MANAGEMENT OF POSTRENAL TRANSPLANT LYMPHORRHOEA- A TERTIARY CARE CENTER EXPERIENCE

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ABSTRACT

BACKGROUND

Lymphorrhoea is a frequent cause of peritransplant fluid collection seen postoperatively after renal transplantation. Most of the lymph leaks resolve without complications within one to two weeks after surgery. Sometimes the leaks are exaggerated, last longer and prevent removal of surgical drain. In addition to prolonging hospital stay, it may lead to loss of protein and fluids, with resultant dehydration, nutritional deficiency and immunologic dysfunction. Persisting lymphorrhoea is the most important cause of lymphocele formation. Surgical damage to lymphatics around iliac vessels of the recipient during bed preparation and lymphatics of donor kidney during procurement or during bench surgery leave behind open lymphatic channels that keep leaking for long periods after transplantation. A number of medical causes have also been identified that lead to lymphorrhoea.

MATERIALS AND METHODS

Only live related donor cases were selected for our study. Two weeks after renal transplantation, the drain fluid was tested for fluid urea, creatinine, sodium, potassium, total protein and albumin to rule out urine leak. A sample was sent for culture and sensitivity to rule out infection. Patients with drain fluid >200 ml. at two weeks were randomized into two groups; one group (study group -20 patients) underwent extra peritoneal povidone iodine instillation via the drain tube, which was clamped for one hour; the other group (control group -19 patients) was managed conservatively by gradual pulling out the drain tube over days. The end point for drain tube removal was less than 50 ml. drain output for two consecutive days. Subsequently patients were discharged from hospital with monthly review that included Ultra Sound Scan of the graft with Doppler study.

RESULTS

7 patients in the study group and 7 patients in the control group had resolution of drain fluid by two and a half weeks. 2 patients in the control group and 13 patients in the study group had resolution of drain fluid by 19-21 days (3-weeks). 9 patients in the control group had a prolonged hospital stay of 3-8 weeks before drain tube could be removed. The total number of days of hospital stay were 3.5 - 4 weeks in patients in the study group and 3.5 - 8 weeks in the control group. Time for normalization of S. Creatinine (Mean ± SD) was 25.3 ± 9.3 in the control group and 18.6 ± 6.8 in the study group. 3 patients in the control group developed symptomatic lymphocele during follow up, and none in the study group.

CONCLUSION

Though this study is limited by the number of patients, results were significant, and in the absence of side effects, our study shows that povidone iodine instillation (extraperitoneal perinephric) may prove to be a simple, safe and effective surgical tool to limit post-operative lymphorrhoea in renal transplant patients.

KEYWORDS

Lymphorrhoea, Lymphocele, Povidone Iodine Instillation, Drain Tube, Conservative Management.

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BACKGROUND

Lymphatic collections frequently form around renal allograft following renal transplantation. Lymphorrhoea is leakage of lymph through surgical drains in the post–operative period while lymphocele is a localized perinephric fluid collection most commonly seen medial to the renal allograft, surrounded by a hard-fibrous capsule. The reported incidence of lymphocele is around 0.6- 51%.[1,2,3] Various surgical and medical causes are responsible for excess lymph formation in post-operative period.

Important Surgical Causes for Lymphorrhoea-

1. Damage to lymphatics during surgical dissection around iliac vessels during bed preparation.
2. Capsular damage and damage to renal hilar lymphatics of the donor either during organ procurement or while

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preparing the donor kidney for explantation during bench surgery.[4]
3. Prolonged warm ischemia time, delayed graft function and acute rejection are recognized causes for lymphorrhoea and lymphocele formation.[5]

Medical Causes Associated with Lymphorrhoea-
Immunosuppression Poses a Definite Risk-
1. Earlier, m-tor inhibitors in association with steroids were associated with a high risk for lymphorrhoea. Tacrolimus, Mycofenalate Mofetil (MMF) and steroids are the present drugs of choice for immune suppression. High doses of MMF (>2 gm/day) are implicated and therefore dosage of MMF should not exceed this dose. Lowering the dose of steroids and diuretics (and thus reducing lymph flow) and also early withdrawal of steroids are recognized to reduce lymphorrhoea and lymphocele formation.[6]
2. ADPKD: Large kidneys in polycystic disease can compress the IVC and reduce lymphatic flow.[7]
3. Anti-coagulation prophylaxis, including post-operative heparin infusion.[8]
4. Blood coagulation abnormalities: Levels of Thrombin, Anti thrombin, and other factors are higher in patients developing lymphatic complications.[9] Postoperative anticoagulation in such patients in the presence of uremia may prevent sealing of open lymphatics.

Recipient Factors-
a. Diabetes Mellitus induced microangiopathy.[10]
b. Older age.
c. Obesity (>30 kg/m).[11]
d. Re-operation / Multiple transplantations.[2]
e. Filariasiss.[12]

A number of surgical techniques are in vogue today to limit postoperative lymphorrhoea-
1. Meticulous Clipping and suturing of both donor and recipient lymphatic vessels.[13]
2. Bipolar coagulation of broken lymphatics.[14]
3. Sparing the lymphatic chain lateral to external iliac artery.
4. Use of hemostatic sealants.[15]
5. Washing the operative field with povidone iodine before wound closure.
6. Compression stockings for four weeks after transplantation.[16]
7. Prophylactic peritoneal fenestration at the end of renal transplantation.[17]

In the present study, we describe a simple technique for controlling prolonged lymphorrhoea in the post-operative period followed in our institute.

MATERIALS AND METHODS

Our present strategy is instilling betadine (5% Povidone Iodine) through the drain tube in patients with significant lymphorrhoea (>200 ml.) above two weeks post operatively. Starting at two weeks, (15th day) 20 ml. of sterile undiluted betadine solution (5%) is placed into the perinephric extra peritoneal space and retained for a period of one hour after which it is drained. This is done once daily for three consecutive days. Drain is left in place till the drainage is less than 50 ml. for two consecutive days.

- Total number of patient who underwent live renal transplant during the study period July 2015- July 2017: 93.
- Total number of patients with drain output more than 200 ml. at the end of two weeks: 39.
- Total number of patients managed conservatively by gradual pulling out of drain tube: 19.
- Total number of patients in study group who were managed with povidone iodine instillation via drain tube: 20.

Intervention**-** (for study group alone).
First Povidone Iodine instillation: day-15; second instillation: day-16; third instillation: day 17.

Inclusion Criteria
1. Live related donor transplant recipients
2. All renal transplant recipients with proven post-operative lymphorrhoea >200 ml.at two weeks.
3. All re-transplantation and re-operation cases.

Exclusion Criteria
1. Deceased donor renal transplant recipients.
2. Patients with evidence of fluids other than lymph-including urine and seroma in the drain fluid.
3. Patients with known allergy to drugs or iodine.
4. Patients with local infection or fever.

Statistical Analysis of Results- Categorical and quantitative variables were expressed as frequency (percentage) and mean ± SD respectively. Comparison of means of quantitative variables between the groups were analyzed by using independent t-test and comparisons with respect to categorical variables were performed by using the Fishcher exact test. For all statistical interpretations, $p < 0.05$ value was accepted as being significant. Statistical analyses were performed with statistical software package SPSS version 17.0.

RESULTS

Results of Study Group**-**
- No. of patients whose drain could be removed by 16 - 17 days-7/20.
- No. of patients whose drain could be removed between 18-21 days-13/20.
- No. of patients whose drain could not be removed by the end of fourth week (28 days): nil.
- No. of patients whose hospital stay extended for 4 weeks or more: nil.
- No. of patients who developed asymptomatic (2.5-3.5) cm. lymphocele, (managed conservatively with no intervention), only follow up: 4/20.

- No. of patients who developed symptomatic lymphocele: nil.

Results of Control Group-

- No. of patients whose drain could be removed by 16-17 days-7/19.
- No. of patients whose drain could be removed between 18-21 days- 2/19
- No. of patients whose drain could not be removed by the end of fourth week (28 days): 10/19
- No. of patients whose hospital stay extended for 3.5-8 weeks or more: 9/19.
- No. of patients who developed asymptomatic (2.5-4.0) cm. lymphocele (managed conservatively with no intervention), only follow up: 3/19.
- No. of patients who developed symptomatic (>5.0.) cm. lymphocele requiring surgical intervention including laparoscopic fenestration: 3/19.

In cases of symptomatic lymphocele, ultrasound guided aspiration of lymphocele followed by povidone iodine instillation into the cavity was done as first step. In one case there was progressive increase in serum creatinine and was taken up for laparoscopic fenestration under general anesthesia.

Local instillation of povidone iodine had no effect on the vascularity of transplant kidney or renal function, nor were there any short term or long term systemic side effects. In all our patients, lymphatic leakage subsided within a week of instillation. Morbidities, such as wound complications, vascular complications like hematomas, renal artery/vein thrombosis, deep vein thrombosis, pulmonary embolism, urologic complications like urinary extravasations, obstruction, reflux and haematuria were not statistically different between study and conservative groups. However, the total number of days of hospital stay was 3.5-8 weeks in patients in the study group and 4.5-8 weeks in the control group.

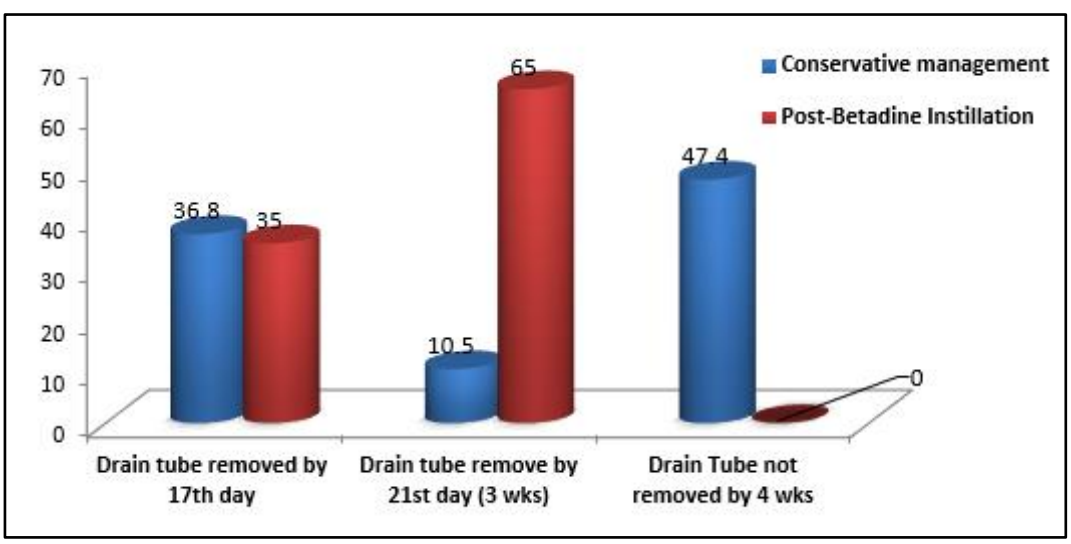
Parameter	Conservative Management (N=19)	Post-Betadine Instillation (N=20)
Age (mean ± SD)	33.7 ± 10.8	38.0 ± 8.0
Male N (%)	8 (42.1)	5 (25.0)
Post OP drain at three weeks (>=400 ml) N (%)	1 (5.3)	2 (10.0)
S. Albumin at 3rd week (Mean ± SD)	2.8 ± 0.2	3.0 ± 0.2

Table 1. Background Characteristics of Patients

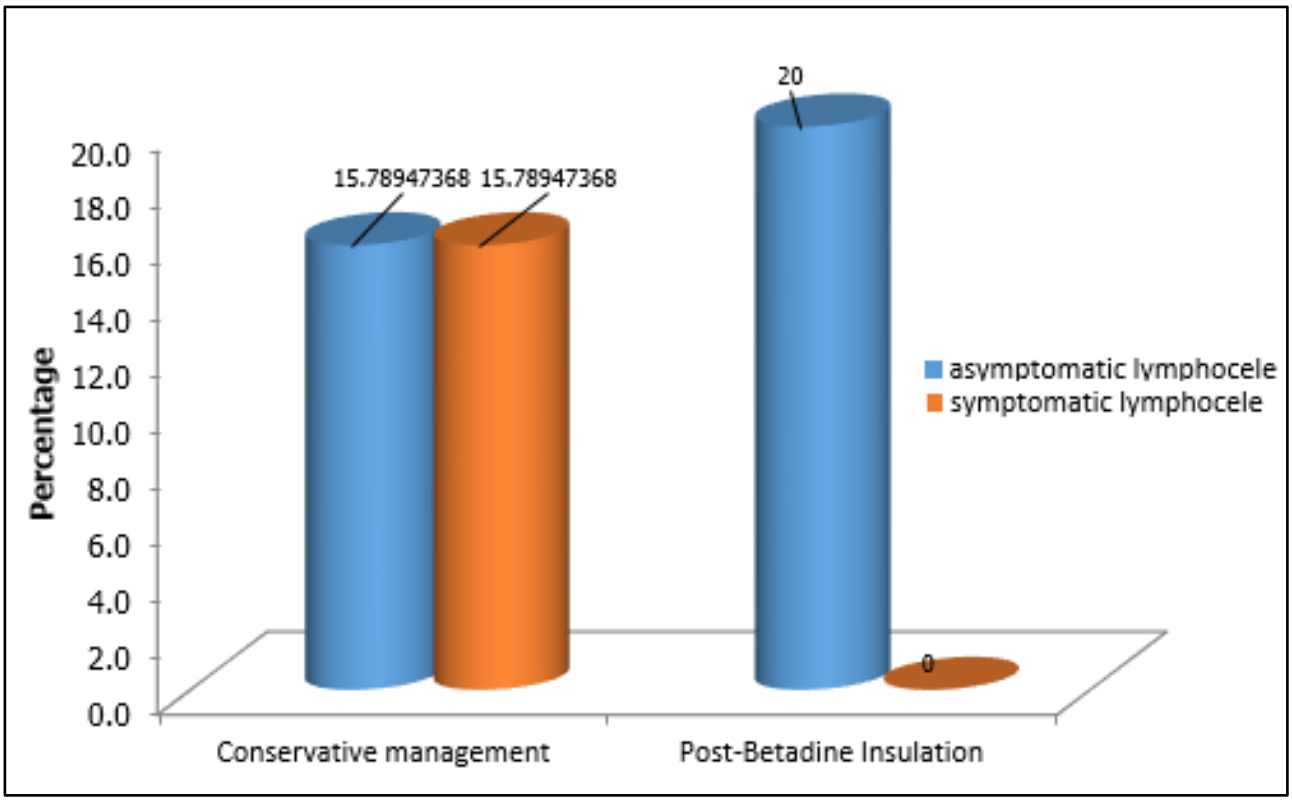
Parameter	Conservative Management (N=19)	Post-Betadine Instillation (N=20)	p
Drain removed by 17th day (2 1/2 weeks)	7 (36.8)	7 (35)	0.912
Drain removed by 3rd week***	2 (10.5)	13 (65)	0.000
Drain not removed at the end of 4th week***	9 (47.4)	0 (0)	0.000
Developed asymptomatic lymphocele	3 (15.8)	4 (20)	0.734
Developed symptomatic lymphocele *	3 (15.8)	0 (0)	0.066
Time for normalization of S. Cr (Mean ± SD)**	25.3 ± 9.3	18.6 ± 6.8	0.015
Hospital Stay >= 4 weeks	9 (47.4)	0 (0)	0.000

Table 2. Comparison of Outcome Variables based on Procedure

*Significant at 0.10 level, **Significant at 0.05 level, *** Significant at 0.01 level.



Graph 1. Comparison of Drain Removal Based on Procedure



Graph 2. Comparison of Asymptomatic and Symptomatic Lymphocele Based on Procedure

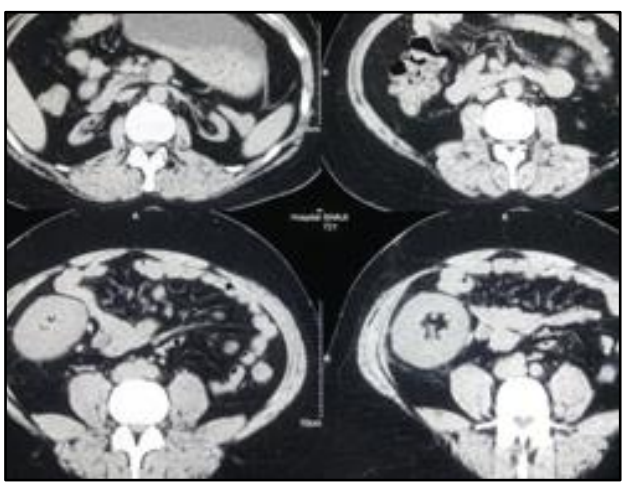


Figure 1. Symptomatic Lymphocoele (12 cm) in Posterior Pararenal Space

DISCUSSION

Lymphorrhoea and lymphoceles are most frequently seen in the first 12 weeks postoperatively after renal transplantation. Persisting lymphorrhoea can lead to protein deficiency and low albumin levels in serum, leading to limb edema, edematous genitalia and generalized edema. Major complications include vein and arterial thrombosis in the external iliac veins and arteries, and DVT (deep vein thrombosis) in lower limbs. Involvement of transplant vessels can cause renal failure. When serum albumin levels are below 2.5 mg%, there is a role for anti-coagulants to prevent vascular complications in these patients. Patients with persistent lymphorrhoea are prone to lymphocele formation. Lymphoceles less than 5 cm. size are usually asymptomatic, but sometimes enlarge and cause severe morbidity. Patients will present with pain, palpable mass, lower urinary tract symptoms, limb edema, obstructive uropathy, secondary graft dysfunction and graft loss. Therefore, prophylactic management for limiting lymphatic complications has a major role in renal transplantation.

The Renal Lymphatic System-

The lymphatics of the kidney drain to two systems: the hilar and the capsular.[18]

Hilar System-

Lymph capillaries within the kidney are blind ending and run in close proximity to inter lobular arteries that drain into pre-collector lymphatics that run along the base of renal pyramids along arcuate arteries. The pre-collectors then follow the interlobar arteries along the renal columns and drain into the hilar lymphatics. Lymph from cortex and medulla thus drain into hilar lymphatics.[19]

The Capsular System-

This consists of capsular, subcapsular lymphatics and peri renal lymphatic vessels. It drains lymph from the outer cortex of the kidney.

There is free communication between the two systems under physiological conditions. Normally, lymph from the kidney drains via the hilar lymphatics.[18] In obstructive uropathy there is a reversion of flow from the hilar to the capsular lymphatics.[20]

Lymphatic System in Renal Allografts-

At the time of harvesting of kidney, peri-renal lymphatics are dissected and opened up. During bench surgery, accessible hilar lymphatics are ligated. In effect, there is no proper channel for lymphatic drainage of the renal allograft lymph

and leakage occurs by back pressure from capsular lymphatics immediately after transplant surgery. In the first week after tranplantation, there is rapid lymphatic neogenesis within the kidney, which may be a response to injury (inflammation of kidney / efflux of lymph).[21] The lymphatic vessel density is maximum in the outer cortex and subcapsular area and a large volume of cells and lymph has been shown to leave the allograft via these lymphatics into the perinephric area. This effect is most notable during allograft rejection which is an inflammatory state. By exiting inflammatory cells this process serves to reduce the inflammation within the kidney in the post–operative period.[22] This natural phenomenon may have short term benefit; however, persistence of these lymphatics may result in excess fluid and lymphocyte loss in the long run, and may also change the normal milieu within the kidney and produce fresh tissue injury.

Effects of Prolonged Lymphorrhoea-

Persisting lymphorrhoea can lead to protein deficiency (hypoalbuminemia), leading to limb edema, edematous genitalia and generalised edema. Major complications include vein and arterial thrombosis in the external iliac veins and arteries, and DVT (deep vein thrombosis) in lower limbs. Involvement of transplant vessels can cause renal failure. When serum albumin levels are below 2.5 mg%, there is a role for anticoagulants to prevent vascular complications in these patients. Patients with persistent lymphorrhoea are prone to lymphocele formation. Lymphoceles less than 5 cm. or volumes less than 140 ml. are usually asymptomatic.[23] but sometimes enlarge and cause severe morbidity. Patients will present with pain, palpable mass, lower urinary tract symptoms, limb edema, obstructive uropathy, secondary graft dysfunction and graft loss. Therefore, prophylactic management for preventing lymphorrhoea and lymphocele formation has a major role in renal transplantation.

It is prudent therefore to take steps to block ongoing lymphangiogenesis and the newly formed lymph vessels. Blocking lymphangiogenesis has been shown to be beneficial in pancreatic islet cell transplantation.[24]

Sclerosing agents like povidone iodine, ethanol, and tetracycline may have a role in blocking these lymphatics. The positive response found in our patients in reducing excess lymphorrhoea after extraperitoneal povidone iodine instillation may be because of its proven sclerosing effect on lymphatics, both peri-renal and around iliac vessels of the recipient. Instillation of povidone iodine into the cavity of the lymphocele after aspiration is an accepted technique in the management of lymphoceles.[1,25] There are recent reports regarding usefulness of extraperitoneal betadine instillation in the management of post renal transplant lymphorrhoea.[26] We have followed similar principles in the conduct of our study.

CONCLUSION

Extraperitoneal povidone iodine instillation is a safe and effective procedure in the management of prolonged lymphorrhoea in renal transplant patients in the post-transplant period; reducing morbidity and hospital stay in these patients and more importantly, reducing the incidence of symptomatic lymphocele in these patients.

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