographics between groups. N.s. = p-value not significant.

Variable		Controls ($n = 41$)	iNPWT ($n = 14$)	p-value
Age (years)	Mean ± SD	57.88 ± 15.27	59.93 ± 13.03	0.65 (n.s)
Sex (Females)	Number (%)	23 (56.10%)	8 (57.14%)	0.95 (n.s)
Hypertension	Number (%)	14 (35.15%)	6 (42.86%)	0.75 (n.s)
Body Mass Index (kg/m^2)	Mean ± SD	26.64 ± 4.25	26.74 ± 3.28	0.94 (n.s)
Micrometastatic ILND	Number (%)	35 (85.37%)	13 (92.86%)	0.66 (n.s)
Number of lymph nodes removed (pathology verified)	Mean ± SD	10.34 ± 3.30	9.79 ± 3.49	0.59 (n.s)
Number of days with suction drains/until discharge	Mean ± SD	5.56 ± 0.23	5.71 ± 0.40	0.74 (n.s)
Total volume in suction drains (ml)	Mean ± SD	876.37 ± 591.50	612.79 ± 442.24	0.13 (n.s)

Table 2 This table shows the distribution of postoperative events in the control and iNPWT groups. N.s. = p-value not significant.

Postoperative events		Controls ($n = 41$)	Inpwt ($n = 14$)	p-value
Seroma	Number (%)	37 (90.24%)	4 (28.57%)	<0.001
Number of seromas treated	Mean ± SD	4.20 ± 3.36	1.07 ± 1.20	<0.001
Surgical site infection	Number (%)	27 (65.85%)	6 (42.86%)	0.13 (n.s)
Lymphedema	Number (%)	21 (51.22%)	5 (35.71%)	0.32 (n.s)

the iNPWT group and 27 of 41 patients (65.9%) in the control group. The effect was trending in favor of iNPWT, but it did not reach statistical significance ($p = 0.13$) (Figure 2(B)). In this study, lymphedema was diagnosed after 178.22 ± 20.89 days. Lymphedema was diagnosed in 5 out of 14 (35.7%) patients in the iNPWT group and 21 out of 41 patients (51.2%) in the control group. The effect was not statistically significant ($p = 0.33$) (Figure 2(C)). Using the event rates for seroma in the iNPWT and control groups, the number of patients who required iNPWT to prevent seroma in one patient is 2 (rounded up from 1.62). Similarly, the number of patients who required iNPWT to prevent SSI and lymphedema is 5 (rounded up from 4.35) and 7 (rounded up from 6.45), respectively. The postoperative treatment costs were calculated using reimbursement codes corresponding to the treatment of each seroma (US$526.95), SSI (US$283.65), and lymphedema (US$283.65) for all patients in the iNPWT and the control groups. The postoperative treatment costs in the iNPWT group additionally include charges for the iNPWT device used (123.75US$) for all patients. Because of the relatively fewer incidences of seroma, SSI, and lymphedema in the iNPWT group, the iNPWT intervention was cost-effective compared to conventional wound care (US$911.2 vs. US$2542.7, $p < 0.05$) (Figure 4). The iNPWT wound dressing was changed in one patient on the second postoperative day due to permeation. All other iNPWT patients were able to wear the dressing until discharge. All iNPWT patients were able to wear the iNPWT dressing underneath the postoperative compression thighs. Hydrocolloid wound bandages such as Duoderm® or similar adhesions were not used in this study. Regional recurrences were confirmed by pathology in 1 of 14 (7.1%) patients receiving iNPWT and 1 of 41 patients (2.4%) in the control group. The difference in regional recurrences was not statistically significant ($p = 0.49$).

Discussion

Patients undergoing ILND for melanoma are subject to a number of postoperative complications, and we investigated whether iNPWT could reduce wound complications and explored whether the treatment improved the socioeconomic burden of ILND. We found that patients treated with iNPWT had a reduced risk of developing seroma that needed treatment and overall had a lower postoperative treatment cost. These findings suggest that prophylactic iNPWT after ILND can decrease patient morbidity and treatment costs for this group of patients.

Patients with malignant melanoma along with a low lymph node tumor burden can now be treated conservatively[11]; however, ILND is still indicated for patients with a high lymph node tumor burden. Lymph node dissection offers regional control and accurate staging for adjuvant therapy[12] and also carries a high risk for complications. Complications are frequent following inguinal lymphadenectomies (ILNDs), and consequently, a number of prophylactic procedures have been proposed to prevent the complications and associated morbidity, such as a minimally invasive lymphadenectomy techniques, prophylactic lymphovenous anastomosis, fascia preservation, and lymphatic flaps; however, their efficacy and oncological safety are yet to be demonstrated by high-quality trials.[13-16] In this study, the incidence of seroma was somewhat higher than the incidence reported previously,[4] and it has been speculated whether surgical complications are generally underreported in the literature.[17,18] In this study, patients were treated at a university hospital that is solely responsible for all melanoma related-ILND in Southern Denmark, which compromises approximately 1.2 million people in a 12,256 km^2 area,[19] and postoperative treatment data were available from other hospitals.

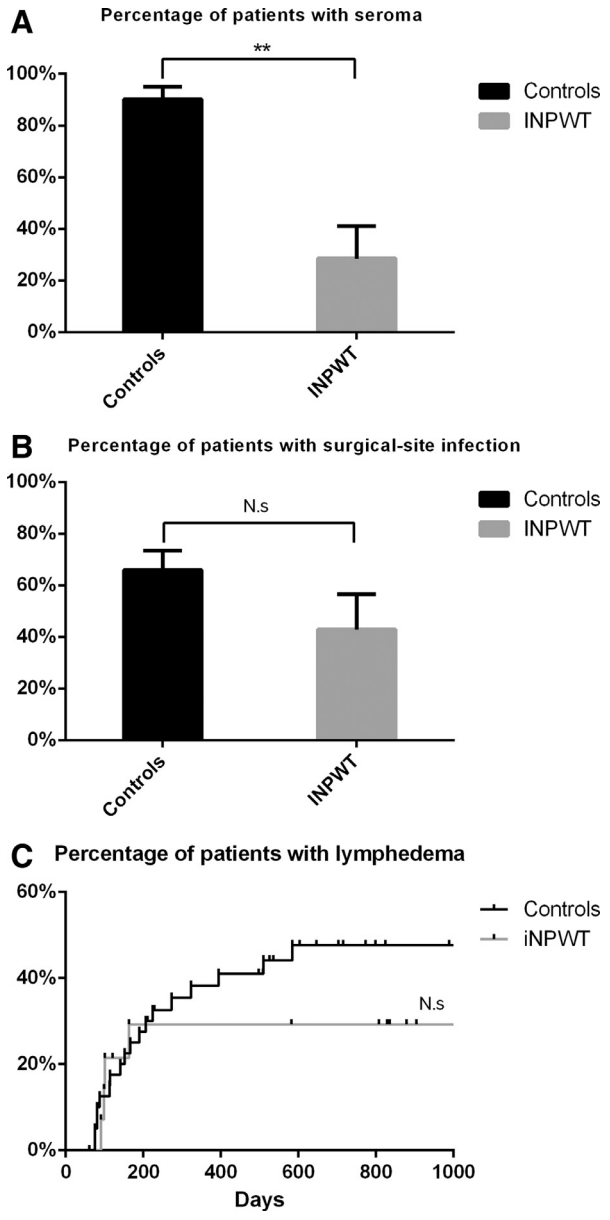

Figure 2 This figure shows the distribution of patients with postoperative complications in the control and iNPWT groups. (A) This figure shows the percentage of patients with one or more seromas in the control and iNPWT groups. The iNPWT group had significantly fewer patients who required treatment for seroma. (B) This figure shows the percentage of patients treated for surgical site infection in the control and iNPWT groups. The relative proportion of patients with surgical site infection was nonsignificantly smaller in the iNPWT than that in the control group. (C) This figure shows the percentage of patients with lymphedema in the control and iNPWT groups over time. Error bars show the standard error. The relative proportion of patients with lymphedema was nonsignificantly smaller in the iNPWT group than in the control group. ** = p-value < 0.001. N.s. = p-value not significant.

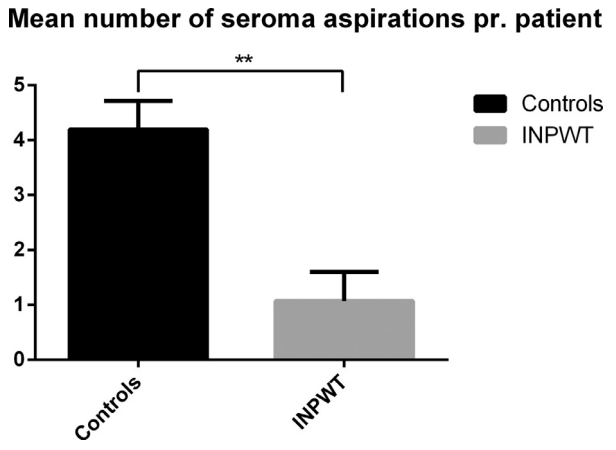

Figure 3 This figure shows the mean number of seromas in each group. The iNPWT group had a significantly lower mean number of seroma cases. Error bars show the standard error. ** = p-value < 0.001.

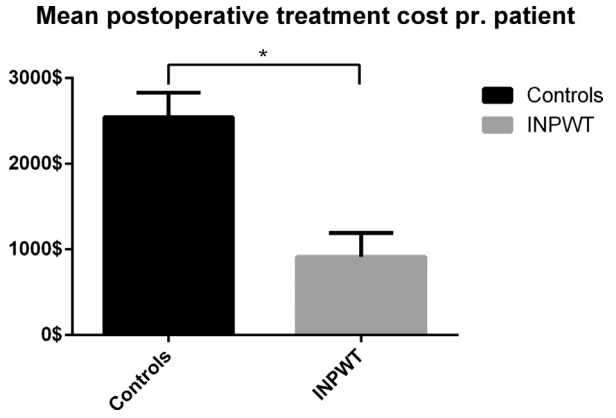

Figure 4 This figure shows the mean treatment costs per patient in the control and iNPWT group. Treatment costs were calculated in US dollars. Treatment costs were included for seroma, surgical site infection, and lymphedema for both groups. For the iNPWT group, the cost of one iNPWT device was added to all patients' costs. The costs of postoperative treatments were significantly lower in the iNPWT group than in the control group. Error bars show the standard error. * = p-value < 0.05.

There are some limitations to this retrospective study. In our previous study, we collected retrospective data using clinical treatment codes.[3] Therefore, the definition and treatment of seroma, SSI, and lymphedema depended on a clinical decision. Healthcare costs were calculated using treatment codes, and therefore, additional related treatment expenses such as lymphedema compression garments, transportation expenditures, and lost wages were not included. In addition, there were no specific healthcare cost reimbursement codes for the treatment of SSI, and therefore, the potential socioeconomic gain of iNPWT application might be underestimated. Finally, there was no treatment randomization in this study; however, patient characteristics and risk factors for wound complications such as increasing age and obesity were similar between groups. iNPWT is thought to increase tissue vascularization and lymphatic drainage,[20,21] which might explain its effect on

seroma formation in this study. Seroma is associated with an increased risk of SSI and lymphedema following lymph node excisions.[3] In this study, however, iNPWT exhibited only a significant effect on seroma formation, but the treatment could potentially be shown to reduce SSI and lymphedema in a properly powered trial. This hypothesis is further supported by another study, which found iNPWT to reduce lymphorrhea and lymphedema following ILND for urogenital cancer.[22] The proangiogenic aspect of iNPWT has raised concerns of a higher risk of cancer recurrence. On the basis of this theorem, iNPWT manufacturers do not recommend the use of the dressing in areas of excised malignancy. In this study, with over 2 years of follow-up, we did not see an increased risk of recurrence in patients who received iNPWT after ILND. Owing to the small size of the study and number of events, this should, however, be interpreted with caution and will need to be confirmed in larger trials.

We are currently conducting a prospective and randomized trial to test whether iNPWT in fact has an effect on the incidence of seroma formation following ILND in patients with malignant melanoma.[23]

Conclusion

iNPWT was observed to reduce seroma formation following ILND in patients with malignant melanoma, as the incidence of seroma formation was significantly lower in patients treated postoperatively by iNPWT. Furthermore, there was a trend that the incidence of surgical site infection was also lower.

Ethical approval

This study was registered with the Danish Data Protection Agency (2012-58-0018) and approved by the Danish Health and Medicines Authority (3-3013-1759/1/).

Conflict of interest

Jens Ahm Sørensen previously received funding from the company Smith & Nephew for another study. The remaining authors have nothing to declare.

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