Treatment of Severe Edema in Children with Nephrotic Syndrome with Diuretics Alone — A Prospective Study

Gaurav Kapur,* Rudolph P. Valentini,* Abubakr A. Imam,† and Tej K. Mattoo‡

*Carman and Ann Adams Department of Pediatrics, Division of Pediatric Nephrology and Hypertension, Children's Hospital of Michigan, Wayne State University, Detroit, Michigan; and †Division of Pediatric Nephrology and Hypertension, Children's Hospital Medical Center of Akron, Akron, Ohio

Background and objective: Severe edema in children with nephrotic syndrome (NS) may be associated with volume contraction (VC) or volume expansion (VE). Usually, severe edema in children is treated with intravenous (IV) albumin and diuretics, which is appropriate for VC patients. However, in VE patients, this can precipitate fluid overload. The objective of this study was to evaluate treatment of severe edema in NS with diuretics alone.

Design, setting, participants, & measurements: Thirty NS patients with severe edema were enrolled in this prospective study in two phases. VC was diagnosed based on fractional excretion of sodium (FeNa) <1%. VC patients received IV albumin and furosemide. VE patients received IV furosemide and oral spironolactone. On the basis of phase 1 observations, FeNa <0.2% identified VC in 20 phase 2 patients.

Results: All phase 1 patients had FeNa <1%. Phase 1 patients when reanalyzed based on a FeNa cutoff of 0.2%; it was noted that VC patients had higher BUN, BUN/creatinine ratio, urine osmolality, and lower FeNa and urine sodium compared with VE patients. Similar results were observed in phase 2. VC patients had significantly higher renin, aldosterone, and antidiuretic hormone levels. In phase 2, 11 VE patients received diuretics alone and 9 VC patients received albumin and furosemide. There was no difference in hospital stay and weight loss in VC and VE groups after treatment.

Conclusions: FeNa is useful in distinguishing VC versus VE in NS children with severe edema. The use of diuretics alone in VE patients is safe and effective.


I diopathic nephrotic syndrome (NS) is a common renal disease in children. Children with severe edema are usually hospitalized and treated with intravenous (IV) albumin and diuretics. In contrast to adults, children are often more severely hypoalbuminemic and edematous, necessitating hospitalization and IV albumin administration. Albumin is routinely used in children because of (1) low serum oncotic pressure due to hypoalbuminemia, (2) reports of diuretic resistance and decreased efficacy in NS (1–4), (3) increased diuresis when diuretics are given after IV albumin (1,5,6), and (4) a reluctance to treat patients with diuretics only because of concerns about dehydroxylation and increased risk of thromboembolic complications.

The routine use of albumin for severe edema (7) in children with NS is based on two mutually exclusive hypotheses proposed for the pathogenesis of edema (8–11). According to the underfill hypothesis, severe hypoalbuminemia decreases intravascular oncotic pressure, leading to circulatory volume depletion and subsequent sodium/water retention (8–11). The overfill mechanism proposes a primary renal defect in sodium excretion leading to sodium/water retention and thereby hypervolemia and edema (8–11). The underfill hypothesis is believed to be more common (7,12). Also, clinically it is not possible to differentiate severely edematous NS patients with intravascular volume expansion (VE) from those with intravascular contraction (VC) (7,12). Hence, the pediatric practitioners are reluctant to only treat the former group of patients with diuretics. The objective of this study was to evaluate the use of diuretics alone for the treatment of severe edema in a subset of children with NS, identified as VE.

Materials and Methods

This is a prospective cohort study of children admitted to the pediatric nephrology service at the Children’s Hospital of Michigan with NS and severe edema (October 2003 to August 2006). The study, which was approved by the Human Investigation Committee at Wayne State University, was conducted in two phases. The difference between the two phases was the criteria used for differentiating VE and VC patients.

Definitions

NS. NS was defined as the presence of profound proteinuria (random urine protein creatinine ratio >3.0) (13), hypoalbuminemia (serum albumin <2.5 g/dl), and edema.

Severe Edema. Severe edema was defined as evidence of 3+ or more pitting edema and ascites. (Pitting edema graded by study personnel on a scale of 0 to 4, with 0 being no edema and 4+ being grossly swollen leg with prolonged pitting upon pressure).
Fractional Excretion of Sodium. Fractional excretion of sodium (FeNa) was calculated on spot urine by the formula FeNa = (urine sodium × serum creatinine)/(plasma sodium × urine creatinine)

Phase 1

Inclusion Criteria. Inclusion criteria included the following: (1) Signed consent for the study [parental consent for all and patient assent (age >12 yr), (2) children aged 1 to 18 yr, and (3) admitted with NS and severe edema.

Exclusion Criteria. Exclusion criteria were (1) altered sensorium, (2) seizures, (3) fever ≥38.3°C, (4) gross hematuria, (5) reduced GFR [<90ml/min/1.73m²] (estimated by Schwartz formula (14)), (6) 25% increase in serum creatinine from baseline value (if available), (7) clinical peritonitis, (8) patients on diuretic(s) and angiotensin converting enzyme inhibitors, and (9) patients with history of clot (arterial or venous) or family history of thrombotic disorders.

Laboratory Evaluation. As per our institutional protocol, the laboratory evaluation of such patients on admission includes serum chemistry (sodium, potassium, bicarbonate, BUN, creatinine, calcium, magnesium, and phosphorus), complete blood count with differential, urinalysis and a spot urine protein, and urine creatinine. The patients’ electrolytes, hemoglobin (Hb) and hematocrit (Hct) were then monitored daily during their hospital stay. The study was designed so that the patients did not have any additional blood draws. The additional tests done upon admission included (1) serum osmolality, (2) urine osmolality, (3) urine sodium (U_\text{Na}), and urine creatinine.

Criteria Used for Diagnosing Intravascular Volume Status. Patients with FeNa <1% were considered as VC and those with FeNa of >1% were considered as VE.

Phase 2

On the basis of phase 1 observations, the FeNa criterion for the VC and VE groups was modified. Patients with FeNa <0.2% were identified as VC and those with FeNa ≥0.2% were identified as VE. The inclusion/exclusion criteria were similar to phase 1, except that the patients on immune suppression at hospitalization were excluded from phase 2. This change was prompted to exclude the potential effects of immunosuppressants on NS and tubular transport, thereby excluding them as a variable in FeNa interpretation. The laboratory workup was similar to phase 1, except that plasma renin activity (PRA), serum aldosterone, and serum antidiuretic hormone (ADH) levels were also checked.

Treatment Plan

The treatment for NS and severe edema was the same for both phases. All patients were treated with (1) fluid restriction to two-thirds of maintenance (15); (2) sodium restriction to <2 mEq/kg per d; (3) prednisone, per International Study of Kidney Disease in Children regimen (16) (started after routine workup for new NS patients and immediately upon admission in relapsed NS patients). The VC group received IV albumin (25%) at 0.5 g/kg twice daily over 2 to 3 h followed by IV furosemide at 1 mg/kg per dose (maximum 40 mg) at the end of albumin infusion for severe edema. The VE group received diuretics, IV furosemide at 1 mg/kg per dose (maximum 40 mg) twice daily, and oral spironolactone at 2.5 mg/kg per d divided twice daily (maximum 100 mg twice daily, dose rounded to 25-mg tablets or its multiples) for severe edema. The criteria for patient withdrawal were (1) a 50% increase in serum creatinine and (2) clinical deterioration as evidenced by (a) development of study exclusion criteria and (b) worsening edema despite treatment.

Analytical Techniques

Serum chemistries were measured by an automated analyzer (Vitrios 250 Chemistry System, Ortho-Clinical Diagnostics, NY). Serum aldosterone was measured by an RIA kit (Coat-a-count aldosterone, DPC, Los Angeles, CA). PRA and serum ADH were assayed at Esoterix Laboratories (Austin, TX).

Statistics

SPSS14.0 was used for statistical analysis. Continuous variables were evaluated as mean ± SD in both groups. The difference between the mean of two groups was compared by independent t test. Treatment trends in each group were evaluated by paired t test. Correlations between laboratory parameters were expressed as a Pearson correlation coefficient (negative r value indicated an inverse correlation; a positive value indicated direct correlation). A P value <0.05 was considered statistically significant for all of the statistics. Because of the wide range for normal hormonal concentrations, hormonal levels were also compared by nonparametric (Kruskal-Wallis test). These data are not shown because results were similar to parametric test (independent t test).

Results

During phase 1 of the study, 16 patients were admitted with severe edema and NS. Of these, six were excluded because of fever (2), medications (2) [enalapril (1) and furosemide (1)], and decrease in GFR to <90ml/min/1.73 m² (1). One more patient was excluded because the treatment was started before laboratory testing. The mean age of the 10 phase 1 patients was 6.9 ± 4.6 yr (range 1.4 to 15). Of these ten patients, 9 (90%) patients were caucasian and 1 (10%) patient was black/African American. Two patients were on immunosuppression (corticosteroids) for their NS. Presenting symptoms were generalized swelling (100%), decrease in urine output (100%), and increased thirst (20%). None of the patients had dizziness, postural hypotension, muscle cramps, delayed capillary refill, or orthostatic hypotension. The laboratory results (Table 1) revealed that of the ten patients with FeNa <1%, five patients (patients # 2, 5, 7, 8, 9; Table 1) had higher U_\text{Na} (>20 mEq/L), and lower BUN, Hb/Hct, and urine osmolality, which did not support VC in these patients. Reanalysis of the data in these patients using FeNa <0.2% as a cutoff for VC was then done, because these patients were on a normal sodium diet (125 to 250 mEq/d) and had a normal GFR (17). These patients could then be divided in two groups: VC group with FeNa <0.2% and VE group with FeNa ≥0.2% (Table 2). VC patients had significantly higher BUN, BUN/creatinine ratio, FeNa, and significantly lower serum and U_\text{Na} concentration compared with VE patients. Although not statistically significant, mean Hb/Hct, urine osmolality, and urine-to-serum osmolality ratio ([U_\text{Osm}]/[S_\text{Osm}]) were higher in the VC group compared with the VE group. These observations prompted us to redefine the FeNa criterion for intravascular volume status, leading to phase 2 of the study.

During phase 2, 42 patients were admitted with severe edema and NS. Of these, 22 patients were excluded [immunosuppression (14), fever (4), and decrease in GFR to <90ml/min/1.73 m² (4)]. The mean age of 20 patients (30% girls, 70%
boys) included in phase 2 was 7.6 ± 4.7 yr. The racial distribution of phase 2 patients included 9 (45%) black/African American and 11 (55%) caucasian. The main presenting symptoms were generalized swelling (100%) and decrease in urine output (100%). None of the patients upon presentation had diarrhea, vomiting, increased thirst, dizziness, postural hypotension, muscle cramps, orthostatic hypotension, or delayed capillary refill. On the basis of FeNa, these patients were grouped as VC (FeNa <0.2%, n = 9) and VE (FeNa >0.2%, n = 11). A comparison between the two groups before treatment is presented in Table 2. Noteworthy were statistically significant higher serum BUN, BUN/creatinine ratio, urine osmolality, and UOsm/SOsm in the VC group as compared with the VE group. Also VC patients had statistically significant lower FeNa and spot UNa. During both phases, there was no significant difference in the mean serum albumin and urine protein/creatinine ratio in the two groups (Table 2).

Table 3 shows treatment effect on patient's BUN, serum creatinine, Hb/Hct, heart rate (HR) and systolic blood pressure (SBP) in the study groups (paired t test). In the VC group there was a decrease in mean Hb/Hct, BUN, and creatinine after treatment. In comparison, VE patients showed an increase in the mean Hb/Hct, BUN, and creatinine, suggestive of mild VC with diuretic therapy. Also, the VC group had an increase in mean HR and SBP with albumin, consistent with mobilization of the extracellular fluid into the intravascular compartment. The VE group showed a decrease in mean HR and SBP, indicating that these patients were not volume contracted at initiation of diuretic therapy.

Percentage weight loss (net weight loss from admission weight) and duration of hospitalization were evaluated as indicators of treatment efficacy. There was no significant difference in duration of hospitalization (VC group 4.04 ± 2.3 d versus VE group 3.30 ± 0.82 d; P = 0.29), percentage weight loss after 1 d of hospitalization (VC group 2.6 ± 1.9% versus VE group 4.06 ± 2.6%; P = 0.13), and at the end of treatment (VC group 8.92 ± 4.8% versus VE group 7.37 ± 3.47%; P = 0.37) between the two groups (Table 4).
Therapeutic Complication

One patient in phase 2 who was classified as VE and only received diuretics for severe edema (FeNa >0.2% on admission) was switched to albumin therapy after 48 h of treatment because of electrolyte abnormalities [included in statistical analysis in VE group for admission evaluation only (Table 2) and not in outcome data (Table 3 and 4)]. This patient’s admission evaluation was: sodium 141 mEq/L, BUN 16 mg/dl, creatinine 0.4 mg/dl, BUN/creatinine ratio 47.5, urine osmolality 1119 mosm/kg, UOsm/SOsm 3.77, FeNa 0.02, PRA 146 ng/dl per h, aldosterone 4 ng/ml, and ADH 5.9 pg/ml. This patient demonstrated initial weight loss (2% in initial 48 h of diuretic treatment) and rise in Hb/Hct. He was switched to albumin plus diuretics per treatment protocol after 48 h of treatment because of rise in serum creatinine (0.7 mg/dl; post-treatment 0.9 mg/dl) that normalized upon stopping diuretics.

Discussion

This is the first study reporting the use of diuretics only in the treatment of a subset of children with NS identified prospectively on the basis of FeNa >0.2% without any complications. Analysis of 217 previously reported patients with NS from 10 studies showed that 42% of patients are normovolemic and 25% are hypervolemic (20). Hence, potentially 67% (normo/euvolemic) of NS patients can be treated with diuretics alone. However, the published literature on diuretics alone in severe edema is mostly limited to reports of its use in patients (usually adults) with chronic edema and obvious signs of volume overload as in GN and chronic renal failure (21-25).

In addition to various studies reporting modest to trivial change in diuretic resistance with albumin (7,26), albumin therapy has been associated with complications related to fluid overload (5). In a study of patients with NS, albumin treatment was associated with delayed response to corticosteroid treatment and more frequent relapses after remission compared with patients not receiving albumin (27). Although the contribution of albumin to progressive tubulointerstitial injury is under investigation (28), clinically it is known that patients with frequently relapsing or treatment-resistant NS have a poor prognosis.

Vande Walle et al. evaluated the pathophysiology of edema in NS under controlled salt and water intake and proposed the presence of a subset of patients with overfilling who can be safely treated with diuretics alone (18,19,29,30). Laboratory indices used in the past to differentiate VE from VC include PRA/aldosterone, atrial natriuretic peptide, FeNa, and urine osmolality (19,30,31). They proposed that patients with NS and VE have normal FeNa and can be managed by diuretics alone.
In their studies, mean FeNa in NS patients with early relapse with hypovolemic symptoms was 0.3%, notably lower than that seen in those without hypovolemic (1.1%) symptoms (18,30). The difference in the FeNa between their study and ours is most likely related to sodium intake of the patients. FeNa for patients on a normal home diet (sodium intake 125 to 150 mEq/d) and normal GFR is 0.2 to 0.3% (17). Therefore, phase 1 results were reanalyzed and criteria for VC and VE changed for study phase 2 using a cutoff of 0.2% for FeNa. Hormonal evaluation in the study groups coupled with a significant inverse correlation between FeNa and levels of the vasoactive hormones supported our hypothesis that avid sodium retention is indicative of hypovolemia and patients not having avid sodium retention are non-hypovolemic. Treatment trends in the VC and VE group on Hb/Hct, HR, creatinine, and no side effects in the VE group receiving diuretics alone also supported study categorization based on FeNa.

Another study (mean age 5.97 ± 2.9 yr) evaluated volume load in minimal-change NS by measuring inferior vena cava diameter on echocardiography and treating all patients with diuretics alone (furosemide and/or amiloride) (32). These patients underwent a starvation period before evaluation.
(32), unlike our study cohort who was on a non-restricted home diet.

The suboptimal response to diuretic-only treatment in one patient could be due to high ADH levels (patient; 5.9 pg/ml, group 1; 5.9 pg/ml, group 2; 1.6 pg/ml). Persistent ADH secretion leading to salt and water retention could be secondary to osmotic (33) or volume-mediated (34) stimulus, as hypothesized by other researchers. The patient was switched to albumin and furosemide per protocol despite no clinical signs and symptoms of dehydration. It is possible that the patient would have continued to respond to diuretics alone because the patient did respond to diuretics alone by losing 2% of the admission weight in the first 48 h of treatment. All other patients treated with diuretics alone showed no complications or change in study outcome criteria.

In conclusion, diuretic therapy alone is safe in pediatric patients with NS presenting with severe edema and FeNa >0.2%. Future studies with larger patient numbers are needed to confirm these preliminary findings, in which severely edematous patients could potentially be treated as outpatients by oral diuretics.

Disclosures
None.

References
27. Yoshimura A, Ideura T, Iwasaki S, Taiga T, Koshikawa S: Aggravation of minimal change nephrotic syndrome by


