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Non-invasive assessment of volume status of children with edema due to steroid sensitive nephrotic syndrome using urinary indices and inferior venacava ultrasonography

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ABSTRACT

Background: It is clinically difficult to assess the intravascular volume status of children with edema in nephrotic syndrome. This makes decision-making challenging, regarding the use of diuretics or albumin infusion in the management of edema. Ideally, hormonal assay and central venous pressure monitoring are accurate but difficult to do as these methods are invasive and expensive to be applied to every child presenting with edema of nephrotic syndrome. Hence, the need for reliable non-invasive investigations to assess the volume status of children with edema. **Aims and Objectives:** The aim of the study was to assess the volume status of children with edema due to steroid sensitive nephrotic syndrome using noninvasive methods such as urinary indices (Fractional excretion of sodium (Fe_{Na}) and urine Potasium index (K index)) and inferior venacava diameter (IVCD) by ultrasonography and to determine the association between them. **Materials and Methods:** In this analytical cross-sectional study, 82 subjects fitting the inclusion criteria were included in the study. Fe_{Na}, K index and IVCD were determined. The volume status was assessed and association between the three calculated (Fischer exact test). **Results:** Out of 82 children, 56.1%, 68.3%, and 63.5% based on FeNa, K index, and IVCD respectively were having hypervolemic volume status. There is a statistically significant association between FeNa and K index and between urinary indices and IVCD. **Conclusion:** The present study supports the overfill hypothesis of edema formation. IVCD like urinary indices is a non-invasive and reliable investigation to determine volume status in nephrotic child with edema.

Key words: Nephrotic syndrome; Intravascular volume; Inferior venacava ultrasonography; Urinary indices

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INTRODUCTION

Edema is a key clinical feature of nephrotic syndrome. It has been suggested that edema may be due to a combination of both the underfill and overfill hypotheses, with the intravascular volume status being hypovolemic, hypervolemic, or normal.[1] It is now recommended that patients with moderate-to-severe edema be assessed for intravascular volume status before initiating therapy with diuretics. Determination of volume status is of significance when it comes to management of the edema. It is clinically difficult to assess the intravascular volume status during the edematous phase of nephrotic syndrome in children. This poses a therapeutic challenge when taking a decision about the use of diuretics or albumin infusion in the management of edema. Hormonal assay and central venous pressure monitoring are more accurate but cannot be applied to every child presenting with edema of nephrotic syndrome.[2] Hence, the need for reliable investigations to assess the volume status of children with edema. Urinary indices such as fractional excretion of sodium (FeNa) and urine potassium index (K index) are quick, simple, and reliable

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tests to evaluate the volume status.[2-5] Measurement of inferior venacava diameter (IVCD) or inferior venacava indices by ultrasonography or echocardiography is also an accurate predictor of the intravascular volume status.[3,4] All the three tests, FeNa, K index, and IVCD have been recommended as basic tests to be done to assess volume status of children with edema with nephrotic syndrome in the recent guideline published by the Indian Society Of Pediatric Nephrology.[6]

Aims and objectives

To assess the volume status of children with edema due to steroid sensitive nephrotic syndrome using noninvasive methods like urinary indices (Fractional excretion of sodium (FeNa) and Urine Potasium index (K index)) and Inferior Venacava diameter (IVCD) by ultrasonography and to determine the association between them.

MATERIALS AND METHODS

In this analytical and cross-sectional study, subjects were children age 1–12 years presenting with edema due to steroid sensitive nephrotic syndrome, not on steroids at time of presentation, at a tertiary care center in South India. Most of the children were the age group 2–7 years as that is the typical age group for steroid sensitive nephrotic syndrome. Children who were on treatment with diuretics or intravenous fluids, those with secondary nephrotic syndrome, with features of glomerulonephritis, those whose IVCD could not be estimated by ultrasonography due to poor cooperation from the patient were excluded from the study (Figure 1). At significance level of 5%, 20% as relative precision, and power of the study 80%, sample size was calculated as 82[2].

Sample size calculated using the formula

$$\text{Sample Size N} = \frac{(Z_{1-\alpha/2})^2 PQ}{D^2}$$

Significance level (α) =5% (1.96)
P= prevalence of Volume expanded =54%[2]
Q=1−P
D=Relative precision 20% of P

Subjects were enrolled by consecutive sampling. The study obtained ethical approval from the Institutional Ethical Committee. Investigations relevant to the study were carried out. Data were entered in Microsoft Excel for Windows 7 and the analysis done by the Statistical Software Package for the Social Sciences Version 23 (SPSS 23).

Urinary indices were calculated as follows:

1. Fractional Excretion of Sodium (FeNa)

$$= \frac{\text{Serum Creatinine} \times \text{Urine Sodium}}{\text{Urine Creatinine} \times \text{Serum Sodium}}$$

Value of ≤0.2% was taken as hypovolemic/Volume Contracted

Value of >0.2% was taken as hypervolemic/Volume Expanded[5]

2. Urine Potassium Index (K index)

$$= \frac{\text{Urine Potassium}}{\text{Urine Potassium} + \text{Urine Sodium}}$$

Value of >0.6 – hypovolemic/Volume Contracted

Value of <0.6 – hypervolemic/Volume Expanded[5]

IVC diameter was measured by ultrasonography by the same qualified radiologist. The maximum and minimum diameters of IVC were measured during the expiratory and inspiratory phase of the respiratory cycle, respectively, using M mode ultrasonography. IVC diameter was measured in millimeters and compared with normal values for age.[7]

Ethics committee clearance

It is approved by the Institutional Ethics Committee of Amala Institute of Medical Sciences on 20/01/2018 Ref number AIMSIEC/01/2018.

RESULTS

Out of the 82 children included in the study, 49 (59.7%) were males and 33 (40.3%) were females, 51 (62.2%) were between 2 and 7 years of age, 25 (30.5%) were having the first episode, while 57 (69.5%) had relapse.

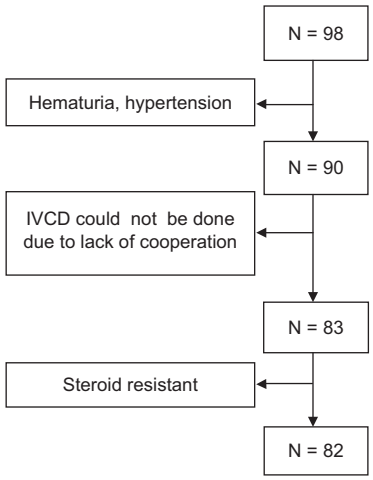

Figure 1: Nephrotic syndrome with edema

Based on FeNa, out of 82 children in the study, 36 (43.9%) were hypovolemic and 46 (56.1%) were hypervolemic. Of the 36 cases classified as hypovolemic, 24 were consistent with hypovolemia on measuring K index. Among 46 cases found to have hypervolemia by FeNa, 44 were hypervolemic when measuring K index as well.

Based on K index, 26 (31.7%) cases were hypovolemic while 56 (68.3%) cases were hypervolemic. Out of the 26 cases that were determined to be hypovolemic by K index, 24 were consistent with being hypovolemic when measuring FeNa. Among 56 cases found to be hypervolemic when measuring K index, 44 were hypervolemic when measuring FeNa.

Statistical analysis was done using the Fischer exact test to find out association between the intravascular volume status as determined by the two urinary indices, FeNa and K index (Table 1). P=0.0001 and is statistically significant.

The intravascular volume status determined by urinary indices was compared to results of volume status obtained by ultrasound measurement of IVCD. The IVCD size denoting hypovolemia was observed in 30 (36.5%) of the 82 cases, in whom 28 had hypovolemia on using FeNa. The IVCD size denoting hypervolemia/normovolemia was observed in 52 (63.5%) of the 82 cases, in whom 44 had hypervolemia on using FeNa (Table 2). Similarly of the 30 who had hypovolemia as determined by IVCD, 22 had hypovolemia using K index. Of the 52 who had hypervolemia/normovolemia, 48 had the same volume status using K index (Table 3).

The association between intravascular volume status as determined by FeNa and IVCD and by K index and IVCD was calculated using the Fischer exact test and P=0.0001 (statistically significant).

DISCUSSION

There is an evidence for both intravascular volume expansion (overfilling/hypervolemia) and intravascular volume depletion (underfilling/hypovolemia) in patients with nephrotic syndrome.[8] Studies have been conducted to predict the volume status of children with edema in nephrotic syndrome using urinary indices by Sahay,[1] Van de Walle and Donckerwolcke[9] and by Iyengar et al.,[2] Almost all of these studies have recruited patients of steroid sensitive nephrotic syndrome. Steroid resistant nephrotic subgroup was studied only by Iyengar et al.[2] In our study of 82 children, based on FeNa 46 (56.1%) were hypervolemic. Based on K index, 56 cases (68.3%) were hypervolemic. Majority of the cases were hypervolemic, favoring the overfill theory of edema formation. This was consistent with Büyükavcı et al., study in Turkey. Of the 32 children studied, 24 cases (75%) were hypervolemic.[4] In the study by Locham et al., 14 out of 16 children had K index suggestive of hypervolemia.[10]

Table 1: Association between intravascular volume status as determined by urinary indices FeNa and K index

K Index	FeNa		Total	P value (Fischer exact test)
	Hypovolemia	Hypervolemia		
Hypovolemia	24	2	26	0.0001
Hypervolemia	12	44	56	
Total	36	46	82	

Table 2: Association between Intra vascular volume status as determined by FeNa and IVCD

IVCD for age	FeNa		Total	P-value (Fisher exact test)
	Hypovolemia	Hypervolemia		
Hypovolemia	28	2	30	0.0001
Normal/Hypervolemia	8	44	52	
Total	36	46	82	

IVCD: Inferior venacava diameter

Table 3: Association between intravascular volume status as determined by K index and IVCD

IVCD for age	K index		Total	P-value (Fisher exact test)
	Hypovolemia	Hypervolemia		
Hypovololemia	22	8	30	0.0001
Normal/hypervololemia	4	48	52	
Total	26	56	82	

IVCD: Inferior venacava diameter

On the other hand, Donckerwolcke et al., in their study in 126 patients with nephrotic syndrome concluded that low FeNa and high K index identifies patients with increased aldosterone levels and indicates functional hypovolemia.[11] Hence, it did Keenswijk et al., who studied the K index as an indicator of hypovolemia in 44 children with nephrotic syndrome.[12] Iyenger et al., found that 50% of steroid responsive children and 36% of steroid non-responders had low K index suggestive of hypervolemia.[2] This may suggest that steroid resistance in nephrotic syndrome may favor hypovolemia. According to our study, there is a significant association seen between FeNa and K index for determining volume status in nephrotic syndrome (P=0.0001) and this association has not been described elsewhere.

Echocardiography and ultrasound are useful in determining intravascular volume status as these techniques are non-invasive.[13] Studies by Büyükavcı et al.,[4] and Donmez et al.,[13] concluded inferior Venacava indices determined by echocardiography to be an easy and reliable method to assess the intravascular volume in patients with nephrotic syndrome. We used ultrasound which is non-invasive, readily available, and rapid method. In our study to determine intravascular volume, IVCD as measured by USG was compared with the normal size expected for the age group for Indian children.[7] Out of the 82 children, 52 (63.5%) children were normo/hypervolemic. In the study by Locham et al., on echo assessment, 17 of the 20 children with nephrotic syndrome had IVC/Aorta ratio in nonhypovolemic range.[10] In an observational study undertaken by Gupta et al., 21 out of 30 children with nephrotic syndrome were classified as hypervolemic based on IVC collapsibility index.[3] Majority of these studies support the overfill or hypervolemic state in children with nephrotic syndrome.

We obtained statistically significant association between the intravascular volume status as determined by urinary indices and the IVCD (P=0.0001). This association has not been described except in the study by Locham et al., where two out of these three children with IVC/Aorta in hypovolemic range had urinary indices commensurate with hypovolemia.[10]

The strengths of our study were that all the investigations and ultrasound measurements were performed before the subjects were started on any medication and that ultrasound measurements were performed by the same expert radiologist who was blinded to urinary indices values and clinical findings of intravascular volume status, thus reducing the bias in measurements.

Limitations of the study

Limitations of the study were that there is not much research that we could find on intravascular volume status assessment using IVCD in nephrotic syndrome children and its association to assessment of volume status using urinary indices. We chose to use IVCD measurement as it is less complicated than calculating indices and can be done using portable ultrasound machines in pediatric ICU or emergency department too. Second, we did not take into account that parents of the children with relapse of nephrotic syndrome might have restricted intake of fluid and sodium based on their prior experience or advice given to them. Finally, there is some expertise necessary to measure IVCD.

CONCLUSION

Although mechanism of edema formation in nephrotic syndrome can be multiple, the present study supports the overfill hypothesis. The present study concluded that IVCD, like urinary indices, is a good indicator of intravascular volume status in edematous patients with nephrotic syndrome.

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Key Message

What is Known

Volume status can be difficult to assess based on clinical parameters in nephrotic syndrome, thus making therapeutic decisions difficult.

WHAT DOES THE STUDY ADD

Children with edema due to steroid sensitive nephrotic syndrome are likely to have hypervolemic intravascular status which can be assessed by inferior venacava diameter and urinary indices.

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Authors Contributions:
KP – Contributed to the conception and design of the work, interpretation of data for the work, drafting the work and revising it critically for important intellectual content, final approval of the version to be published, agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **JJ-** Contributed to acquisition, analysis, interpretation of data for the work, initial drafting of the work and final approval of the version to be published, agree to be accountable for all aspects of the work; **VKP-** Contributed to initial drafting and revising the manuscript, final approval of the version to be published; agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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