Role of early povidone iodine instillation in post-renal transplant lymphorrhea: A prospective randomized study

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ABSTRACT

Objective: The aim of the present study was to prospectively evaluate the role of early povidone iodine instillation in the management of post-renal transplant lymphorrhea.

Material and methods: Live-related renal transplant recipients operated between January 2002 and December 2015 were included in the study. Significant lymphorrhea was defined as >50 mL lymph from drain beyond postoperative day 5. Such patients were randomized into two groups by simple randomization using a computer-generated random list: group A (received 0.5% povidone iodine instillation) and group B (no instillation). Absolute risk reduction and numbers needed to treat were calculated to estimate the effect of povidone iodine instillation for the treatment of lymphorrhea and decrease in the incidence of lymphocoele.

Results: A total of 1766 patients underwent renal transplant during this period. One hundred seventeen patients with lymphorrhea through the drain underwent randomization into group A (n=61) and group B (n=56). In group A, 58 patients had successful resolution within 2 weeks, whereas in group B, 34 patients had successful resolution within 2 weeks. Overall, 9 (14.75%) patients in group A and 29 (51.78%) patients in group B had lymphatic collections (both symptomatic and asymptomatic). Symptomatic lymphocoele was present in 1 patient in group A and 7 patients in group B on follow-up. Absolute risk reduction was 10.8%, and for every symptomatic lymphocoele prevented, 10 patients needed povidone iodine instillation.

Conclusion: Povidone iodine instillation after 5 days of transplantation aids in the early resolution of post-renal transplantation lymphorrhea, as well as reduces the incidence of future lymphocoele.

Keywords: Lymphocoele; lymphorrhea; povidone iodine; renal transplantation.

Introduction

Lymphatic collections after renal transplantation have a reported incidence of 0.8%-49% across various studies.1,2 Most of these collections occur within the first 3 months of transplantation. Lymphatic complications include lymphorrhea or lymphorrhagia if there is lymphatic leak from surgical drain or abdominal wound and lymphocoele if they form a pseudocystic cavity with non-epithelial hard fibrous capsule.3

The incidence of symptomatic lymphocoele is lower, approximately 5.2%.4 Classically, the most common presentation is sleep disturbance owing to urinary frequency,5 although various authors have reported elevated serum creatinine as the most common presentation.1,2 Symptomatic lymphocoele may be associated with significant morbidity in the form of wound dehiscence, iliac vein thrombosis, or even graft dysfunction.6 This translates into prolonged hospital stay, as well as high treatment costs. The existing literature describes the management of transplant-related lymphocoele, but there is not enough discussion on the management of lymphorrhea in the early post-operative period that may reduce the associated
morbidity. An intervention during the early period of increased lymphatic discharge after transplantation would likely decrease the chances of formation of an encapsulated lymph filled cavity later on. This is important since lymphocoele has an adverse effect on the graft apart from the treatment-related morbidity and economic burden.

The aim of the present study was to study the effect of early instillation of povidone iodine through the drain in patients with significant lymphorrhea after renal transplantation with regard to the resolution of lymphorrhea and future lymphocoele formation.

Material and methods

Study design
The present study is a prospectively designed randomized controlled trial.

Study population
Live-related renal transplant recipients undergoing renal transplantation at a tertiary care hospital in Northern India from January 2002 to December 2015 and who developed significant lymphorrhea through the drain were included in the study. The study protocol was approved by the institute’s ethics committee (IEC code: PGI/BE/69/2001). Written and informed consents were obtained from all individuals who participated in the study gave prior to inclusion. The sample size was calculated using Z-test with pooled variance. A sample of 60 patients in each group was required to achieve 83% power at a significance level of 0.05 to reduce the duration of lymphorrhea by 20%.

Inclusion criteria
Patients with significant lymphorrhea defined as a drain output >50 mL beyond postoperative day 5 were included in the study. Urinary leak was eliminated by measuring the drain and serum creatinine. A drain fluid creatinine greater than the serum creatinine confirmed urinary leak.[7]

Exclusion criteria
Patients with hemorrhagic drain output, presence of fever, and wound infection or dehiscence were excluded from the study.

Treatment and follow-up
All renal transplants in the study were live-related renal transplants where the allograft was retrieved by laparoscopic donor nephrectomy and the graft was placed in the right iliac fossa. The renal artery was anastomosed to the internal iliac artery or external iliac artery, whereas the renal vein was anastomosed to the external iliac vein in transplant recipients. An abdominal drain was placed medial to the renal allograft following which abdominal closure was done in layers. After transplantation, patients who met the inclusion criteria were randomized into two groups by simple randomization using a computer-generated random list (list generated on 12/15/2001): group A received 0.5% povidone iodine instillation and group B served as the control group. In group A, 20 mL of 0.5% povidone iodine was instilled into the drain three times daily followed by clamping of the drain for 1 h. Daily drain output was measured after subtracting 60 mL from the total output in group A. If drain output was <50 mL in 24 h then the instillation was stopped. Ultrasonography (USG) was performed 24 h later, and if there was no significant residual collection (<50 mL estimated volume), then the drain was removed. Other indication for drain removal was persistent lymphorrhea at 3 weeks after transplantation despite povidone iodine instillation. In group B, the patients did not receive any instillation and were observed for up to 3 weeks. They underwent removal of the drain after the resolution of lymphorrhea or at 3 weeks after transplantation, whichever was earlier. In both groups, the patients underwent USG to check for lymphocoele at 1 month and then 3 monthly thereafter for 1 year.

Outcomes
The primary outcome analyzed was the resolution of lymphorrhea, whereas the secondary outcomes measured were the incidence of asymptomatic and symptomatic lymphoceles, length of hospital stay, and total cost of treatment. The total cost of treatment included the price of surgery, hospitalization (bed charges, nursing charges, and consumables), and drug treatment at our hospital for the duration of admission of the transplant recipient (minimum of 2 weeks). Absolute risk reduction and numbers needed to treat were calculated to estimate the effect of povidone iodine instillation for the treatment of lymphorrhea. Fisher’s exact test or chi-square test was used for categorical data; descriptive statistics and t-test were used for continuous data. Data were analyzed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

Results
A total of 1766 patients underwent renal transplantation from January 2002 to December 2015. Of the 1766 patients, 138 (7.8%) developed lymphorrhea. After excluding the patients as per the exclusion criteria, 124 patients were enrolled for the study, and 117 patients completed the 1-year follow-up duration as defined by the study protocol. These patients were randomized into group A (n=61) and group B (n=56) (Figure 1). The overall mean follow-up was 83.5 months in group A and 81.3 months in group B. The mean ages were 40.5±10.4 years in group A and 38.4±12.5 years in group B, and this difference was not statistically significant (p=0.235). The mean duration of lymphorrhea was different in the two groups (12±2.8 in group A vs. 15±3.1 in group B; p=0.003) (Table 1). In group A, 58 pa-
Patients had successful resolution of lymphorrhea within 2 weeks, and 61 patients had successful resolution within 3 weeks. In group B, 34 patients had successful resolution of lymphorrhea within 2 weeks. Of the remaining 22 patients, 10 had resolution of lymphorrhea on week 3, whereas for the remaining 12 patients with persistent lymphorrhea, the drain was removed at 3 weeks.

In group A, 8 (13.1%) patients had asymptomatic lymphocele, whereas 1 (1.6%) patient had symptomatic lymphocele during follow-up (Figure 2). In group B, 22 (39.3%) patients had asymptomatic lymphocele, and 7 (12.5%) patients had symptomatic lymphocele during follow-up. There was an absolute risk reduction of 37.0% for lymphocele formation in group A (95% confidence interval (CI) 21.21%-52.86%), and the number needed to treat was 3 (95% CI 1.9-4.7). For symptomatic lymphocele only, the risk reduction was 10.86% (95% CI 1.63%-20.09%), and the number needed to treat was 10 (95% CI 5.0-61.3). The symptoms associated with lymphocele are tabulated in Table 2.

The mean duration for the detection of symptomatic lymphocele was 5 months. Asymptomatic lymphoceles were detected either at 3 months or at 12 months when USG was done as per the study protocol. The lengths of hospital stay were 20±4.1 days in group A and 27±7.2 days in group B, and this difference was statistically significant (p<0.001). The overall treatment cost was significantly higher in group B than in group A (Table 1). No patient had any complication after povidone iodine instillation, such as infection, thrombophlebitis, or graft dysfunction.

**Discussion**

Post-renal transplant lymphatic collections have been attributed to surgical, as well as medical, risk factors. The surgical factors include severing of the lymphatics during preparation of the graft bed (especially with the use of the external iliac artery for anastomosis), injury to the hilar lymphatics of the allograft, renal decapsulation, and retransplantation. The most important medical risk factors include acute graft rejection and newer immunosuppressants, such as mTOR inhibitors. Symptomatic lymphoceles have been documented in the literature in varying frequencies (1%-26%). With the growing use of USG, the incidence of asymptomatic lymphoceles is as high as 50% although most of them will not require any intervention.

There is evidence in the literature to support that high drain output in the early postoperative period is associated with an increased.
risk of subsequent lymphocoele formation.\textsuperscript{19} However, the literature is lacking regarding early intervention to treat high drain output after renal transplantation and its impact on the prevention of lymphocoele. The present study has highlighted the role of povidone iodine in the early management of lymphorrhea to decrease the incidence and morbidity associated with lymphatic complications after renal transplantation.

In the initial 2-3 days after renal transplantation, the drain fluid largely consists of blood/serum with minor contribution from the lymph. Thereafter, it consists of predominantly lymph. The lymph does not coagulate due to the absence of platelets and low level of clotting factors. This is one of the reasons why it is difficult to stop lymphorrhea. However, under certain circumstances, such as trauma or shock, lymphatic thrombosis is known to occur.\textsuperscript{10} Clotting of the lymph may also be promoted by polysaccharide treatment in the operative field and has been tried after radical prostatectomy.\textsuperscript{11} The role of tranexamic acid in the management of seroma after oncological surgeries has been studied with encouraging results, but such a study in renal transplant recipients is lacking, more so because of concerns regarding graft thrombosis.\textsuperscript{12}

Povidone iodine has been used to manage post-transplant lymphocoele for >30 years.\textsuperscript{13} The mechanism of action of povidone iodine is not known but presumed to be sclerosis with the chelation of proteins. Concerns have been raised regarding the increase in the incidence of infections with the use of prophylactic antibiotics. The role of the antiseptic effect of povidone iodine is disputed and may not contribute to significant reduction in the infection rates.\textsuperscript{15} The concentration of povidone iodine used across various studies is also variable. The initial studies have used 10% concentration, whereas the later ones have used 5% concentration.\textsuperscript{16,17} Taking cues from the management of chyluria using sclerotherapy, it can be learned that a lower concentration of povidone iodine may also have a similar effect on the lymphatic leak.\textsuperscript{18} Hence, a low concentration of povidone iodine was used to avoid the side effects associated with povidone iodine instillation. A 0.5% concentration was used, and no any adverse effects were found. Further, the effects of instillation were clearly evident by the early resolution of lymphorrhea (12 days in group A vs. 15 days in group B) and the lower incidence of symptomatic, as well as asymptomatic, lymphocoele in group A than in group B. The results obtained in our study might indicate that before the formation of actual lymphocoele and all the inflammatory reaction thereof, a lower concentration of povidone iodine may be sufficient although this proposition still needs further validation. Other agents whose use has been reported include Au colloid, sodium tetradecyl sulfate, oxytetracycline, bleomycin, fibrin glue, 95% ethanol, and streptomycin.\textsuperscript{4,19-21}

Early instillation of povidone iodine was performed with an aim to cause the resolution of lymphorrhea. The instillation was started as early as 5 days after transplantation in all patients in group A. The median times for resolution of lymphorrhea were 12±2.8 days in the povidone iodine group (group A) and 15±3.1 days in the control group (group B). The timing of instillation of povidone iodine after transplantation has not been reported in a consistent or standardized manner which may be the reason for the lack of consensus as far as the overall results of sclerotherapy are concerned. This may be due to the fact that most studies have focused on treating the symptomatic lymphoceles and, therefore, have waited for variable amount of time for asymptomatic lymphoceles to become symptomatic.\textsuperscript{22} Moreover, the initial size of the lymphocoele cavity cannot predict the need for percutaneous drainage and sclerotherapy, adding to the variability.\textsuperscript{22} Most of the studies have reported the management of established lymphocoele rather than lymphorrhea, and therefore it would be incorrect to compare the resolution of these two entities. The fact that the resolution time of lymphocoele is lower than that of lymphorrhea in the present study implies that an early treatment of lymphorrhea reduces the treatment period, translating into low cost and hospital stay. This has been shown conclusively in the present study. The median hospital stay was nearly 30% longer in group B than in group A, and the cost of treatment was also approximately 30% higher in group B than in group A (Table 1).

In the present study, the management was started right from prolonged drainage after transplantation, and lymphatic complications were observed to reduce by early intervention. Few other studies also have observed patients with lymphorrhea. In a study of prolonged wound drainage after renal transplantation performed by Kiberd et al.,\textsuperscript{9} out of 392 renal transplant recipients, 63 (16%) patients developed prolonged wound drainage which was defined as drain output >50 mL/day beyond postoperative day 7. Further, 2.7% of patients with no prolonged drainage developed lymphocoele on follow-up against 13% of patients with prolonged drainage, thereby suggesting the association of prolonged drainage with lymphocoele formation. Fockens et al.\textsuperscript{24} evaluated 108 transplant patients for wound morbidity and found that of 12 patients who developed wound complications, prolonged wound

| Table 2. Symptoms associated with post-renat transplant lymphocoele |
|-------------------|------------------|
| Symptom                        | No. of patients (n) |
| Hydroureteronephrosis leading to graft dysfunction | 5 |
| Urinary frequency              | 1                |
| Right lower limb edema         | 1                |
| Bulge in the right iliac fossa | 1                |

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Written informed consent was obtained from the authors. The study was approved by the institutional ethics committee and was performed in accordance with the principles of the Declaration of Helsinki. The protocol was prospectively evaluated by an institutional review board. The patients were randomized into two groups: group A received 10 mL of 10% povidone iodine and group B received 20 mL of 5% povidone iodine. The patients received no financial support.

In conclusion, lymphorrhea is not an uncommon complication following renal transplantation which is often neglected. Untreated lymphorrhea may increase the risk of future lymphocele formation. Early povidone iodine instillation after 5 days of transplantation plays a significant role in the resolution of lymphorrhea, as well as decreasing the incidence of future lymphocele formation.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Sanjay Gandhi Post Graduate Institute of Medical Sciences (IEC code: PGI/BE/69/2001).

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.


**Conflict of Interest:** The authors have no conflicts of interest to declare.

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**References**


