Intravenous Albumin and Diuretic in Nephrotic Syndrome with Severe Edema: Our Experience and Literature Review

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Abstract
Background and Aim: Steroids are the mainstay of initial treatment in children with Idiopathic Nephrotic Syndrome (INS). The role of diuretics in children with NS is less clear in comparison to adults. In cases with severe or refractory edema, furosemide is often combined with albumin infusion (0.5 to 1 g/kg) to provide symptomatic relief.

Methods: This study was a retrospective chart review of 17 patients with a diagnosis of Steroid Dependent Nephrotic Syndrome (SDNS) admitted for relapse of NS with severe edema who were resistant to diuretic therapy alone. The patients were treated as per unit protocol with an infusion of 100 ml intravenous albumin 20% over 4 hours and 2 doses (one in the morning at 10 AM and the other in the evening at 6 PM) of furosemide 1mg/kg for 3 days. Response to therapy and adverse events were evaluated.

Results: The mean age of the study population was 10.58±1.5 years. All of the patients had severe edema and none of them had responded to intravenous diuretics alone. After co-administration of intravenous albumin infusion and furosemide, the mean weight loss per day per patient was 0.87±0.16 kg.

Conclusion: A significant improvement was noted in all of the patients following co-administration of albumin and furosemide without any adverse events.

Keywords: Nephrotic syndrome; Steroid; Diuretic; Child.

Conflict of interest: The authors declare no conflict of interest.


Introduction
Nephrotic Syndrome (NS) represents a distinct glomerulopathy with cardinal features of heavy proteinuria, edema, hypoalbuminemia and hyperlipidemia. The characteristic nephrotic range proteinuria is defined as a spot protein/creatinine ratio >2 mg/mg, early morning urine protein of 3+/4+, or urine albumin excretion >40 mg/m² per hour. Idiopathic NS is the most common form of NS in children, responsible for a majority (>90%) of the cases before 10 years of age (1). NS can cause significant complications, thereby leading to increased morbidity and mortality.

It affects the quality of life of children (2,3) Steroids are the mainstay of initial treatment in children with Idiopathic Nephrotic Syndrome (INS). Most (90%) of the children with INS achieve remission within 4 weeks of initiation of steroids. These patients are labelled as Steroid-Sensitive Nephrotic Syndrome (SSNS). About 10% of the cases do not attain remission despite therapy with daily steroids over 4 weeks, who are known as Steroid-Resistant Nephrotic Syndrome (SRNS) (1,4).
Furthermore, Steroid Dependent Nephrotic Syndrome (SDNS) is defined as two consecutive relapses during alternate day steroids or within 14 days of its discontinuation (1). The role of diuretics in children with NS is less clear in comparison to adults. Supportive care with diuretics is often required in children with significant edema as the clinical effects of therapy in the form of diuresis are seen 5 to 10 days after initiation of steroids. In cases with severe or refractory edema, furosemide is often combined with albumin infusion (0.5 to 1 g/kg) to provide symptomatic relief (1). Albumin infusion should be administered cautiously and the patient should be monitored closely for complications like hypertension, volume overload, pulmonary edema and congestive heart failure. (5,6,7) We report our experience with the combined use of intravenous albumin infusion and diuretics in severely edematous patients with SDNS.

**Methods**

This study was a retrospective chart review of 17 patients with a diagnosis of Steroid Dependent Nephrotic Syndrome (SDNS) admitted for relapse of NS with severe edema. All of the patients had failed to respond to intravenous diuretics (2 doses of furosemide 1 mg/kg) alone. The patients were treated as per unit protocol with 100 ml intravenous albumin 20% as an infusion over 4 hours and 2 doses of furosemide 1 mg/kg for 3 days. Response to therapy and adverse events were evaluated.

**Results**

The mean age of the study population was 10.58±1.5 years. Laboratory evaluation revealed a mean serum creatinine of 0.74±0.16 mg/dl, mean albumin of 2.37±0.29 mg/dL, and proteinuria of 42.47±2.09 mg/m2/hour. After co-administration of intravenous albumin infusion and furosemide, the mean weight loss per patient per day was 0.87±0.16 kg. None of our patients had any adverse events and there was no evidence of DVT on lower limb Doppler in any of the patients. None of the patients developed AKI at baseline or during the course of hospital stay.

**Discussion**

Nephrotic syndrome (NS) is a common renal disorder in the pediatric population. Although the majority of the patients respond to treatment with steroids, attainment of an optimal therapeutic response may take several weeks (8). Various pathophysiologic mechanisms have been suggested for edema formation including underfill and overfill hypotheses. The edema and hypoalbuminemic state that ensues have several clinical consequences ranging from infections to thrombotic events among others. (9-20) Symptomatic treatment plays an important role in this period and assumes an even greater significance in patients who fail to respond to immunosuppressive treatment. Albumin helps protect against intravascular contraction by increasing oncotic pressure and improves the delivery of furosemide to the kidney as a result of increased protein-binding (21). A limited number of studies have evaluated clinical response to a combination of albumin and furosemide for nephrotic syndrome in the pediatric population. Weiss et al. reported weight loss in 24 children with NS treated with albumin and furosemide (22). In a study by Haws et al., combined therapy with diuretics resulted in a mean weight loss of 0.4 kg (1.2% of the body weight) (6). This weight reduction persisted in children whose proteinuria improved, but it was transient in children who continued to have proteinuria. Another prospective study of 14 children with NS also noted a transient decrease in abdominal circumference and body weight (23). Dharmaraj et al. conducted a crossover study and reported increased diuresis and natriuresis with combination therapy compared to the use of diuretics alone (24). In the present study, a substantial drop was noted in the patients’ weight after co-administration of furosemide and IV albumin. More importantly, no significant adverse events were observed with this combination in our series. Our experience with a combination of intravenous albumin and a diuretic in severely nephrotic children was quite reassuring. Several studies examining the effect of co-administration of albumin and diuretics on edema in adults with NS have also demonstrated a transient modest clinical benefit; however, definitive recommendations have not been established due to lack of robust evidence (25-29). Moreover, the administration of albumin and diuretics in pediatric patients may produce a more profound increase in the urine output compared to adults, especially in patients with depleted intravascular volumes (24,27). Interestingly, one study found that adding albumin failed to improve diuresis compared to furosemide.
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alone in adult patients with hypoalbuminemia due to other causes (e.g. cirrhosis with ascites) (30,31). The Indian Academy of Pediatrics (IAP) guidelines recommend administration of albumin 20% (0.5 to 1 g/kg) as an infusion over 2-4 hours together with intravenous furosemide (1 to 2 mg/kg) (1). However, in patients with laboratory evidence of volume expansion (FENa >0.2%), the use of diuretics alone produces diuresis similar to that seen with the use of combined albumin and diuretics in volume contracted patients (20). According to several studies mentioned above, the beneficial effects tend to be transient, and repeat doses are often required. Patients receiving albumin infusions should be closely monitored for respiratory distress, features of fluid overload, congestive heart failure, anaphylaxis, and pulmonary edema (6,7,32).

Conclusion
Controlling edema in patients with nephrotic syndrome is important for symptomatic relief and improved functionality. The use of intravenous albumin infusion in conjunction with diuretics helps to induce diuresis and decrease edema in patients who are refractory to conventional therapy. It is vital to perform a careful evaluation of the volume status of the patient, and certain indices can assist in classifying them as either ‘volume contracted’ or ‘volume expanded’. Albumin should be infused slowly (preferably over 4 hours) to prevent life-threatening complications, and the patients should be closely monitored for adverse events. Only a handful of studies have evaluated the use of albumin/furosemide for INS-associated edema, and none of them has been specifically conducted on children with SDNS. A significant improvement was noted in all of the patients following co-administration of albumin and furosemide without any adverse events. Large, well-designed studies need to be conducted, especially on patients that are dependent on or resistant to treatment with steroids.

Conflict of Interest
The author declares no conflicts of interest.

Financial Support
Not declared.

References
13. Epstein AA. Concerning the causation of edema in chronic parenchymatous nephritis; method for its alleviation. The American journal of medicine 1952;
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13(5):556–561. https://doi.org/10.1016/0002-9343(52)90020-x


