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ARTICLE

Clipping inguinal lymphatics decreases lymphorrhoea after lymphadenectomy following cancer treatment: results from a randomized clinical trial

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ABSTRACT

Background: Post-operative lymphorrhea is a well-known complication of inguinal lymph node dissection. However, the interventions to reduce the duration of drain *in situ* have not been sufficiently elaborated.

Objectives: We evaluated the potential role of intra-operative mapping of lymphatic leakage with peri-incisional methylene blue injection and clipping of lymphatics after inguinal block dissection in reducing postoperative lymphorrhea.

Methods: We randomized 39 inguinal dissections done for various malignancies such as for carcinoma penis, urethra, malignant melanoma, rectum into 19 dissections (Interventional group) and 20 dissections (Control group). In the interventional group, after the completion of inguinal dissection, two ml of methylene blue dye was injected 4–8cm from the incision to identify the leaking lymphatics and they were clipped.

Results: The primary outcome was the decrease in duration of days of drain *in situ* and was found to have significant reduction of 3.07 days in the interventional arm. (p value-0.02). The secondary outcome was the reduction of 21 ml of mean drain output in the interventional group ($p = 0.09$). The number of lymphatics clipped was not found to have statistical correlation with the duration of drain *in situ* and the mean drain output.

Conclusion: The intraoperative mapping of lymphatic channels using methylene blue after inguinal dissection reduces the number of days of drain *in situ*.

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Introduction

Inguinal lymph nodal metastasis is common from cancers arising from the skin, penis, rectum and vulva. Incidence of complications of inguinal lymph nodal dissection ranges from 5 to 87% with the reported incidence of post-operative lymph fistula as high as 67% [1].

Currently, closed suction drains are inserted at the time of inguinal lymph node dissection (ILND) to decrease fluid collection and promote early adherence of flap surfaces. However, closed suction drains cause discomfort, require patient compliance, interfere with mobilisation and are sometimes retained for longer durations due to persistent lymphatic leak [2]. Various techniques like collagen sealant patch, fibrin glue, omental flap pediculoplasty, use of harmonic scalpel, negative pressure wound therapy have been described in the literature to decrease post-operative lymphorrhoea, but with mixed results and no randomized study has standardized the technique for clinical utility [2–8].

Methylene blue is dark green crystalline salt which is cheap and easily available in developing countries as compared to patent blue or isosulfan blue. It is commonly used in identification of sentinel node for melanoma and breast [9]. We hypothesised that leaking lymphatic channels could be prophylactically identified by peri-incisional injection of methylene blue dye intraoperatively and clipping of these lymphatics might lead to a reduction in postoperative lymphorrhea leading to early removal of drain.

Patients and methods

This investigator-designed, single institution and randomized phase II study was approved by the institutional ethical and regulatory board. (Approval No. ITRC/14/02) All patients who underwent therapeutic complete inguinal dissections or ilio-inguinal dissections for penile cancers, skin cancers, soft tissue sarcomas, urethral cancers and rectal cancers during 2017 to 2018 were included in the study.

Exclusion criteria:

i. Patients with unresectable primary tumor and ulcerated inguinal metastasis.
ii. Patients with history of previous surgery of the inguinal region other than sentinel node biopsy.
iii. Patients undergoing popliteal dissection as part of the procedure in lower limb malignancies.
iv. History of previous radiotherapy of the inguinal region.

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v. History of previous chemotherapy and evidence of lymphedema
vi. Patients undergoing only superficial inguinal block dissection
vii. Dissections where the inguinal block dissection wound communicates with scrotal sac or thigh wound.
viii. Dissections requiring flap for cover.

The randomization was done centrally by telephone in a computer-generated randomization and operative surgeons were informed about the arms of randomization after the completion of lymphadenectomy. A total of three operative surgeons were involved in the study and the numbers of the dissections performed by the surgeons ranged were four to eighteen in number.

Technique

The standard inguinal lymph node dissection was performed as described below. Briefly, an 8- to 14-cm lazy-S incision was made, 3–4 cm below the groin crease. After the incision, the skin flaps were raised to the level of the Scarpa fascia using electrocautery, which was also used to seal any visible leaking lymphatic vessels. The boundaries of the dissection of lymphatic tissue were the inguinal ligament superiorly, the sartorius muscle laterally, the adductor longus muscle medially, and the apex of femoral triangle inferiorly. The floor of the dissection was the femoral vessels and the pectineus, with the superficial and deep nodes removed. The saphenous vein inside the femoral triangle was ligated and dissected. The sartorius muscle transposition was done to cover the exposed femoral vessels.

Intervention group: After the completion of standard inguinal dissection, before the closure of the wound, two ml of methylene blue was injected intracutaneously with a 26-gauze needle into 12–16 sites around the inguinal incision four to eight centimetre from the wound edge (Figure 1(A–D)). Specific care was taken not to contaminate the wound with spillage of the methylene blue. Soft massage over the inguinal region was done for five minutes.

The leaking lymphatic vessels at the edges and under-surface of the flap were identified by the presence of methylene blue seeping through the cut-open end of lymphatic channels. These were clipped using LIGACLIP® (Product code LT 100 and LT 200, Ethicon, Johnson and Johnson Ltd.). The number of lymphatic channels that were clipped was noted.

Control group: Incision closed without any dye injection.

In both the interventional and control groups, suction catheter of 16 F calibers (ROMA VAC SET- Closed Wound Suction Unit, Romsons Scientific and Surgical Industries Pvt. Ltd) was inserted through the skin and was connected to a closed suction drain system. The iliac suction drains were connected separately through a separate suction drain system. The inguinal drains were regularly de-clotted and they were removed once the drain output had come down less than 25 ml over twenty-four hours.

Sample size was calculated using nQuery Advisor 7.0. Corresponding to a reduction in days of drain by two days, with one side alpha of 20% and power of 80%, expected sample size was 39. In a total of 31 subjects, 39 consecutive complete inguinal dissections were planned (as part of ilioinguinal dissections), enrolled and randomized (1:1 randomization) in this study. All study participants provided written informed consent approved by the institutional review board. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline (Table 1).

Outcomes and statistical analysis

The primary outcome was reduction in the duration of drain *in situ* in the interventional group compared to control group. The secondary outcome was reduction in the mean drain output.

All analysis were intention to treat and were performed using SPSS version 17.0 (IBM). Comparison of mean duration of days of drain *in situ* and mean drain output was done using the Independent 'T' test and Chi- Square test. Scatter plots were prepared and Pearson and Spearman's coefficient were calculated to find corelation between mean drain output and other factors.

Results

Between January 2017 to December 2018, a total of 50 patients were screened and 39 were randomized to intervention arm and control arm. The follow-up period for each patient extended from the day of randomization till the day of drain removal. The baseline patient characteristics of the two groups are described in Table 2. Both the arms were well balanced with slight female preponderance in the control arm. The most common primary was penile carcinoma in both the groups.

The mean duration of the suction drain retained *in situ* was 11.53 ± 3.84 days (Range 6–19 days) and 14.60 ± 4.35 days (Range 11–23 days) in the interventional and the control arms respectively. Patients in the intervention group had inguinal drains retained for 3.07 ($p = 0.02$) less days, which was significantly less as compared to the control group as summarized in Table 3. On the post-operative day (POD) 10, 31% and 5% dissections in the interventional arm and control group respectively were free of drains. 89.5% and 65% of dissections in the interventional group and control group respectively were drain free on POD 18. There was a trend towards decrease in the duration of drain *in situ* irrespective of the primary site of the tumour.

There was reduction of 21 ml of mean drain output in the interventional group in comparison to the control group ($p = 0.09$) and the trend is described in Table 4. The reduction in drain output between the two arms begins from POD 1 and continues till drain removal.

The mean number of lymphatic channels clipped in the intervention group was ten (Range- six to eighteen). On evaluating for each primary, no difference was seen in drain output and duration of drain in days, within each arm (Table 4).

Body mass index was found to be significantly associated with mean drain output, however there was no association

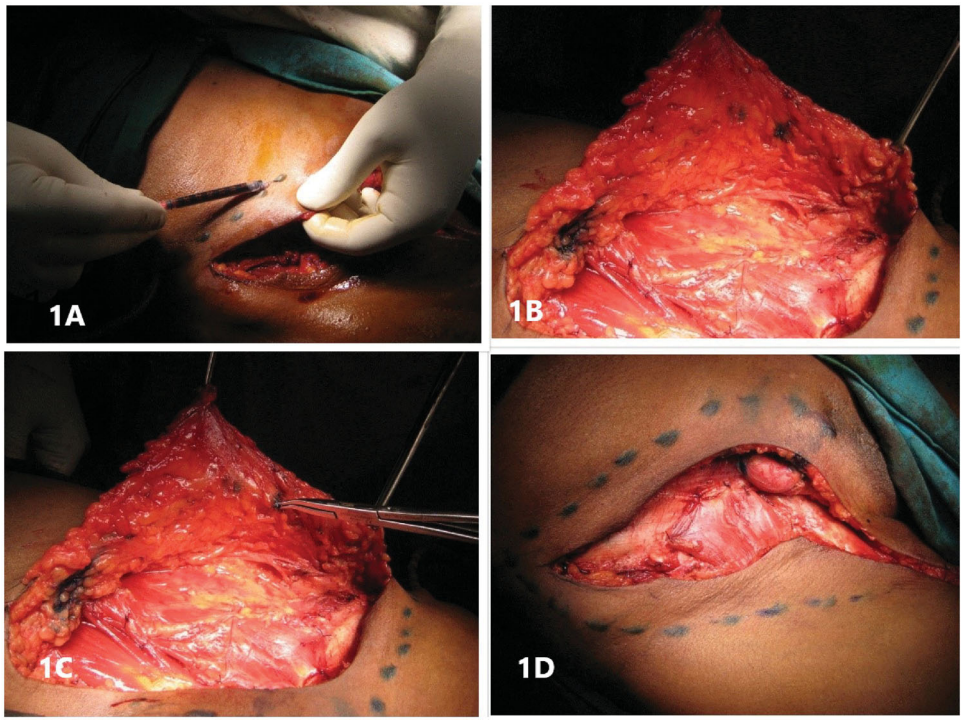

Figure 1. (A) Methylene blue injected intracutaneously into 12–16 sites 4–8 cm from the incision edge. (B) Identification and clipping of leaking lymphatic channels. (C) Surgical site after clipping the lymphatics. (D) Wound prior to the closure.

with number of lymphatics clipped, duration of drain *in situ*. (r_p −0.68 and $p = 0.001$). There was no statistical significance found between the number of lymphatics clipped, number of inguinal lymph nodes dissected or lymph node positivity and duration of drain *in situ*. Similarly, no correlation was seen with mean drain output.

The specific complications in the interventional group include discoloration of drain and urine in one patient. There was temporary tattooing of the injected site in 4 patients and no active intervention was needed. At the dye injection site, minor skin necrosis was noted in two dissections and was managed conservatively. In complications unrelated to the intervention, in both groups, one patient each developed wound erythema due to surgical site infection, which was managed by hiking up antibiotics and one patient each developed superficial skin necrosis which was managed by debridement and secondary suturing.

Discussion

To the best of our knowledge, this study is the first randomized clinical trial conducted in defining the role of intraoperative identification of lymphatic channels in reducing the duration of post-operative lymphorrhea in the inguinal lymph nodal dissections.

The lymphatic system of the inguinal region is divided into two groups: superficial inguinal nodes comprising of 4-25 nodes and deep inguinal nodes comprising of 1−3 nodes. The efferent lymphatics from the superficial group converge to join the deep inguinal nodes. Ilioinguinal block dissections lead to transection of lymphatic channels leading to collection of protein rich, platelet devoid lymph in the dead space [10]. Furthermore, the oblique incision used for groin dissection are more prone to lymphatic leak [11]. We hypothesized that intraoperative identification of these divided superficial lymphatics during lymph node dissections can minimize lymphorroea and lead to early drain removal.

Various methods have been studied to reduce the lymphatic drainage from inguinal dissections. Different energy sources including Hormonic scalpel and Electrothermal bipolar vessel sealing system have been tried to reduce lymphatic leak but with mixed results [7,12]. Similarly, the use of fibrin sealants has not shown any conclusive benefit in reducing drain output [3–5]. Another approach has been to use equine collagen sealant patch coated with human fibrinogen and thrombin to act as tissue sealant and occlude the dead space [2]. Epidermal vaccum therapy has shown promising results in reducing drain output and duration of drainage [8]. Novel surgical techniques like omental flap pediculoplasty and fascia lata preservation have shown to reduce lymphoedema rates but have greater associated surgical morbidity [6].

The concept of intraoperative mapping of identifying lymphatic leak has been applied by few researchers previously. Indocyanine green is being increasingly used to visualise lymphatic channels and assessment of lymphedema status. Bernier et al. in their review concluded that ICG increases the sentinel node detection sensitivity rate when used along with radiotracer [13]. However, when Mistry et al. used indocyanine green to identify transected lymphatics in breast axillary dissection, 70% of the patients still developed seroma [14]. Patent Blue V has been used to identify groin lymph leaks [15,16]. Isosulfan blue has been used extensively for identification of sentinel nodes in cutaneous melanoma, squamous cell carcinoma, merkel cell carcinoma and breast malignancy. Nakamura et al. performed a similar study by

Table 1. CONSORT 2010 Flow Diagram.

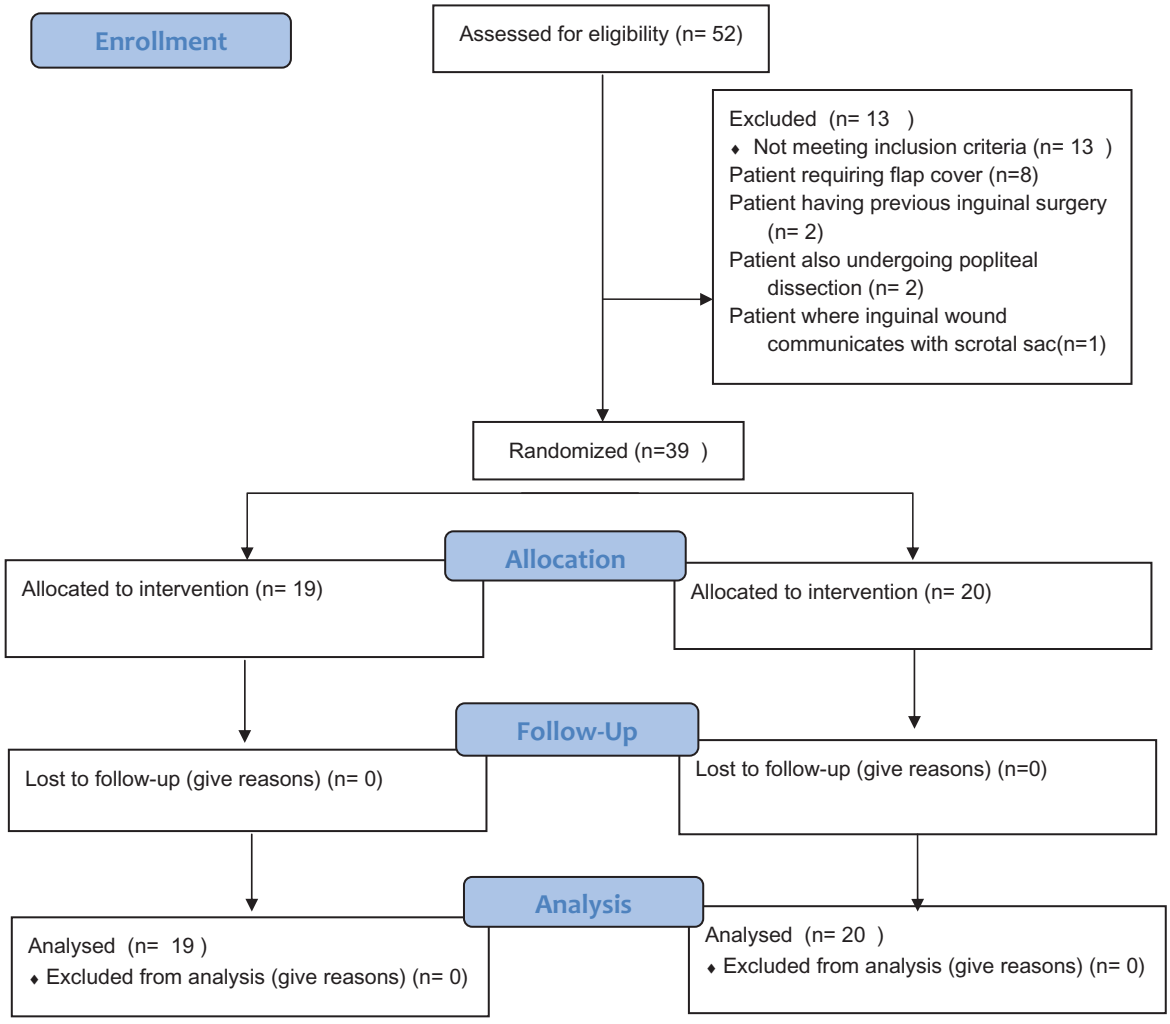

Table 2. Demographic and pathological profile.

Parameters	Arm 1	Arm 2
Total No. of patients	17	19
Total No. of inguinal dissections	19	20
Mean age of the patients (years)	56.32	56.5
Gender (Male :Female)	18:1	16:4
Mean body mass index (kg/m^2)	22.89	23.75
Comorbid illness (Diabetes)	28.16%	20%
Site		
Carcinoma Penis	13	10
Scrotal Squamous cell carcinoma	–	1
Malignant Melanoma of Foot	2	3
UrethralTumours	1	3
Squamous cell carcinoma - Leg	2	–
Anorectal Malignancies	1	3
Mean No. of. LN dissected (Range)	10.11 ± 4.50 (3–20)	9.35 ± 3.01 (4–16)
Mean No of LN positivity	1.53 ± 1.02	1.60 ± 0.99

injecting isosulfan blue circumferentially around the inguinal dissection wound. In their study, the mean number of lymphatics identified and clipped were 3 (Range: 0–6), which is comparatively less than those in our study. They also found a significant decrease in the mean number of days of suction catheter insertion along with a reduction in the mean drain output [17].

Methylene blue has already been established as a safe alternative to isosulfan blue for identification of sentinel node in various malignancies [9]. Although one study reported 8.2% incidence of injection site mass, the economic advantage and absence of anaphylactic reaction make it a suitable alternative [18]. The technique was associated with minimal complications like temporary tattooing of the skin. An additional time of only 10 min was required at the end of surgery prior to the closure of the wound.

In our study, neither the extent of disease nor the extent of dissection affected the mean drain output or drain *in situ* days in the interventional arm. There was no correlation between the number of lymphatic channels ligated and the end points. Lymphatic channels of small calibers themselves which were identified during the perilesional dye injection might close themselves without much contribution to the drain output. As an institutional practice, we bunch ligate the distal transected end of deep lymphatic channels rather than dividing them with electrocautery, thus preventing any leak from them

The trial is limited by its relatively small sample size and subsequent phase 3 validation studies will be required. Another limitation is its short follow up period. The authors

Table 3. Comparison of reduction in duration of days.

	ARM 1		ARM 2	
Post operative Days of drain removal	Total no. of dissections	Percentage of drain free groins	Total no. of dissections	Percentage of drain free groins
8	1	5.2	0	0.0
10	6	31.5	1	5.0
12	8	42.1	5	25.0
14	11	57.8	6	30.0
16	15	78.9	9	45.0
18	17	89.4	13	65.0
20	18	94.7	15	75.0
22	19	100.0	19	95.0
24	––	––	20	100.0
Mean days of drain in situ ± SD	11.53 ± 3.84		14.60 ± 4.35	p = 0.025

Table 4. Comparison of mean drain output.

Post op day	Arm1 Mean ± SD (in ml)	Arm2 Mean ± SD (in ml)
Day 1	69.7 ± 40.1	109.5 ± 64.9
Day 3	66.7 ± 42.1	117.4 ± 73.5
Day 5	57.1 ± 32.1	88.4 ± 69.4
Day 7	47.9 ± 26.4	67.3 ± 48.5
Day 9	51.3 ± 26.3	53.4 ± 29.5
Day 11	48.6 ± 34.5	48.7 ± 25.4
Day 13	40.6 ± 27.7	48.2 ± 22.4
Day 15	43.7 ± 37.7	39.5 ± 25.1
Day 17	32.5 ± 3.5	47.8 ± 23.0
Day 19	25.0 ± 0	34.0 ± 16.3
Day 21	–	50.0 ± 0
Day 23	–	25.0 ± 0
Mean drainage output (in ml)	52.57 ± 21.77	73.38 ± 27.73 (p = 0.09)

have compared their technique to electrocautery sealing of superficial lymphatic vessels, whereas, various other methods have for vessel sealing have also been proposed. The correlation data presented here is hypothesis generating and needs prospective validation with larger sample size. Studies that can validate the site of injection of methylene blue, timing of clipping of the lymphatics, choice of the dye, and also the long term follow up including its role in reducing the lymphedema provides scope for clinical research in the future.

Conclusion

The intraoperative mapping and clipping of lymphatic channels using Methylene blue after inguinal dissection is beneficial in reducing the duration of days of drain *in situ*. This study provides a novel perspective of prophylactically reducing post-operative lymphorrhea associated with the inguinal dissections.

Disclosure statement

The study design complies with the Declaration of Helsinki ethical standards.

Funding

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

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