

**Research Article**

## Albumin and Furosemide vs Furosemide Alone in Severe Edema of Pediatric Nephrotic Syndrome

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**Introduction:** The treatment of severe edema in a child with nephrotic syndrome is generally managed by furosemide. Hypoalbuminemia diminishes the amount of albumin-bound furosemide and diminishes the furosemide delivery to the ascending limb of the loop of henle and ultimately diminishes the diuretic effect.

**Objectives:** To compare the therapeutic outcome of albumin and furosemide combination (Intervention group) and furosemide alone (control group) in terms of clinical and biochemical parameters

**Methods:** Open labeled Quasi-experimental study was conducted in department of pediatrics VSSIMSAR, Burla from October 2016 to September 2018 after institutional ethics committee approval .40 subjects were included as per predefined inclusion and exclusion criteria, out of which 20 subjects were placed in intervention group and 20 in control group alternatively by random allocation.

**Results:** Data expressed as mean  $\pm$  standard deviation. P value  $<0.05$  was considered to be significant. Body weight, abdominal circumference, serum sodium, serum potassium values decreased significantly after receiving respective drugs (at 1hr and 24 hr) as compared to pretreatment value (at 0hr) but the mean difference among both the groups from pretreatment value to 24 hrs after treatment was not statistically significant In both groups urine output increased significantly after receiving respective drugs as compared to pretreatment and mean difference at 24hrs was found statistically significant. In (F) group serum Albumin decreased significantly at 24 hrs of post treatment as compared to baseline value. In (A+F) group Serum Albumin increased significantly at 24 hrs of post treatment as compared to baseline. In (F) group the mean percentage of inferior vena caval collapsibility index (IVCCI) remains same at 1hr and 24hrs of post treatment but in (A+F) group IVCCI decreased significantly at 1hr but returning to baseline value at 24hrs of post treatment.

**Conclusion:** The present study conclude that the add on effect of diuretics therapy when co-administrated albumin infusion priming is therapeutically better and equally safe than intravenous furosemide alone in management of severe edema in children with nephrotic syndrome.

**Keywords:** Nephrotic syndrome, edema, albumin, furosemide.

**Introduction**

Nephrotic syndrome (NS) is one of the common chronic disorder of glomerular

dysfunction characterized by defective glomerular barrier and altered capillary permeability resulting in nephrotic range

proteinuria ( $>3.5\text{g}/24\text{ hr}$  or urine Protein creatinine ratio  $>2$ ) and hypoalbuminemia ( $\leq 2.5\text{g}/\text{dl}$ ) which decreases plasma oncotic pressure and causing edema, hyperlipidemia (serum cholesterol  $>200\text{mg}/\text{d}$ )<sup>[1,2]</sup>. More than 95% nephrotic syndrome in children are primary (idiopathic) only 3-5% are secondary and caused by renal involvement in some systemic diseases<sup>[3]</sup>. The current mainstream therapy consists of corticosteroids, which induce remission in 90–95% of children; but approximately 50 % of these frequently relapse and become steroid dependent. However severity of edema depends upon amount of fluid leak from intravascular compartment to extravascular compartment as a result of proteinuria which may have different clinical manifestations such as massive generalized edema (ascites), parietal edema, scrotal or vulval edema, hydrothorax. The treatment of edema in patients with nephrotic syndrome is generally managed by dietary sodium restriction and loop diuretics. Loop diuretics are generally employed because other less potent agents can have blunted or absent diuretic action<sup>[4]</sup>. Since Loop diuretics have a ceiling dose; this is the dose that shows maximal natriuretic response so repeated infusion of ceiling dose are more effective than increasing dose of loop diuretics<sup>[5]</sup>. The cortical collecting tubules are the primary site to contribute to the edema formation in nephrotic syndrome. These are primarily made up of principal and intercalated cells which function to reabsorb sodium and water and excrete potassium. Because most diuretics are highly protein-bound, they tend to become trapped within the vascular compartment, thereby maximizing their rate of delivery to the kidney. In NS however, the degree of protein binding is reduced due to hypoalbuminemia, resulting in a larger extravascular space of distribution and diminished rate of delivery to the kidney<sup>[6]</sup>. Earlier studies like Inoue *et al.*<sup>[7]</sup> and Na *et al.*<sup>[8]</sup> have demonstrated that maximal effect of intravascular volume expansion of albumin nephrotic children is noted with in 30 to 60 minutes of intravenous infusion, so intravenous furosemide is given

60min after start of albumin infusion can cause binding of furosemide to albumin and may enhance delivery of this albumin – furosemide complex to proximal tubule for secretion of furosemide into tubular lumen and increase its diuretic effect by changing the pharmacokinetics of furosemide. But its clinical efficacy is controversial as other studies have failed to show any difference in the results from comparisons between ways of using diuretics: on a stand-alone basis or in association with albumin. In nephrotic children, albumin may be essential when a circulatory volume depletion is present (under filling hypothesis)<sup>[9,10]</sup>, while albumin infusion may be dangerous when the circulatory volume is not depleted (overfilling hypothesis<sup>[11,12]</sup>). In the clinical setting, it is not easy to differentiate circulatory volume contraction from volume expansion, and various parameters, unfortunately not easily available in the routine clinical setting, have been proposed as biomarkers, such as the ratio urinary potassium (uK)/urinary sodium + uK (an index of aldosterone bioactivity)<sup>[9]</sup>, central venous pressure or the inferior vena cava diameter<sup>[13,14]</sup>. Cyclic changes in thoracic pressure in a healthy person may result in the collapse of approximately 50% of the IVC diameter. The maximum IVC diameter (IVCdmax) was measured as the maximum anterior-posterior dimension at end-expiration using the leading edge technique (inner edge to inner edge of the vessel wall). The minimum IVC diameter was measured at end-inspiration (IVCdmin)<sup>[14]</sup>. IVC diameter was measured approximately 3 to 4 cm from the junction of IVC and right atrium. The diameter variation of vena cava can be of range 13 to 28 mm and mean 20 mm. There was no significant relation of vena cava diameters to height, weight or body surface area based on previous studies<sup>[14, 15]</sup>.

The IVC collapsibility index was the difference between the maximum and minimum IVC diameters divided by the maximum IVC diameter, expressed as a percentage<sup>[13,14]</sup> ( $[\text{IVCdmax} - \text{IVCdmin}] / \text{IVCdmax} \times 100\%$ ).

The present study has been designed to gain greater insight in to evaluation and assessment of the effect of albumin and furosemide combination versus furosemide alone in severe edema of children with Nephrotic syndrome.

## Methods

An Open labeled Quasi-experimental study was conducted during Oct 2016 –Sept 2018 in diagnosed cases of nephrotic syndrome in pediatric age group presenting to the Inpatient department (IPD) of pediatrics. Children with proteinuria more than 3.5gm/24 hr or spot urine protein creatinine ratio > 2 were considered as study subjects and those having severe edema (massive generalised edema, ascites, Parietaledema, scrotal/vulval edema, hydrothorax) and/or severe hypoalbuminemia (Serum albumin <1.5gm/dl) were included in the study and those who were critically ill / ICU admitted patients, who received oral or parenteral diuretics therapy or intravenous fluid therapy within last 72 hours, and those who were suffering from acute kidney injury, coexisting cardiac, hepatic disease or having severe malnutrition were excluded from the study

40 children with nephrotic syndrome were included as per predefined inclusion and exclusion criteria and every alternative child was allotted in (F) group and (A+F) group respectively (20 children were placed in control group and 20 were in intervention group). Where (F) group was treated with furosemide (2mg/kg) IV stat only,

(A+F) group treated with 20% human albumin (0.5gm/kg, over 1 hour) and furosemide (2mg/kg IV, 1 hr after start of albumin). Clinical, biochemical parameters and echocardiographic status were assessed at start of intervention (0 hour) and then 1 hour and 24 hours.

- I. Body weight (kg) was estimated by electronic digital read out type of weighing scale with a resolution of  $\pm 100$ gm (Hoffen digital electronic weighing scale)
- II. Abdominal circumference (cm) was measured around the umbilicus in supine position by using a non-stretchable fibre measuring tape with calibration 1 to 150cm( Hasthip measuring tape)
- III. Serum Sodium (mmol/lit) was measured by direct ion selective electrode method.
- IV. Serum Potassium (mmol/lit) was measured by direct ion selective electrode method.
- V. Serum Albumin (g/dl) was estimated by Bromocresol green reagent method.
- VI. Urine Output (ml/kg/hr) was kept in urobag of maximum capacity 2000ml and measured in ml/kg/hr(Romsons ROMO 10 urine bag with moulded handle)
- VII. Inferior vena cava collapsibility index (%) was measured by ECHO (by Philips)

Statistical analysis was done using Microsoft excel 2007 and SPSS software 23.0 version. Continuous variables were evaluated as mean  $\pm$  SD in both groups. A *P* value <0.05 was considered statistically significant for all of the statistics.

## Results

**Table 1** Body weight status (kg)

	0 hr	1 hr	24 hr
(F) (n=20)	22.52 $\pm$ 6.79	22.33 $\pm$ 6.73	21.78 $\pm$ 6.78
(A+F)(n=20)	25.12 $\pm$ 7.72	24.85 $\pm$ 7.66	23.83 $\pm$ 7.65

**Table 2** Abdominal circumference status (cm)

	0 hr	1 hr	24 hr
(F) (n=20)	53.72 $\pm$ 4.58	53.65 $\pm$ 4.58	52.87 $\pm$ 4.56
(A + F) (n=20)	57.02 $\pm$ 5.89	56.73 $\pm$ 5.78	55.72 $\pm$ 5.83

**Table 3** Serum sodium status (mmol/l)

	0 hr (mean $\pm$ SD)	1 hr (mean $\pm$ SD)	24 hr (mean $\pm$ SD)
(F) (n=20)	138.25 $\pm$ 3.41	136.30 $\pm$ 3.52	133.95 $\pm$ 3.18
(A + F) (n=20)	138.55 $\pm$ 3.61	136.25 $\pm$ 3.46	132.05 $\pm$ 2.98

**Table 4** Serum Potassium status (mmol/l)

	0 hr	1 hr	24 hr
(F) (n=20)	3.90 $\pm$ 0.54	3.84 $\pm$ 0.54	3.65 $\pm$ 0.53
(A) + (F) (n=20)	3.96 $\pm$ 0.62	3.83 $\pm$ 0.64	3.52 $\pm$ 0.53

In both the groups i.e (F) and (A+F), body weight, abdominal circumference, serum sodium, serum potassium values decreased (at 1hr and 24 hrs) after receiving respective drugs as compared to pre-treatment value (0hr) and this decrease in body weight was found statistically significant ( $p < 0.05$ ) at 24hrs of post treatment in both the groups.

**Table 5** Urine output status(ml/kg/hr)

	0 hr	1 hr	24 hr
(F) (n=20)	0.93 $\pm$ 0.38	1.13 $\pm$ 0.36	1.61 $\pm$ 0.46
(A+F) (n=20)	1.15 $\pm$ 0.48	1.35 $\pm$ 0.46	2.01 $\pm$ 0.69

In both the groups i.e (F) and (A+F), urine output increased (at 1hr and 24 hrs) after receiving respective drugs as compared to pretreatment value (0hr) and this increase in urine output was found statistically significant ( $p < 0.05$ ) at 24hr of post treatment in both the groups.

**Table 6** Serum albumin status(g/dl)

	0 hr	1 hr	24 hr
(F) (n=20)	1.63 $\pm$ 0.25	1.63 $\pm$ 0.25	1.52 $\pm$ 0.23
(A + F) (n=20)	1.51 $\pm$ 0.37	1.83 $\pm$ 0.27	2.57 $\pm$ 0.37

In (F) group value of Serum Albumin remain same at 1hr of in post treatment and decreased at 24 hrs of post treatment as compared to baseline value i.e at 0 hr.

In (A+F) group Serum Albumin increased at 1hr and 24 hrs of post treatment (as compared to Baseline at 0 hr).

**Table 7** Inferior vena cava collapsibility index (IVCCI) status (%)

	0 hr	1 hr	24 hr
(F) (n=20)	37.45 $\pm$ 2.51	37.45 $\pm$ 2.51	37.45 $\pm$ 2.51
(A + F) (n=20)	42.55 $\pm$ 2.37	39.55 $\pm$ 2.61	42.55 $\pm$ 2.37

The mean difference of these parameters among both the groups i.e (F) and (A+F) from pre-treatment value (0hr) to 24 hours is not significant ( $p > 0.05$ ).

But this decrease in these parameters (from pretreatment value to 24 hours post treatment) is more in (A+F) group than (F) group.

The mean difference of urine output among both the groups i.e (F) and (A+F) from pre-treatment value to 24 hours is found to be statistically significant ( $p < 0.05$ ).

In F group, at 24 hrs of post treatment, Serum Albumin decreased from baseline value i.e at 0 hour is statistically significant ( $p < 0.05$ ).

In A+F group, at 24 hrs of post treatment, Serum Albumin increased from baseline value i.e at 0 hour is statistically significant ( $p < 0.05$ ).

In (F) group, the mean percentages of IVCCI remain same at 1hr and 24 hrs of post treatment as compared to baseline value i.e at 0 hr.

In (A+F) group, the mean percentage of IVCCI decreased at 1hr of post treatment and then returning to baseline value at 24 hrs of post treatment.

In (A+F) group, at 1hr of post treatment the mean decrease of IVCCI from baseline value i.e at 0 hour is statistically significant ( $p<0.05$ ).

### Discussion

Various clinical trials regarding the use of albumin and furosemide to treat severe edema in children with nephrotic syndrome have been published. Current study reveals decrease in body weight and abdominal circumference, serum sodium, serum potassium, (from pretreatment value to 24 hours post treatment) is more in (A+F) group than (F) group which is in accordance with the earlier studies like Zelal Bircan *et al.* in 2000 and is most probably due to albumin affecting on the pharmacokinetic properties of furosemide and may assist its delivery to its site of action. Increase in urine output is more in (A+F) group than (F) group which is in accordance with the earlier studies like Rajmohan *et al.* in 2009 and is due to albumin infusion prior to diuretics may induce diuresis with an increase in renal plasma flow and free water clearance in children with nephrotic syndrome. In this study the decrease in Serum albumin (from pretreatment value to 24 hours post treatment) in (F) group most probably due to increased diuresis leading to loss of more albumin in urine. The increase in Serum albumin (from pretreatment value to 1 hour, 24 hours post treatment) in (A+F) group most probably due to infusion of albumin leading to more albumin with in intravascular compartment which is more significant after 24 hours of post treatment. As per this study decrease in IVCCI at 1hr of post treatment which is in accordance with a study by Zelal Biracan *et al.* in 2000 may be due to albumin infusions transiently increase plasma volume and oncotic pressure at 1 hour post

treatment and then returning to baseline at 24 hours.

None of the patient allotted to either group had developed any adverse effect during hospital stay.

### Conclusion

The present study conclude that the add on effect of diuretics therapy when co-administrated albumin infusion priming is therapeutically better and equally safe than intravenous furosemide alone in management of severe edema in children with nephrotic syndrome in terms of clinical (body weight, abdominal circumference), biochemical (serum sodium, serum potassium, serum albumin, urine output) and echo cardiographic features (inferior vena cava collapsibility index).

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