

Comparison of Albumin versus Fresh Frozen Plasma in the Treatment of Children with Diuretic-Resistant Oedema in Idiopathic Nephrotic Syndrome at a Tertiary Hospital

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ABSTRACT

Introduction: Diuretic-resistant oedema is a common problem in children with idiopathic nephrotic syndrome (NS), largely driven by hypoalbuminaemia. Co-administration of human albumin with frusemide improves diuretic response, but albumin is costly and often unavailable in resource-limited settings; fresh frozen plasma (FFP) has been proposed as a cheaper alternative. **Aim of the Study:** To compare the efficacy and cost of human albumin versus fresh frozen plasma (FFP), each co-administered with frusemide, in the treatment of diuretic-resistant oedema in children with idiopathic NS. **Methods & Materials:** This randomized clinical trial was conducted in the Department of Pediatrics and Pediatric Nephrology Ward, Chittagong Medical College Hospital (CMCH), Chattogram, Bangladesh, from July 2020 to June 2021. A total of 100 children aged 1–12 years with idiopathic NS, diuretic-resistant oedema, and serum albumin <1.5 g/dL were randomly allocated by block randomization into an albumin group (n=50; intravenous 20% albumin 1 g/kg/day followed by intravenous frusemide) and an FFP group (n=50; intravenous FFP 15 mL/kg/day followed by intravenous frusemide). Clinical and laboratory parameters were monitored daily until dry weight was achieved. Data were analyzed using SPSS version 23.0, with p<0.05 considered statistically significant. **Results:** Baseline demographic, clinical, and biochemical parameters were comparable between groups (mean age 5.7±2.9 vs 6.3±2.9 years, p=0.121; male-female ratio 2.6:1 vs 1.4:1, p=0.105). Abdominal girth declined by 10.7±2.1% in the albumin group versus 9.8±2.4% in the FFP group (p=0.058), and body weight declined by 11.7±3.9% versus

10.7±4.2% (p=0.229), neither difference reaching statistical significance. Dry weight was achieved significantly earlier with albumin (median 13 days, IQR 12–14) than with FFP (median 14 days, IQR 13–15; p<0.001). The FFP group required a significantly larger infusion volume (median 330 mL vs 100 mL) and more infusions (2 vs 1; p<0.001), but its median treatment cost was significantly lower (750 BDT, IQR 500–1000) than albumin (6400 BDT, IQR 6400–12,800; p<0.001). No treatment-related complications were observed in either group. **Conclusion:** Albumin achieves dry weight faster than FFP, but the two regimens show comparable overall efficacy in reducing oedema. Given its substantially lower cost, FFP may serve as a feasible, cost-effective alternative to albumin for managing diuretic-resistant oedema in children with idiopathic NS in resource-limited settings.

Keywords: Albumin, Plasma, Oedema, Nephrotic, Diuretic, Children

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INTRODUCTION

Nephrotic syndrome (NS) is a clinical syndrome defined by massive proteinuria (greater than 1 gm/m² per day), hypoalbuminaemia (less than 25 g/L), hyperlipidemia (>220mg/dl), generalized oedema. The disease has various complications and is caused by increased permeability through the damaged basement membrane in the renal glomerulus, especially in form of loss of negativity. NS is a well-established chronic disease in children. The estimated annual incidence of nephrotic syndrome in healthy children is two to seven new cases per 100,000 children younger than 18 years.^[1] Many glomerular disorders in childhood present with NS, vast majority of which are idiopathic NS, best defined as podocytopathy due to mutation or fusion and altered function of the podocytes with

resultant massive proteinuria. The incidence of idiopathic NS is 1.15–16.9 per 100000 children having ethnical and regional variations. The cause remains unknown, but the pathogenesis of idiopathic NS is thought to involve immune dysregulation, systemic circulating factors, or inherited structural abnormalities of the podocyte.^[2] Massive generalized oedema (anasarca) is common in children with idiopathic NS and is a primary clinical indication of hospital admission for diuretic management. In these children, the selective loss of large amounts of albumin in urine lead to hypoalbuminaemia and decreased oncotic plasma pressure favouring fluid sequestration in the interstitial fluid compartment, and secondarily triggers renal Na⁺ and fluid retention to preserve intravascular volume

and blood pressure, hence preventing an “underfill” state. In over-fill models, intravascular fluid volume is typically average or expanded and result from inappropriately stimulated Na⁺ and fluid retention and decreased GFR.^[3] Children of NS with anasarca have increased parental anxiety and multiple emergency hospital visits. Peripheral oedema may be uncomfortable, leading to functional restraint, restricted leg movement, and impaired mobility. Oedema may also cause increased skin tension, resulting in blistering, skin breakage and exudates extrusion, offering an encouraging environment for bacterial infection.^[4,5] Based on the pathogenesis of oedema in NS, one of the primary strategies in managing oedema is salt and fluid restriction with the addition of a loop

diuretic for severe or symptomatic oedema.^[6] However, response to diuretics alone might be blunted, especially in an under filled state, where neurohormonal systems are activated in an attempt to maintain intravascular volume. Approximately 25% of children with NS might be hypovolemic at presentation, as assessed by the clinical, laboratory, and echocardiographic parameters.⁷ Diuretics alone might aggravate hypovolemia and intravascular depletion.

In children with massive oedema and hypoalbuminaemia, impaired diuretic responsiveness may be overcome by administering larger doses of loop diuretics, either orally or intravenously.^[8,9,10] Loop diuretics are delivered into the proximal tubule through an organic anion secretory pathway and enter the tubular lumen of the ascending limb of the loop of Henle where they act to inhibit the Na/K/2Cl co-transporter. This approach results in the excretion of a more significant amount of the drug in the urine and, consequently, a more excellent natriuretic response. Another clinical option is to infuse loop diuretics in combination with salt-poor human serum albumin. Such concomitant infusions of human albumin mixed with a loop diuretic effectively enhance the delivery of the loop diuretic to the luminal sites where their action on reabsorption of NaCl occurs.^[8] As hypoalbuminemia lowers the amount of the albumin-bound fraction of the diuretic, it also decreases the amount of diuretic delivered to its site of action in the nephron. In this way, co-administration of albumin with frusemide, a loop diuretic, is believed to improve drug delivery into the kidneys and hence diuresis.^[2,9,10,11,12] But albumin is very costly and sometimes out of reach of patients in developing and resource limited countries like Bangladesh. Fresh Frozen Plasma (FFP) could be an alternative in such situations.^[13] FFP is human donor plasma either recovered from a single whole blood donation or obtained by plasma pheresis. Its specification

requires frozen within a specific period after collection from a donor and stored at a defined temperature, typically -30°C. After thawing, although diluted with citrate anticoagulant, FFP contains near normal levels of many plasma proteins, including procoagulant and inhibitory components of the coagulation cascades, acute phase proteins, immunoglobulins and albumin.^[14] Though clinical use of FFP has grown steadily over time in many countries, side effects were seen more often and more severe with FFP transfusion than albumin infusion, which has hindered its wide spread usage over albumin.^[15,16]

Very few studies compared the human albumin and FFP in different hypovolemic states and reported that FFP could be considered an economically suitable alternative for albumin.^[13,17] FFP is cheaper and can be made easily available compared to human albumin in our context. So, FFP might be logically considered for clinical use as albumin is costly and its availability and purity are limited. As there is limited evidence from published data regarding the efficacy and outcome of low cost FFP in reducing oedema, this study was undertaken in the Department of Pediatrics and Pediatric Nephrology ward, CMCH, Chattogram to compare albumin's efficacy and cost with that of FFP in treating hypoalbuminaemia in children of idiopathic NS with diuretic resistant oedema.

METHODS & MATERIALS

This randomized clinical trial was conducted in the Department of Pediatrics and the Pediatric Nephrology Ward of Chittagong Medical College Hospital (CMCH), Chattogram, Bangladesh, from 1 July 2020 to 30 June 2021. Children aged 1–12 years admitted with idiopathic nephrotic syndrome (NS) and diuretic-resistant oedema with serum albumin <1.5 g/dL were screened according to predefined inclusion and exclusion criteria and randomly allocated to either the albumin group or the fresh frozen plasma

(FFP) group using block randomization (block size 4). A total of 100 children (50 in each group) were enrolled. All participants received standard supportive management, including fluid and salt restriction, oral prednisolone, and diuretic therapy. Children in the FFP group received intravenous FFP (15 mL/kg/day over 3–4 hours) followed by intravenous furosemide (1 mg/kg/day), whereas those in the albumin group received intravenous 20% human albumin (1 g/kg/day over 4 hours) followed by the same dose of intravenous furosemide. Clinical parameters, including pulse, respiratory rate, blood pressure, weight, intake-output, abdominal girth, bedside urine protein, oedema status, and treatment-related complications, were monitored daily until achievement of dry weight. Data were collected using a pretested structured case record form and analyzed using SPSS version 23.0. Continuous variables were expressed as mean ± standard deviation or median (interquartile range), while categorical variables were presented as frequencies and percentages. Comparisons between groups were performed using Student's *t*-test or the Mann–Whitney *U* test for continuous variables, the Chi-square test or Fisher's exact test for categorical variables, and repeated-measures one-way ANOVA for longitudinal comparisons. A *P*-value <0.05 was considered statistically significant. Ethical approval was obtained from the Ethical Review Committee of Chittagong Medical College, and written informed consent was obtained from the parents or legal guardians of all participants before enrollment.

RESULTS

Table 1 shows the mean age was 5.7 years, and the age range was 1-12.0 years in the albumin Group. In the FFP group the mean age was 6.3 years, with the age range was 1-12.0 years. It reveals no significant difference in the age distribution between two groups.

Table 1
Age distribution of the patients stratified by two groups.

Age (years)	Albumin group (n=50)	FFP group (n=50)	P value
1-5	27 (54.0)	18 (36.0)	0.147*
6-10	21 (42.0)	27 (54.0)	
11-12	2 (4.0)	5 (10.0)	
Mean (±SD)	5.7±2.9	6.3±2.9	0.121†
Range	1-12.0	1-12.0	

FFP: Fresh Frozen Plasma; SD: Standard deviation. Data were expressed as frequency (percentage). *P* value derived from *Chi-square test; †Unpaired *t*-test.

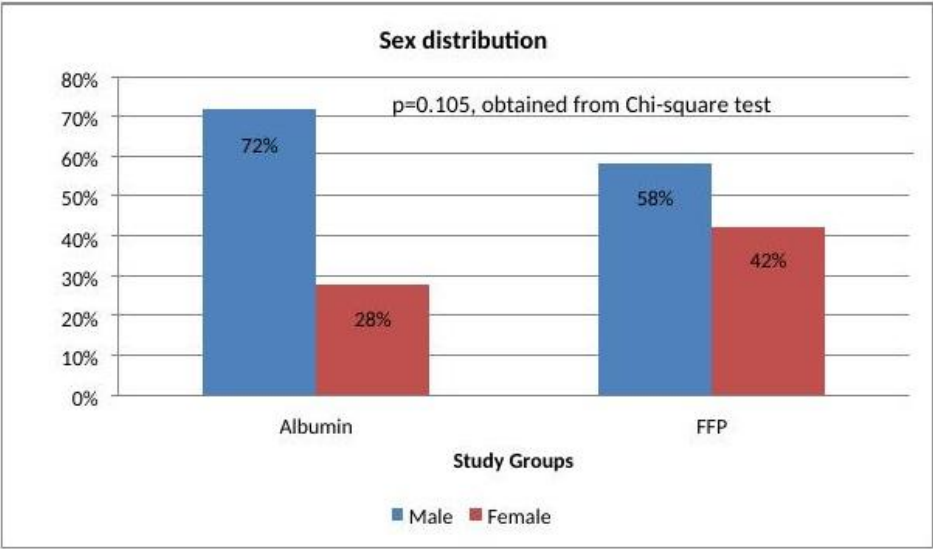


Figure 1 Sex distribution of the patients between two groups.

Figure 1 shows a male predominance in both groups with a male-female ratio of 2.6:1 in the albumin Group and 1.4:1 in the FFP group. However male patients were proportionately higher in the albumin Group than the FFP Group (72% versus 58%). It was statistically insignificant (p=0.105).

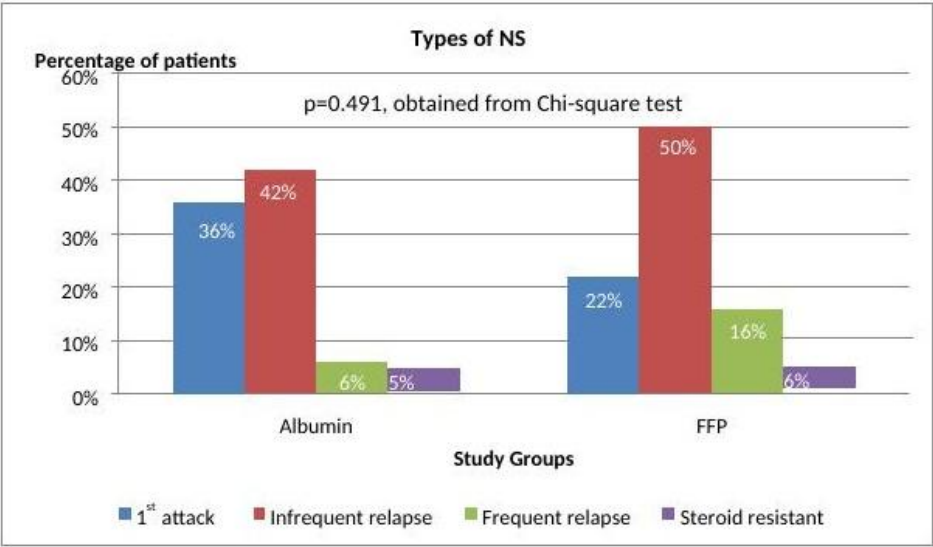


Figure 2 Distribution of the patients by their types of NS between two groups.

Figure 2 shows majority of the NS patients were of IFRNS in both groups (42% in albumin group and 50% in FFP group respectively). No significant difference was found in distribution of types of the patient in two groups. Table II shows there were no significant differences between the two study groups in terms of their baseline clinical characteristics, like body weight, temperature, heart rate, respiratory rate, blood pressure, body surface area, and abdominal girth.

Table II
Baseline clinical characteristics of the patients stratified by groups.

Variables	Albumin group (n=50)	FFP group (n=50)	P value†
Body weight (kg)	20.2 ±8.1	22.6 ±7.6	0.151
Temperature (°F)	98.6±0.2	98.6±0.1	0.815
Heart rate/min	90 ±10	88 ±10	0.215
Respiratory rate/min	22 ± 5	21 ± 4	0.814
SBP (mmHg)	94 ± 6	96 ± 6	0.130
DBP (mmHg)	61 ± 6	62 ± 6	0.112
Body surface area (m²)	0.9±0.3	0.9±0.1	0.051
Abdominal girth (cm)	60.5±9.8	62.9±10.1	0.232

FFP: Fresh Frozen Plasma; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SD: Standard deviation. Data were expressed as mean ± SD. P value derived from †Unpaired t-test.

Table III shows 70% of the patients in the albumin group had 4+ bedside urine albumin compared to 60% of that of the FFP group; this difference was not statistically significant. Similarly, serum albumin level and serum creatinine level were also comparable between the two groups.

Table III
Baseline biochemical characteristics of the patients stratified by groups.

Variables	Albumin group (n=50)	FFP group (n=50)	P value
Bedside urine albumin +++	15 (30.0)	20 (40.0)	0.295*
Bedside urine albumin ++++	35 (70.0)	30 (60.0)	
Serum albumin (mg/dl)	1.2±0.3	1.2±0.3	0.086
Serum creatinine (mg/dl)	0.54±0.01	0.53±0.03	0.069

FFP: Fresh Frozen Plasma. Data were expressed as frequency (percentage). SD: Standard deviation. P value derived from *Chi-square test.

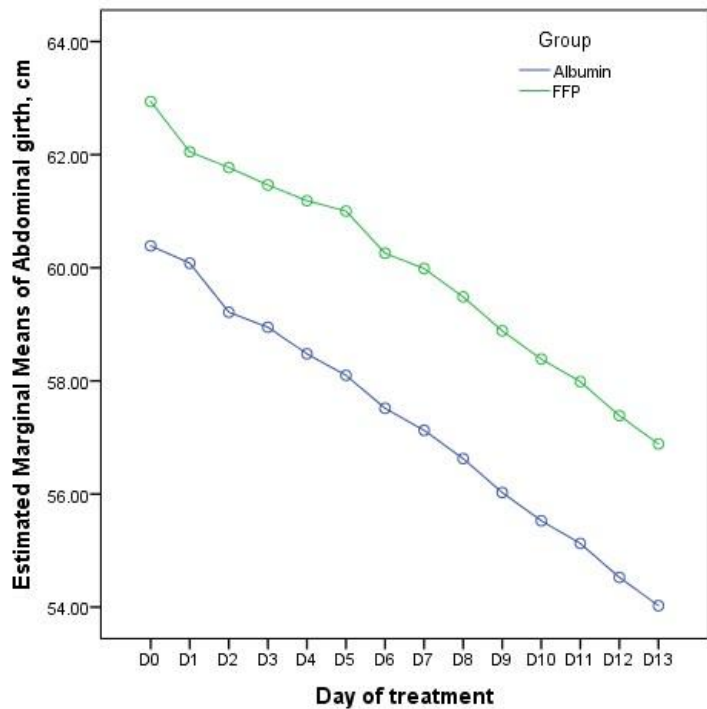


Figure 3 Change in the abdominal girth over time between two groups.

Figure 3 shows that abdominal girth reduced from 60.5 cm to 54.0 cm in 13 days after treatment onset in the albumin group. In the FFP group, similar trends were also noted, with 62.9 cm on baseline (D0) and 56.8 cm at D13. These reductions of abdominal girth from baseline to D13 were significant in both groups. However, between the two groups, the difference regarding abdominal girth reduction was not significant at any time point (P >0.5 at all time points as evident by repeated measures ANOVA test).

Table IV
Changes in abdominal girth of the patients of both groups after therapy.

Abdominal girth (cm)	Albumin group (n=50)	FFP group (n=50)	P value†
Before therapy	60.5±9.8	62.9±10.1	0.232
After therapy	57.9±7.5	59.9±7.8	0.144
% of decline	10.7±2.1	9.8±2.4	0.058

FFP: Fresh Frozen Plasma; Data were expressed as mean±SD. SD: Standard deviation. P value derived from †Unpaired t-test.

Table IV shows the percentage of decline in abdominal girth after 13 days of treatment initiation was higher (10.7%) in the albumin group compared to 9.8% in the FFP group. However, this difference failed to reach statistical significance.

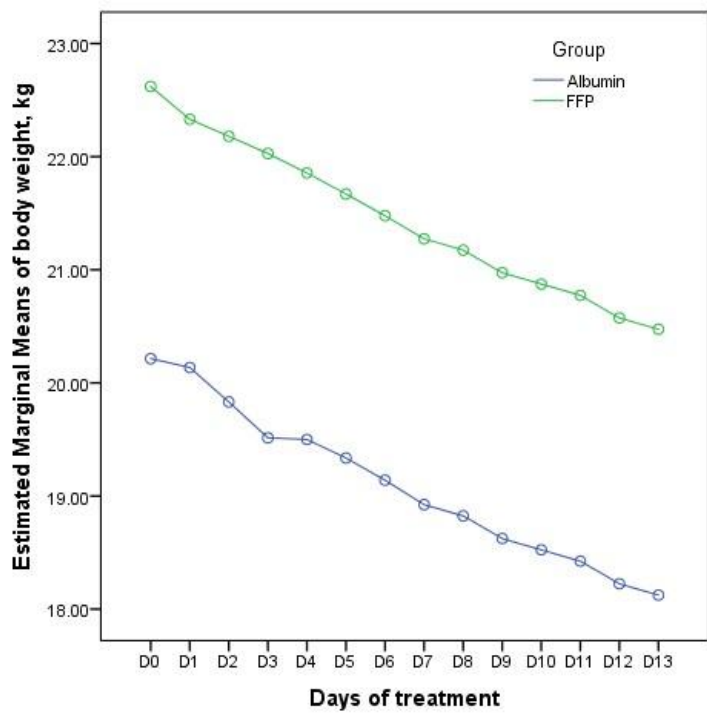


Figure 4 Changes in the body weight over time between two groups.

Figure 4 shows that body weight reduced from 20.5 kg to 18.1 kg after 13 days of treatment onset in the albumin group. In the FFP group, similar trends were also noted, with a body weight of 22.6 kg at baseline (D0) and 20.4 kg on day 13. These reductions of body weight from baseline to

D13 were significant in both groups. However, there was no difference between the two groups regarding body weight at any time point ($P > 0.5$ at all time points as evident by repeated measures ANOVA test).

Table V shows the percentage of decline in body weight after thirteen days of treatment initiation was similar in both groups without statistical significance.

Table V
Changes in body weight of the patients of both groups after therapy.

Body weight (kg)	Albumin group (n=50)	FFP group (n=50)	P value†
Before therapy	20.2 ±8.1	22.6 ±7.6	0.151
After therapy	18.1±7.9	20.4±7.5	0.130
% of decline	11.7±3.9	10.7±4.2	0.229

FFP: Fresh Frozen Plasma; Data were expressed as mean±SD. SD: Standard deviation. P value derived from †Unpaired t-test.

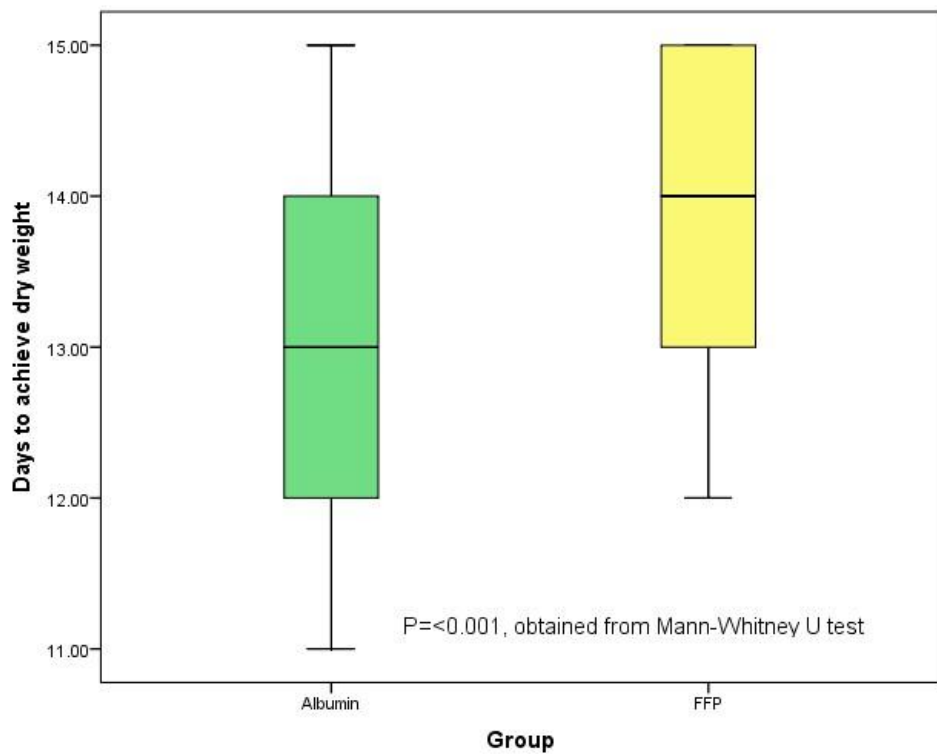


Figure V Comparison of days required to achieve dry weight between two groups.

Figure 5 shows the median (IQR) day to achieve dry weight in the albumin group was 13 (12-14) days compared to 14 (13-15) days in the FFP group. This difference was statistically significant, indicating dry

weight was achieved faster in the albumin group.

Table VI shows the median amount of infusion was significantly higher in the FFP group than in the albumin group (330 ml and 100 ml respectively in the FFP and albumin group, $p<0.001$). The median number of albumin infusions required was

1 unit (100ml) compared to 2 units (660ml) in the FFP group. The median (IQR) cost of the necessary FFP and albumin was 750 (500-1000) BDT and 6400 (6400-12,800) BDT, respectively. Median cost of FFP was significantly lower in comparison to albumin, and the difference was statistically significant.

Table VI
Comparison of the amount of infusion and cost of albumin and FFP in both groups.

Variables	Albumin group (n=50)	FFP group (n=50)	P value*
Amount of infusion (ml)	100 (100-200)	330 (330-990)	<0.001
Number of infusions required	1 (1-2)	2 (2-3)	—
Cost (BDT)	6400 (6400-12,800)	750 (500-1000)	<0.001

FFP: Fresh Frozen Plasma; Data were expressed as median (IQR). BDT: Bangladeshi taka. P value derived from *Mann-Whitney U test.

DISCUSSION

The management of oedema in patients with NS is sometimes challenging. The reasons proposed for the lack of patient response to diuretics include a decreased delivery of the diuretics into the tubular lumen, hypoalbuminaemia, and binding of the diuretics to urinary albumin.^[8,18] In the present study, the diuretic effect of co-administration of albumin with frusemide was compared with that of FFP with frusemide in a group of children with idiopathic NS admitted in the Department of Pediatrics and Pediatric Nephrology ward in CMCH. Frusemide was given along with either human albumin or FFP in the nephrotic syndrome with hypoalbuminaemia having massive oedema. The study revealed that both human albumin and FFP have similar efficacy in reducing oedema, as evident by gradual weight reduction, but human albumin acts faster than FFP to achieve dry body weight. It is to be noted that there is a study in the literature that compared the efficacy of these two regimens for diuresis in nephrotic children.^[13] So, in the following section, the present study findings were compared with the results of Roy et al., who demonstrated similar efficacy for diuresis of these two regimens.^[13]

The mean age of the patient in the present study was 5.7 years and 6.3 years in albumin Group and FFP groups respectively, without any statistical differences. In the study of Roy et al., the mean age was 6.9 years and 6.3 years respectively in the albumin and FFP group, similar to the present study.^[13]

Regarding sex distribution, present study shows that there was male predominance in both groups, with a male-female ratio of 2.6:1 in the Albumin Group and 1.4:1 in the FFP Group. Male predominance in this study was similar to other studies.^[13,19,20] In the study of Huque et al., overall male-female ratio was 2.08:1, and in the study of Roy et al., overall male-female ratio was 1.7:1.^[13,19] The male:female ratio was 1.9 in a nationwide survey of the incidence of NS in Japanese children.^[20]

In the present study majority of the NS patients were of IFRNS (42% and 50% respectively in albumin and FFP group). This is simultaneous to the study of Roy et al.^[13]

Both the groups were comparable at baseline in terms of other clinical and laboratory parameters. Clinical characteristics of the patients in the present study were also similar to the study of Roy et al. and Huque et al. conducted in other tertiary hospitals of Bangladesh.^[13,19] It is to be noted that most of the present study patients had serum albumin level <1.5 gm/dl according to the inclusion criteria, and both the groups were comparable in terms of the distribution of mean serum

albumin level. The mean albumin level was 1.2 mg/dl and 1.3 gm/dl in the albumin and FFP groups, respectively, similar to the present study.

Reduction of abdominal girth was an outcome parameter in the study of Haque et al., who compared the efficacy of mannitol and frusemide with that of albumin and frusemide in the treatment of diuretic resistant oedema in childhood NS.^[19] After thirteen days of treatment, abdominal girth reduced significantly from baseline in both groups and the percentage of decline was similar in both groups. Present study showed the rate of decline was $10.7 \pm 2.1\%$ and $9.8 \pm 2.4\%$ in albumin and FFP groups, respectively ($p=0.058$). Huque et al. also reported similar decrease in abdominal girth in both groups.^[19]

Another outcome measurement was the change in body weight after treatment in both groups. The present study demonstrated that body weight reduced significantly in both groups from baseline after thirteen days of treatment. A similar reduction of body weight was also reported by Haque et al.^[19]

The number of days to achieve dry weight was the main efficacy parameter in the present study. The current study indicated that dry weight was achieved significantly earlier in the albumin group compared to the FFP group. The median (IQR) day to achieve dry weight in the albumin group was 13 (12-14) days compared to 14 (13-15) days in the FFP group ($p<0.001$). In contrast to these findings, Roy et al. reported no significant differences between albumin and FFP group regarding time required to achieve dry weight.^[13] The number of days required to gain dry weight in the albumin group was 6.66 ± 3.710 days and in the FFP group was 6.66 ± 3.038 days.

There was a clear difference in the present study regarding the total amount of infusion and number of infusions. A significantly higher amount was needed in the FFP group compared to the albumin group. This was consistent with the findings of Roy et al., where patients in the albumin group required 1.44 ± 0.697 albumin infusions and patients in the FFP group required 3.11 ± 1.5 infusions of FFP.^[13] It signifies that albumin is more potent than FFP.

As human albumin is comparatively more costly than FFP, there was a significant cost difference in both the present study groups [median cost was 6400 BDT in the albumin group and 750 BDT in the FFP group]. A similar cost difference was also reported by Roy et al.^[13] This higher cost of treatment with human albumin is a critical issue in developing countries with relapsing illnesses like NS. Moreover, NS is more common in resource-limited countries of Asia.^[20,21]

In the present study, both the groups were given infusions with strict supervision and monitoring of clinical symptoms of fluid overload, and no side effects were observed in any group. Previous studies also did not report any complications following co-administration of albumin-frusemide, FFP-frusemide or mannitol-frusemide.^[13,19]

LIMITATIONS

This was a single-center, unblinded trial with a relatively small sample size that did not satisfactorily evaluate the hazards of blood product use.

CONCLUSION

It has been concluded from this study that albumin-frusemide co-administration achieves dry weight earlier than co-administration of FFP-frusemide in the treatment of diuretic resistant oedema in children of idiopathic NS. But despite such earlier response in albumin-frusemide co-administration, FFP could be a feasible and justified alternative treatment option for the same patients in view of cost-effectiveness on one hand, with similar efficacy on the other hand, in resource-limited countries.

RECOMMENDATION

Considering the lower cost of FFP with clinical effectiveness, it may be a choice, especially in resource-limited settings like ours, for co-administration with frusemide to treat diuretic-resistant oedema in children of idiopathic NS. However, double-blind future large-scale studies are essential to validate the present study results.

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