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Original Article

Does endoscopic sclerotherapy in filarial chyluria affect renal function and morphology? A prospective study using dimercaptosuccinic acid renal scan

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Dimercaptosuccinic acid renal scan;
Relative renal function;
Renal scarring

Abstract *Objective:* To look for change in relative renal function and document renal scarring following endoscopic renal pelvic instillation sclerotherapy (RPIS) in patients with chyluria by dimercaptosuccinic acid (DMSA) renal scan.
Methods: A prospective study was performed between November 2015 and September 2016. All patients with biochemically documented chyluria who underwent RPIS using either 1%-silver nitrate or 0.1%-povidine iodine were included. Patients received either 3-, 6- or 9-doses. DMSA renal scan was performed before and 2–3 months after sclerotherapy.
Results: Of the 34 patients, 22 were males. Mean age was 41.08 ± 16.64 years (range, 15–70 years). Thirty-two patients (94.1%) responded to therapy while two did not respond even after 9-doses. Average follow-up was 8.94 ± 3.70 months. The mean relative renal function (pre-instillation) of normal kidney was 50.76% ± 3.55% while that of affected renal unit (side of instillation) was 49.20% ± 3.44% (range, 43.0%–61.0%). After instillation therapy, the mean relative renal function of normal side was 52.26% ± 3.57% while that of affected renal unit was 47.50% ± 3.56% (range, 41.0%–54.0%). The relative renal function did not change >5% from the baseline value in any patient except one (in which the differential function increased paradoxically by 12%). Two patients developed renal scar in post-instillation renal scan.
Conclusion: Endoscopic sclerotherapy in chyluria is safe and effective. The relative renal

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function does not deteriorate by more than 5%. There is a small risk of development of renal scar. More studies involving larger number of patients are needed to answer this dilemma.

1. Introduction

Chyluria is not uncommon in parts of Asia, Africa and Central and South America [1,2]. The initial treatment of chyluria comprises dietary modification and medical management [1]. Patients who do not respond to medical management (non-responders) or recur after initial response (recurrence) are usually treated with endoscopic renal pelvic instillation sclerotherapy (RPIS) or surgical chylo-lymphatic disconnection. RPIS is associated with variable success rates ranging between 60% and 100% [3–6]. RPIS has short- and long-term side effects, most being minor in nature [7–10].

Lymphatic filariasis, the most common cause for chyluria, is considered a neglected disease. Literature search using PubMed and Medline revealed only 515 articles on chyluria that were published between March 1900 and April 2017 using keywords "filarial chyluria" "endoscopic sclerotherapy in chyluria" "sclerotherapy complications" "silver nitrate instillation" "povidone iodine instillation" and "instillation therapy in chyluria" (also includes search for references from individual articles). Out of these, about 200 were case reports while there were 37 articles on RPIS.

While some sort of renal functional imaging is recommended before RPIS, the mode of investigation is unclear. Similarly, after undergoing RPIS the rationale for functional imaging is unclear. With our experience of treating a large number of patients with RPIS, we realized that RPIS is safe but we never looked into the impact of RPIS on renal function in a scientific fashion. A review of literature also revealed that the impact on the function of the affected kidney has not been studied in a systematic fashion. The radionuclide DMSA-renal scan gives information on the differential renal function and also gives good parenchymal images. The present study was conducted to document any deterioration of relative renal function and appearance of renal scar after RPIS.

2. Materials and methods

After obtaining approval (9950/Ethics/R.Cell-16 dated 25/April/2016) from Institutional Ethics Committee of King George's Medical University, a prospective study was conducted between November 2015 and September 2016. Written informed consent was obtained from all participants. All patients with biochemically confirmed chyluria who underwent RPIS were included in the study.

Patients refusing consent for participation in the study, milky urine not because of chyluria, patients with urinary tract or other malignancy, pregnancy, known medical renal disease, compromised renal function (serum creatinine >110 mmol/L), uncontrolled diabetes mellitus and history of contrast allergy were excluded (13 patients). Nine patients were excluded as an early date for radionuclide renal scan could not be obtained because of administrative issues.

A pre-RPIS DMSA renal scintigraphy was performed 2 h after injection of technetium DMSA (111 MBq). One anterior, one posterior and two posterior oblique images were taken by gamma camera with the patient in supine position. Either povidone iodine (0.1%) or silver nitrate (1%) was used as sclerosant and was instilled at 8-h interval [3,4]. The volume of sceloroscant to be instilled was calculated by measuring the renal pelvic volume by retrograde pyelography. The patients received a total of either 3-, 6- or 9-doses depending on the clinical response. This decision for number of doses was based on gross clearance of chylous urine and was also based on patient's tolerance and/or complications. The decision to continue another 3-doses was taken during morning rounds and if urine was milky then another 3-doses were given. A DMSA-renal scan was repeated after 2–3 months of RPIS using the same protocol as outlined above.

The relative (split) renal function was defined as abnormal if the absolute renal function of a single kidney was less than 40% or the change of relative renal function was more than 5% after RPIS [11,12]. The appearance of renal scar on DMSA scintigraphy was also considered abnormal [12]. The parameters recorded included clinical evaluation, urinary and blood investigations (including urea, serum creatinine), treatment given, renal scan findings and follow-up information. Patients who could not undergo both a pre- and post-instillation renal scan were excluded.

2.1. Statistical analysis

Statistical analysis was carried out using SPSS 16.0 version (Chicago, IL, USA). Discrete variables were compared using Chi square test or Fischer's exact test, wherever applicable. Continuous variables were compared using independent *t*-test or Mann–Whitney *u*-test. The $p < 0.05$ was considered as statistically significant.

3. Results

Of 34 patients, 22 (64.7%) were males (Table 1). The mean age of participants was 41.08 ± 16.64 years (range, 15–70 years). All patients underwent DMSA-renal scan 1–7 days before and again 2–3 months after RPIS. Thirty-two patients (94.1%) responded to RPIS while two patients (5.9%) failed to respond even after completion of 9-doses. Over a

Table 1 Clinical and demographic parameters.

Variable	Value
Age (year)	
Mean ± SD	41.08 ± 16.64
Range	15–70
Male/Female, *n* (%)	22 (64.7)/12(35.3)
BMI (kg/m^2)	
Mean ± SD	24.23 ± 2.73
Range	19.40–31.90
Right/Left, *n*	17/17
Rural/Urban, *n* (%)	29 (85.3)/5(14.7)
Primary/Recurrent, *n* (%)	18 (52.9)/16 (47.1)
Grades at presentation-I/II/III, *n* (%)	3(8.8)/23(67.7)/8(23.5)
Duration of current episode (days)	
Mean ± SD	9.76 ± 6.47
Range	1–24
Total disease duration (months)	
Mean ± SD	46.47 ± 61.28
Range	1–240
Povidine iodine/silver nitrate, *n* (%)	26(76.5)/8(23.5)
Instillation doses- 9/6/3, *n* (%)	29 (85.3)/1 (2.9)/4 (11.8)

BMI, body mass index.

mean follow-up of 8.94 ± 3.70 months, three additional patients experienced recurrence. Thus, the overall success rate of RPIS in the present cohort was 85.3% (29 out of 34). However, the five patients who failed initial RPIS, experienced remission with additional medical management and did not require further RPIS till last follow-up.

The mean pre-therapy urinary triglycerides (TG) and cholesterol levels were 406.31 ± 371.48 mg/dL (range, 48.5–1721.0 mg/dL) and 27.19 ± 30.44 mg/dL (range, 2.8–122.0 mg/dL), respectively. Both urinary TG ($p = 0.0001$) and cholesterol ($p = 0.001$) decreased significantly after RPIS (Table 2). The changes in bloodurea and serum creatinine levels have been depicted in Table 2.

Before RPIS, the mean relative renal function on the normal (unaffected) renal unit was 50.76% ± 3.55% (range, 39.00%–57.00%) while that on the affected renal unit (side of instillation) was 49.20% ± 3.44% (range, 43.00%–61.00%). After instillation therapy, the mean relative renal function of the normal side was 52.26% ± 3.57% while that of affected renal unit was 47.50% ± 3.56% (range, 41.00%–54.00%, $p = 0.001$).

None of the patients had differential renal function change of >5% of the baseline value except for one patient. In this patient the differential renal function paradoxically increased from the pre-instillation value of 49% to the post-instillation value of 61%. Out of the 34 patients, 25 and nine patients, respectively, showed decreased and increased relative renal function after instillation in comparison to their baseline values on the renal unit that received RPIS.

In two patients (one Grade II and another Grade III, 5.9%), the post-instillation DMSA scan revealed a photopenic area at the upper pole suggestive of renal scar (Fig. 1). In these two patients, the mean pre-instillation relative renal function was 45.00% and 42.75% ($p < 0.001$) after instillation. Both patients had received 9-doses of 1% silver nitrate as sclerotherapy. One had developed acute pyelonephritis following RPIS but the other had not experienced any other post-operative complication.

Overall, complications were noted in eight patients (23.52%). Clavien-Dindo Grade-I complications including transient post-operative fever in one (2.9%), dysuria in three (8.8%), transient hematuria (managed with hydration) in four (11.8%) and raised serum creatinine (1.9 mg%) and blood urea (80 mg%) in one patient each (2.9%) were observed. Grade-II complications including flank pain in four (11.8%) and pyelonephritis in one (2.9%) patient were recorded.

4. Discussion

Chyluria is usually a manifestation of lymphatic filariasis. Filariasis has varied presentations; however, its presentation as chyluria usually brings the patient to the attention

Table 2 Comparison of renal function before and after instillation.

Parameter	Pre instillation	Post instillation	*p*-Value
Bio-chemical (mg/dL)			
Blood urea	28.83 ± 11.21	31.00 ± 11.36	0.07
Serum creatinine	0.84 ± 0.22	0.91 ± 0.27	0.21
Urinary triglycerides (mg/dL)			
Mean ± SD	406.31 ± 371.48	17.26 ± 40.70	0.0001
Range	48.5–1721.0	0.9–230	
Urinary cholesterol (mg/dL)			
Mean ± SD	27.19 ± 30.44	2.03 ± 2.76	0.001
Range	2.8–122.0	0.3–13.0	
DMSA scan, normal side, $n = 34$			
Mean ± SD	50.76 ± 3.55	52.26 ± 3.57	0.001
Range	39.0–57.0	46.0–59.0	
Split function, affected side, $n = 34$			
Mean ± SD	49.20 ± 3.44	47.50 ± 3.56	0.001
Range	43.0–61.0	41.0–54.0	

DMSA, dimercaptosuccinic acid.

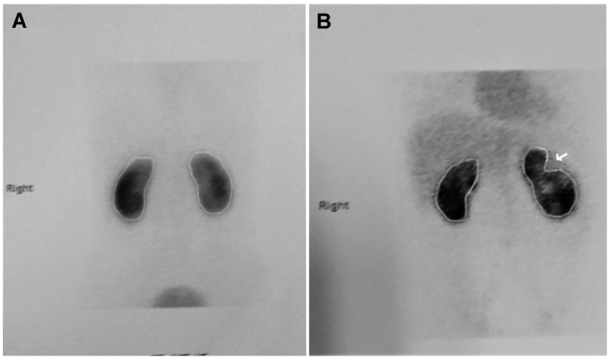

Figure 1 Dimercaptosuccinic acid renal scans. (A) Pre instillation renal scan with no scar; (B) Post instillations scan with renal scar at upper pole and poor uptake (white arrow).

of urologist. Lymphatic filariasis has been labeled "neglected disease" by the World Health Organization (WHO) and "modern understanding" and research on this topic is scant [13].

Today, there are management guidelines for most urological diseases provided by academic societies like the American Urology Association (AUA), European Association of Urology (EAU) and others. Unfortunately, chyluria escaped the attention of most organizations. With no clear guidelines and lack of high-quality research for chyluria the clinicians are left to treat this condition based on institutional practices and individual preferences.

Of the many aspects that are ambiguous in the management of chyluria an important dilemma is the role of post-RPIS functional imaging. In RPIS, a sclerosant is instilled within the pelvicalyceal system so that it enters the thin lymphatics channels causing sterile inflammation and subsequent fibrosis. There is a possibility that the sclerosant may also enter the renal tubules (pyelo-tubular backflow) causing inflammation and sclerosis thus impacting renal function.

Endoscopic sclerotherapy has been associated with several adverse effects on the affected renal units [14]. However, serious adverse effects were mostly observed with higher concentrations of silver nitrate (3% and 5%). Today, the concentration of sclerosant used (povidone iodine -0.1%—0.2%, silvernitrate 1%) is fairly dilute to avoid complications [9,14]. At some institutions, there is a protocol of advising post-instillation intravenous urography (IVU). However, IVU is not very sensitive in detecting small changes in renal function and cortical scars [15]. Radio-nuclide DMSA renal scan has the benefit of not only estimating the relative renal function but also is a sensitive tool to detect acute pyelonephritis and renal scars [16,17]. There are no previous studies looking on the effect of instillation therapy on the affected renal units. In this prospective study, we evaluated the effects of instillation therapy on the affected kidney by DMSA-renal scan. An additional benefit of this study was to be able to give recommendations regarding regular functional studies after RPIS.

Our success rate of RPIS therapy was 85.25% at a mean follow-up of 9 months, which is similar to other studies in the literature [4,6]. One patient had elevation of serum creatinine probably due to acute pyelonephritis and transient sepsis. Another patient had elevation of blood urea which was possibly due to dehydration. The elevated values normalized after antibiotics and adequate hydration.

Overall, there was trend towards decreased relative renal function for majority of patients but the values remained within the defined normal ranges (within $\pm$ 5% change from baseline values). In one patient we noticed that the relative renal function increased by 12% after RPIS on the affected side. This paradoxical increase could be due to normal variation found in scintigraphy or assessment technique.

Two patients (5.9%) showed renal scarring in post-instillation DMSA scan. Both these patients had received 9-doses of 1% silver nitrate. On comparing patients with or without scarring, none of the parameters evaluated (like clinical presentation, urinary TG, urinary cholesterol and RPIS) predicted the development of renal scarring. One patient developed renal scar possibly due to post-instillation complication of acute pyelonephritis following RPIS. The other patient probably developed scar due to the sclerosant itself. The sclerosing agents possibly enter through pyelo-tubular channel and cause chemical inflammation and consequent scarring. Pyelo-tubular backflow may be exerggerated by forceful instillation or instillation of large volume of sclerosing agent. Slow instillation and measurement of pelvic cavity before RPIS will possibly avoid this unnecessary complication.

Radionuclide DMSA-renal scan, although not reported in the context of RPIS, has been used to measure relative renal function in other studies for various indications. For example, it has been used to study impact of extracorporeal shockwave lithotripsy (for renal stones) and percutaneous renal surgery on the affected renal unit using estimation of relative renal function [18,19]. These studies showed that DMSA-renal scan can effectively determine relative renal function 2—3 months after intervention. Our study showed decreased renal function in most of the patients (73.52%) after RPIS. However, these changes were within the normal limits of relative renal function.

Disease duration, choice of sclerosing agent and its doses and urinary and blood parameters did not affect the relative renal function changes. Similarly, number of doses and amount (mL) of sclerosing agent instilled did not affect renal function significantly.

The long-term outcome of acute pyelonephritis and renal scarring have been reported in children with vesicoureteral reflux (VUR) [20]. These include development of hypertension and renal insufficiency [21]. Two patients who developed renal scar will be followed with repeat DMSA scan after 6 months to see the status of their renal scar.

The optimum time of renal scan (DMSA) to detect renal scar is debatable. Most authors believe that acute scan is not necessary due to temporary nature of parenchymal lesion and over time and renal lesion may disappear [22,23]. Camacho et al. [24] performed DMSA-renal scan just after acute pyelonephritis in patients with VUR and found abnormal renal scan in 40 (26%) cases; in the follow-up, renal cortical lesion persisted in only 15 patients. We performed DMSA scan 2—3 months after instillation to detect renal functional changes as well as detection of renal scar.

From the results of this study, it is difficult to make a recommendation about routine post-RPIS functional

imaging. Although, there was no significant deterioration after RPIS, two patients developed renal scars. The reason for renal scar was acute infective pyelonephritis but in another patient the cause remained uncertain. Larger studies are needed to answer this delimma.

This study is unique as there is no previous study evaluating the effects of RPIS on affected kidney in patients of chyluria. We have systemically measured the relative (split) renal function by DMSA-scan and also looked for renal scarring that may have long-term consequences. Our study has certain limitations including small sample size. We performed renal scan after 2—3 months of endoscopic sclerotherapy. Renal scan if performed sooner or later may affect the chance of detecting morphological changes like renal scar. With DMSA renal scan, we could not measure the change in glomerular filtration rate (GFR) of individual kidneys. However, it was not feasible to get two different renal scans (DMSA and diethylenetriamine pentaacetic Acid [DTPA]) on the same patient. The advantage of DMSA scan was that it gave information about formation of renal scars.

5. Conclusion

There was a trend toward slightly decreased relative renal function in most (74%) of the patients; however, renal function remained within normal range. No demographic or biochemical factor predicted the appearance of renal scar after RPIS therapy. There was a small risk of renal scar formation following RPIS. Sclerosing instillation therapy in chyluria is safe for kidneys. Larger prospective studies with long-term follow-up are required to better understand the effects of endoscopic sclerotherapy on renal function and its clinical significance.

Conflicts of interest

Then authors declare no conflict of interest.

Author contributions

Study design: Apul Goel.
Data acquisition: Bimlesh Purkait, Satyawati Deswal, Apul Goel.
Data analysis: Bimlesh Purkait, Monica Agrawal.
Drafting of manuscript: Bimlesh Purkait, Apul Goel, Manoj Kumar, Monica Agrawal.
Critical revision of the manuscript: Bhupendra Pal Singh.

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