Original Article

Use of furosemide stress test for edema control and predicting acute kidney injury in children with nephrotic syndrome

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ABSTRACT

Background: Furosemide stress test (FST) involves measurement of 2-h urine output after giving 1 mg/kg of furosemide in clinically euvolemic patients and has been shown to identify those with severe and progressive acute kidney injury (AKI). **Objectives:** To assess whether using FST could help in deciding whether to give diuretics only, or combination of diuretics with albumin infusion, in children with nephrotic syndrome with edema to prevent AKI. **Materials and Methods:** This prospective, pilot cohort study was conducted on the use of FST to manage edema in children with nephrotic syndrome. Consecutive patients 1–14 years were enrolled from October 2016 to April 2017 from the pediatric nephrology outpatient department of a tertiary care center. They were assessed for fluid overload using their present and baseline weight. Patients with fluid overload of ≥10% were screened for AKI by measurement of serum urea and creatinine and monitoring of urine output in the next 24 h. Systemic infections were excluded using clinical and laboratory criteria. AKI was defined using the pediatric RIFLE score. Children with fluid overload of ≥10% were given intravenous furosemide 1 mg/kg provided; they had no clinical signs of intravascular dehydration or shock. Urine output was measured over the next 2 h. Children with urine output <1 ml/kg/h after FST were presumed to be at risk for progressive AKI. Differences between the average heart rate, serum albumin, and urea/creatinine ratio were analyzed by independent t-test. **Results:** A total of 67 children with nephrotic syndrome were reviewed, and 34 with fluid overload of >10% were analyzed for inclusion in the study. Of them, 11 were excluded and 23 were finally analyzed. 19/23 had urine output >1 mg/kg/h in next 2 h and none had serum creatinine increase >0.3 mg/dl or >150% of the baseline value. 4 had urine output < 1 ml/kg/h. Significant difference was found in the post-FST heart rate and urea/creatinine ratio between the children who had urine output >1 ml/kg/h and which had < 1 ml/kg/h after furosemide. These children were assumed to be at risk for severe and progressive AKI as per FST and were thereafter given furosemide with albumin to prevent further intravascular dehydration. **Conclusion:** FST may be used as a bedside test to help identify the children with nephrotic syndrome with intravascular dehydration who are at high risk for AKI and helps rational use of diuretics.

Key words: *Nephrotic syndrome, Edema, Relapse*

Nephrotic syndrome in children is characterized by heavy proteinuria, hypoalbuminemia, and edema [1]. The presence of edema may range from relatively mild, in the form of periorbital puffiness only to gross anasarca. In most of the patients with steroid-sensitive nephrotic syndrome, the edema resolves with corticosteroids alone. Generalized edema is a common cause for admission in children with nephrotic syndrome in relapse. These children are at risk for various complications including acute kidney injury (AKI), serious infections, and vascular thrombosis during relapse [2-4]. Even with edema of more than 10–20%, most of the children tend to have relative intravascular hypovolemia [5]. Use of diuretics is warranted in patients with significant edema or symptomatic fluid overload. Intravenous infusions of albumin may be required when patients have clinical evidence of intravascular hypovolemia despite gross anasarca [6]. Furosemide stress test (FST) involves measurement of the 2-h urine output after 1 mg/kg of furosemide in furosemide naive patients or 1.5 mg/kg in those with prior exposure to furosemide in clinically euvolemic patients and has been shown to be able to identify those with severe and progressive AKI [7]. We hypothesized that FST could help in the clinical decision without much delay due to laboratory investigations, whether to give only diuretics to children with nephrotic syndrome presenting with edema or combination of diuretics with albumin infusion at initial presentation. The aim of this study is to determine if FST could be used to manage the edema and to predict AKI in children with nephrotic syndrome.

MATERIALS AND METHODS

This was a pilot prospective cohort study on the use of FST to manage the edema in children with nephrotic syndrome in relapse. Consecutive patients with nephrotic syndrome 1–14 years old were

enrolled from the pediatric nephrology outpatient department of a tertiary care center of India from October 2016 to April 2017. Children with nephrotic syndrome in relapse or those with the first episode of nephrotic syndrome with edema were assessed for fluid overload using their present weight and baseline weight. Baseline weight was the latest recorded weight of the child taken when he/she was in remission and taken as the as weight recorded when child during the last visit to the outpatient department or the last recorded weight for children with the first episode.

All patients with fluid overload of ≥10% as per the weight at admission were screened for AKI by measurement of serum urea and creatinine and monitoring of urine output in the next 24 h as inpatients. Serum albumin and complete blood counts were done in all children along with c-reactive protein, blood culture, and relevant investigations depending on the symptoms of the child including a chest X-ray if the child was symptomatic with cough or had increased work of breathing, ascitic fluid examination if clinical features suggestive of spontaneous bacterial peritonitis and blood culture to rule out presence of serious systemic infections.

AKI was defined using the pediatric RIFLE score by eGFR criteria [8]. Children with a serum creatinine ≥150% of baseline or serious systemic infection at presentation were excluded. The children who refused inpatient admission were also excluded as close monitoring of urine output was imperative. Children assessed to have intravascular dehydration were also excluded. Children admitted in hospital with estimated fluid overload of ≥10% were given intravenous furosemide 1 mg/kg single dose. The urine output was then measured over next 2 h and documented in ml/kg/h. The children with tachycardia (heart rate more than 2 standard deviation higher than the appropriate for age) and/or systolic blood pressure less than the fifth centile for age and/or capillary filling time more than 3 s were excluded from the FST and were given albumin and/or intravenous fluids as determined by the clinical condition of the patient. Children with urine output <1 ml/kg/h after FST were presumed to be at risk for progressive AKI.

Differences between the average heart rate, serum albumin, and urea/creatinine ratio were analyzed. Serum urea, creatinine, albumin, sodium, and potassium were repeated 24 h till the child was documented to be in remission as determined by urine by dipsticks to be negative or trace for 3 consecutive days and/or urine protein creatinine ratio <0.5 mg/mg. Intravenous furosemide at 1 mg/kg was repeated 12 h later if no clinical signs of intravascular dehydration were present and fluid overload was still estimated to be ≥10%. Children with urine output <1 ml/kg/h after FST were administered 20% albumin at 1 g/kg as a slow intravenous infusion over 4 h with intravenous furosemide at 1 mg/kg 2 h after starting albumin infusion. Any complications post-FST including hypotension, hypokalemia, and hyponatremia were also recorded.

RESULTS

A total of 67 children with nephrotic syndrome attended the pediatric nephrology clinic during the period. Of these, 14 were steroid dependent, 30 were frequently relapsing, 6 were infrequently relapsing, 8 were steroid-resistant nephrotic syndrome (who were previously in complete or partial remission), and 9 had first episode of nephrotic syndrome. The standard ISPN guidelines were used to classify the children with nephrotic syndrome as steroid dependent, frequently relapsing, and infrequently relapsing [9]. These 67 children had 41 relapses during the study period. Their baseline characteristics are as given in Table 1. Total 34 children had fluid overload of >10% and were recruited in the study. However, 7 of them were further excluded as 3 had serious systemic infection at presentation (2 had spontaneous bacterial peritonitis, and one had pneumonitis). Parents of 2 other children did not consent for hospital admission and had to be excluded. 2 other children who presented with gross anasarca and oliguria of >24 h duration and were found to have >150% rise in serum creatinine as compared to their last recorded creatinine were also excluded. Fig. 1 depicts the children enrolled in the study. In total 4 children (2 with 10-20% and 2 with >20% dehydration) were detected to have features of intravascular dehydration and were also excluded.

Three of the remaining 23 children had fluid overload of more than 20%. Rest of the 20 children had fluid overload of more than 10%. These 23 children were given intravenous furosemide (1 mg/kg). 19 of them had urine output >1 mg/kg/h in next 2 h and none of them had an increase in serum creatinine >0.3 mg/dl or ≥150% of the baseline value at admission at 12 h and 24 h after injection furosemide. In the remaining 4 children, the urine output was < 1 ml/kg/h. Table 2 shows the baseline and post-FST parameters in these children. A significant difference in heart rate was seen in children who did not

Table 1: Baseline characteristics of the children with nephrotic syndrome (n=67)

Age in months*	19–150 months, mean 52 (3.7)
Age at onset of nephrotic syndrome in months*	16–66 months, mean 29 (1.2)
Males n (%)	41 (61.19)
FRNS. n (%)	30 (46.87)
SDNS, n (%)	14 (20.89)
IFRNS, n (%)	6 (8.95)
SRNS, n (%)	8 (11.94)
Total number of relapses, n	41
Children with 1 relapse, n	18
Children with 2 relapses, n	10
Children with>2 relapses, n	1 (had 3 relapses)
Drug therapy of children who relapsed	
Children on low-dose alternate day steroids, n	11
Children on levamisole, n	4
Children on mycophenolate mofetil, n	4
Children on cyclophosphamide, n	2
Children on cyclosporine or tacrolimus, n	11
Baseline systolic BP*	102.6±8.4
Baseline diastolic BP*	64±7.6
Baseline heart rate*	98±5

***Values in mean (SD). SD: Standard deviation, FST: Furosemide stress test, BP: Blood pressure**

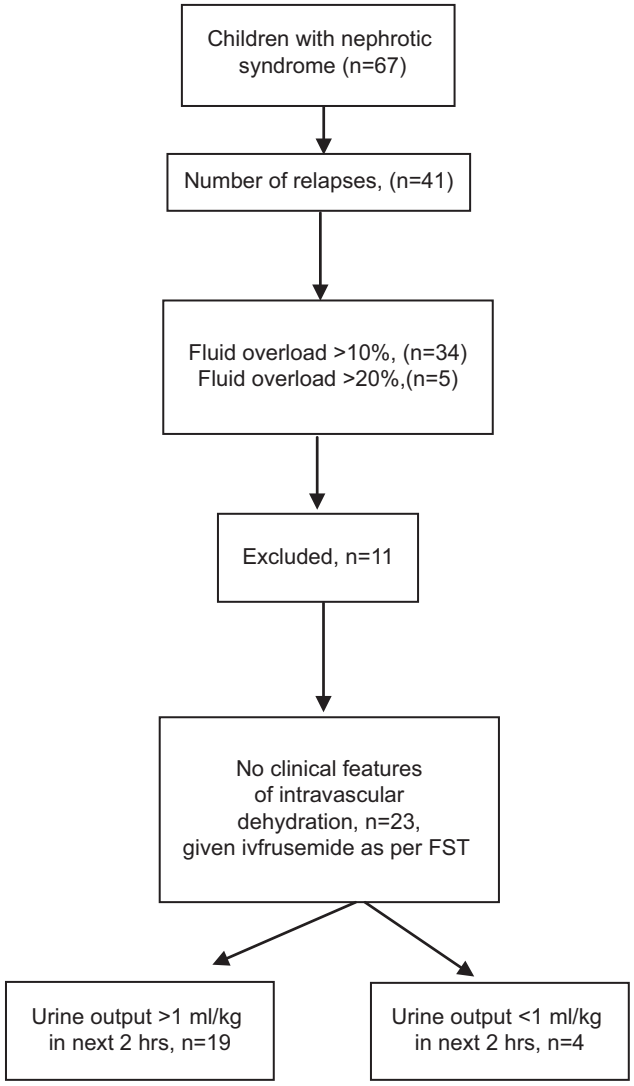

Figure 1: Flow chart showing patients with nephrotic syndrome

respond to FST which was not observed in children who responded to FST whereas no significant difference in blood pressure was found between the two groups. Table 3 shows the difference in urea/creatinine ratio, serum albumin, and heart rate in these 2 Groups of children who had urine output >1 mg/kg/h in next 2 h and those who did not after FST. A significant difference was seen in the heart rate and urea/creatinine ratio between the children who responded to FST and those who did not. The children with urine output <1 mg/kg/h in 2 h after furosemide were assumed to be at risk for severe and progressive AKI as per the FST and they were administered 20% albumin at 1 g/kg as a slow intravenous infusion over 4 h. None of them had a serum creatinine increase of more than 0.3 mg/dl or ≥150% of the baseline value at admission, at 12 h and 24 h. None of the children developed dyselectrolytemia or hypotension following FST.

DISCUSSION

Accurate assessment of whether the edematous child is in fluid overload or has intravascular volume depletion is imperative

Table 2: Pre- and post-FST clinical parameters in responders and non-responders

Clinical characteristics	Pre-FST	Post-FST	p
Children who responded to FST (n=19)			
HR*	100±4	103±3	0.08
Systolic BP*	106±2	104±3	0.12
Diastolic BP*	68±3	70±2	0.14
Children who did not respond to FST (n=4)			
HR*	98±4	114±6	0.03
Systolic BP*	104±3	102±2	0.11
Diastolic BP*	70±2	68±3	0.12

FST: Furosemide stress test

Table 3: Clinical and laboratory parameters post-FST in responders and non-responders

Clinical characteristics	Children who responded to FST (n=19)	Children who did not respond to FST (n=4)	p
Heart rate*	92±7	120±16	p=0.03
Urea/creatinine ratio*	16±4	26±2.3	p=0.01
Serum albumin*	1.9±0.40	1.3±0.34	p=0.08

***Values in mean (SD). SD: Standard deviation, FST: Furosemide stress test**

to avoid complications of worsening fluid overload on the one hand and further dehydration on the other. The most centers rely on clinical and biochemical criteria for use of diuretics and/or albumin for the management of edema. Use of echocardiography for the assessment of intravascular volume status has also been described but may not be readily available.

Children with nephrotic syndrome are exposed to various potential risk factors for AKI, including intravascular volume depletion, infection, exposure to nephrotoxic medication, and renal interstitial edema leading to vascular congestion [10,11]. They are therefore inherently at risk of developing AKI. We wanted to use a bedside test which along with the clinical examination of the edematous child could help in tailoring the management of edema in children with nephrotic syndrome such that we could identify the children at risk for AKI. We could not find any previous study using the FST for the same. The FST has been however shown to identify those at risk of severe and progressive AKI which is one of the dreaded complications of children with generalized edema with nephrotic syndrome.

We found that none of the children with urine output >1 mg/kg/h in 2 h after furosemide had a rise in serum creatinine or fall in urine output to <1 mg/kg/h in next 24 h. Our study also demonstrated that children assessed to have intravascular hypovolemia by FST in the form of reduced urine output after furosemide had significantly higher serum urea to creatinine ratio and heart rate as compared to children who had urine output <1 mg/kg/h in 2 h after furosemide. These children thus had evidence of intravascular dehydration which was unmasked by FST as seen

by the significant difference in heart rate post-FST in children who did not show adequate response to FST. Furthermore, there was a significant post-FST rise in urea/creatinine ratio in children who did not respond to FST as compared to those who did. This suggests that if treated by diuretics alone these children may have a worsening of intravascular dehydration leading to AKI. We gave this subset of children with urine output <1 mg/kg/h after FST a combination of albumin and furosemide and none of them had a rise in serum creatinine or fall in urine output. Similarly, in children, who were assessed to have features of intravascular dehydration clinically and were given 20% albumin infusion slowly over 4 h with intravenous furosemide and not furosemide alone initially, none had a rise in serum creatinine or urine output <1 mg/kg/h in the next 24 h.

This compares very favorably with the previous studies which have shown the incidence of AKI in children with nephrotic syndrome to be 8.5–58.6% [3,12]. This may be partly explained by the exclusion of children with serious systemic infections and high baseline criterion. Even so, our study highlights that management of edema combining FST and clinical bedside examination could help to identify children with low intravascular volumes and thus show the treating physicians that the edema in these children is unlikely to resolve with diuretics alone. This, in turn, drastically brings down the incidence of AKI in children with nephrotic syndrome. Therefore, while the use of furosemide in AKI per say has not to be of any benefit [13], but its cautious use alone or in combination with albumin may help reduce the edema in children with nephrotic syndrome prevent AKI in such patients.

The strength of our study lies in its prospective cohort design which has helped us to minimize bias. An obvious limitation of our study is the lack of controls or randomization. Furthermore, being a pilot study, a statistically significant sample size could not be calculated. However, our study demonstrates marked reduction in an important complication, namely AKI using protocol based on simple readily available clinical parameters and use of response to diuretics. It is therefore recommended that larger randomized trials be undertaken to conclusively prove the use of FST to determine if only diuretics or combination of albumin with diuretics could play a role in preventing AKI in children with edema in nephrotic syndrome relapses.

CONCLUSION

Use of FST in children with nephrotic syndrome may help in rational use of diuretics in children with nephrotic syndrome and to identify those at risk for AKI.

REFERENCES

1. Ulinski T, Aoun B. Pediatric idiopathic nephrotic syndrome: Treatment strategies in steroid dependent and steroid resistant forms. Curr Med Chem 2010;17:847-53.
2. Tain YL, Lin G, Cher TW. Microbiological spectrum of septicemia and peritonitis in nephrotic children. Pediatr Nephrol 1999;13:835-7.
3. Kato S, Chernyavsky S, Tokita JE, Shimada YJ, Homel P, Rosen H, *et al*. Relationship between proteinuria and venous thromboembolism. J Thromb Thrombolysis 2010;30:281-5.
4. Rheault MN, Wei CC, Hains DS, Wang W, Kerlin BA, Smoyer WE. Increasing frequency of acute kidney injury amongst children hospitalized with nephrotic syndrome. Pediatr Nephrol 2014;29:139-47.
5. Wang SJ, Tsau YK, Lu FL, Chen CH. Hypovolemia and hypovolemic shock in children with nephrotic syndrome. Acta Paediatr Taiwan 2000;41:179-83.
6. Dharmaraj R, Hari P, Bagga A. Randomized cross-over trial comparing albumin and furosemide infusions in nephrotic syndrome. Pediatr Nephrol 2009;24:775-82.
7. Koyner JL, Davison DL, Brasha-Mitchell E, Chalikonda DM, Arthur JM, Shaw AD, *et al*. Furosemide stress test and biomarkers for the prediction of AKI severity. J Am Soc Nephrol 2015;26:2023-31.
8. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. Kidney Int 2007;71:1028-35.
9. Bagga A. Revised guidelines for management of steroid-sensitive nephrotic syndrome. Indian J Nephrol 2008;18:31-9.
10. Rheault MN, Wei CC, Hains DS, Wang W, Kerlin BA, Smoyer WE. Increasing frequency of acute kidney injury amongst children hospitalized with nephrotic syndrome. Pediatr Nephrol 2014;29:139-47.
11. Koomans HA. Pathophysiology of edema and acute renal failure in idiopathic nephrotic syndrome. Adv Nephrol Necker Hosp 2000;30:41-55.
12. Goldstein SL, Kirkendall E, Nguyen H, Schaffzin JK, Bucuvalas J, Bracke T, *et al*. Electronic health record identification of nephrotoxin exposure and associated acute kidney injury. Pediatrics 2013;132:e756-67.
13. Bagshaw SM, Gibney RT, Kruger P, Hassan I, McAlister FA, Bellomo R. The effect of low-dose furosemide in critically ill patients with early acute kidney injury: A pilot randomized blinded controlled trial (the SPARK study). J Crit Care 2017;42:138-46.

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