

Albumin versus fresh frozen plasma in managing diuretic resistant edema in children with idiopathic nephrotic syndrome

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ABSTRACT: This study was carried out to compare the efficacy, cost effectiveness and outcome of albumin with fresh frozen plasma (FFP) in the treatment of diuretic resistant edema in childhood idiopathic nephrotic syndrome. **Methods:** Fifty four patients with idiopathic NS were enrolled in this prospective analytic study. Patients with moderate to severe edema with serum albumin <15 gm/L were given albumin and FFP dividing into two groups. Group-A, received intravenous albumin- 1 gm/kg/day and Group-B intravenous FFP 15ml/kg/day. Total number of albumin and FFP infusion were determined by edema reduction. Cost effectiveness was also calculated. **Results:** Diagnosis of NS and biochemical parameters were same in both groups. Dry weight was achieved in Group-A in 6.66 ± 3.710 days and in Group-B 6.66 ± 3.038 days. In Group-A the number of albumin infusion required was 1.44 ± 0.697 and Group-B FFP infusion required was 3.11 ± 1.5 ($p=0.0001$). Group A needed 4608.00 (\$57.6) taka for albumin whereas Group B needed only 2177.00(\$ 27.2) taka for FFP ($p=0.0001$). No significant complications were observed in both the groups. **Conclusion:** FFP costs half than albumin and same duration required reducing edema but the cost-effectiveness may place FFP as a better choice especially in developing countries of the world.

KEY WORDS- Fresh frozen plasma, Albumin, Edema, Nephrotic syndrome, Cost

I. INTRODUCTION

Nephrotic syndrome(NS) is a common childhood kidney disease characterized by massive proteinuria (> 1 gm/m²/day), hypoalbuminemia(<2.5 gm/dl) generalized edema and hypercholesterolemia(>250 mg/dl)¹.Edema is one of the cardinal clinical features of NS. It may vary from mild periorbital puffiness to generalized edema (anasarca)¹.

Treatment of the nephrotic edema remains controversial. In many cases of NS, the edema resolves spontaneously. Polyuria which results in edema resolution is induced by steroid treatment and usually begins after urine is protein free. However this can take several days. Medical supportive treatment is aimed at increasing urinary sodium and water excretion. It is indicated when NS is steroid-resistant or the edema is massive and leads to adverse effects such as oliguria, respiratory distress, pain from scrotal or labial swelling, and arterial hypertension². Children with severe edema are usually hospitalized and treated with intravenous (IV) albumin and diuretics if euvolemic or hypotensive. In contrast to adults, children are often more severe hypoalbuminemic and edematous, necessitating hospitalization and IV albumin administration. Albumin is routinely used in children because of low serum oncotic pressure due to hypoalbuminemia², but there are reports of diuretic resistance and decreased efficacy in NS^{2,3,4}; increased diuresis when diuretics are given after IV albumin and reluctance to treat patients with diuretics only because of intravascular volume depletion, dehydration and increased risk of thromboembolic complications^{5,6,7}.

Diuretics (loop diuretics, thiazide diuretics, and aldosterone antagonists) and albumin are the most often used supportive medications. Diuretics are potent natriuretic agents. Many nephrotic patients have an impaired natriuretic response to loop diuretics. There are some pharmacokinetic factors which have been identified in animal models that can modify diuretic response in patients with NS. Even moderate hypoalbuminemia in an animal-model diminishes the renal clearance of active furosemide and enhances its metabolism by the kidney to the inactive glucuronide⁸The renal clearance can be improved by premixing furosemide with albumin. Intravenous infusion of albumin in combination with diuretics has been advocated as an effective method for treating edema in NS^{7,9}. But albumin is very costly and sometimes out of rich of patients in developing countries like ours. Bangladesh is a small land with huge population and a small per-capita income of 1190\$¹⁰. So, use of other colloid like fresh frozen plasma (FFP) with or without diuretic is a good option for treating edema in NS. Though there is scarcity of published data regarding its effectiveness, it has been used in our institution over the years and we have experienced happy outcome with no complications. So, this study was intended to compare the cost effectiveness of albumin and FFP in edema management in patients with idiopathic nephrotic syndrome in a tertiary care referral center.

II. II.METHODS

Fifty four consecutive patients from 1-16 year of age with idiopathic NS admitted in the department of Pediatric Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU) from January 2013 to December 2013 who met the inclusion criteria were enrolled in this prospective analytic study. Children with secondary nephrotic syndrome were excluded from the study. Informed written consent was obtained from every participant. Confirmation of the diagnosis of initial attack nephrotic syndrome or relapse nephrotic syndrome were based on (1) history (2) physical examination (3) relevant investigations that includes- urine routine examination and culture sensitivity, 24hrs urinary total protein or spot urinary protein creatinine ratio, serum albumin, serum cholesterol, complete blood count, serum creatinine, serum electrolytes, X-ray chest.

Fluid overload was observed through history and physical examinations. All the patients were managed with fluid restriction (400 ml/m² + previous day output), salt restriction (1-2 meq/kg/day) and bed rest and associated infection and asthma were screened and treated. Oral prednisolone was given at a dose of 60mg/m²/day. Beside these, 2 mg/kg/day oral furosemide or combination of furosemide & spironolactone was given for 3 days to achieve desired diuresis or more than 1% weight loss per day in anasarca or symptomatic fluid overload patient after assessing volume status. Anasarca was defined as huge edema with genital swelling. If therapeutic goal of relief from oedema had not been reached, then we considered these patients as ‘diuretic resistant’ and divided into two groups (Group-A, Group-B) in consecutive fashion. . The Group-A study population was with intravenous albumin, 1 gm/kg/day in single daily dose over 4 hours followed by intravenous furosemide 1 mg/kg/day. Salt poor 20% human albumin was administered which was osmotically equivalent to 200ml of plasma. The Group-B study population was with intravenous FFP 15ml/kg/day over 2 hours followed by intravenous furosemide 1 mg/kg.

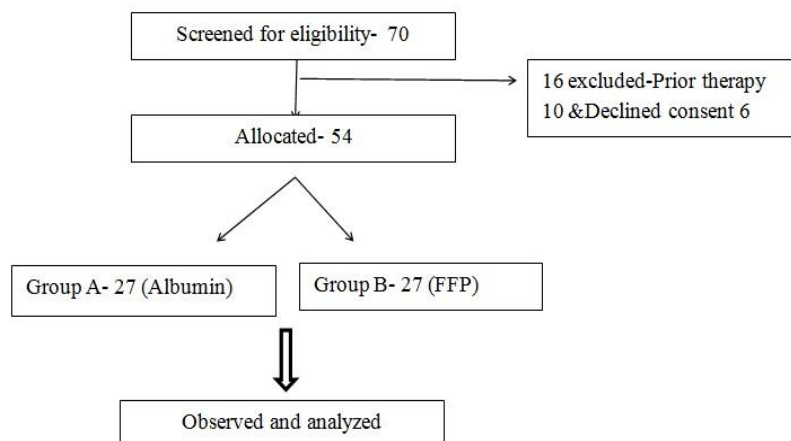


Diagram: Patient allotment

Proper screening and cross matching was done before FFP infusion. The study was approved by the Institutional Ethical Board.

Efficacy of both groups of drugs was observed day to day by recording daily pulse, blood pressure measurement, weight chart, intake-output chart, dependent edema and scrotal swelling upto achievement of dry weight. Dry weight was defined as euvolumic state with normal blood pressure and without edema. The patient's urine was collected over 24 hours from 8 a.m. to 8 a.m. of the next day. Any complications of these agents were also recorded. The numbers of infusion and cost were calculated and compared between two groups. Data were reported as mean \pm standard deviation (SD) and *P*-value <0.005 was considered significant.

III. RESULTS

Fifty four patients both male and female were included in this study. The mean age was 6.9 year and the age range was 1-15 year in Group-A and in Group-B, the mean age was 6.3 year with the age range was 1-15 year (Table;1). Male-female ratio was 1.4:1in group A and 2:1 in Group B. Diagnosis of NS and biochemical parameters were more or less same in both groups (Table:2). Dry weight was achieved in Group A in 6.66 ± 3.710 days and in Group B 6.66 ± 3.038 days. In Group A the number of albumin infusion required was 1.44 ± 0.697 and Group B FFP infusion required was 3.11 ± 1.5 (Table: 3). Group A needed 4608.00 (\$57.6) taka for albumin whereas Group B needed only 2177.00(\$ 27.2) taka for FFP. No significant complications were observed in both the groups.

Table-1: Age distribution in Group A and Group B

Age (year)*	Group A	Group B
1-5	12	15
6-10	12	9
11-15	3	3
Total	27	27
Male-Female ratio:		
M:F	16:11(1.4:1)	18:9(2:1)

*Mean age 6.9 year in Group A and 6.3 year in Group B.

Table-2: Clinical type of NS and biochemical parameters in Group A and Group B

NS	Group A	Group B	<i>P</i> -value
1 st attack	8	9	
Infrequent relapse	9	9	
Frequent relapse	9	8	
Steroid resistant	1	1	
Biochemical parameters			
S. albumin (gm/L)	12.259 \pm 2.137	11.85 \pm 2.727	0.405
S. creatinine (mg/dl)	0.53	0.49	0.317

Table-3: Comparison of days required to dry, number of infusion and cost of albumin and FFP in both groups

	Group A	Group B	<i>P</i> -value
No of Albumin (mean)	1.44 \pm 0.697		0.0001
No of FFP (mean)	-	3.11 \pm 1.055	
Cost (\$)	Tk-4608.0(57.6)	Tk-2177.0(27.21)	0.0001
Days required to achieve dry weight	6.66 \pm 3.710	6.66 \pm 3.038	0.463

IV. DISCUSSION

The pathophysiology of the nephrotic edema is complex, involves multiple mechanism. So its treatment is diverse. Many clinical situations can be found in edematous nephrotic patients¹². Proteinuria causes reduced oncotic pressure leading to shift of fluid from intravascular to extravascular space and hence intravascular volume depletion which causes renal hypo-perfusion. Renal hypo-perfusion causes increased proximal reabsorption of salt and water. Hypovolemia stimulates renin-angiotensin aldosterone mechanism, increase ADH secretion and inhibits atrial natriuretic peptide, all three cause renal salt and water retention¹¹. The fourth possible mechanism of edema formation in NS includes changes of permeability of the capillary wall¹³.

This is the first study of first of its kind reporting the use of FFP in the treatment of moderate to severe edema in children presenting with idiopathic NS. The aim of using FFP in combination with diuretics was to reduce edema and achieve dry weight in children with NS. It has been observed in different studies that albumin in combination with diuretic can reduce edema in children with nephrotic syndrome^{7,14}. Though, some studies differ in synergistic effect of albumin and furosemide¹⁵. But it is now recommended in many guidelines and in text^{16, 17}. Another study by Haque SS et al.(2014) had shown the use of mannitol and furosemide in resistant edema without any significant difference with albumin and furosemide¹⁸. The use of FFP in combination with diuretic for the same purpose has not been studied much and there is scarcity of published data. So, this study was intended with a view to compare the cost effectiveness of FFP and albumin in reducing edema in childhood NS targeting to achieve dry weight.

In this study the target population was age and sex matched and type of NS also was almost similar. Biochemical parameters chiefly serum albumin and serum creatinine was also same in both the groups.

Number of days required to gain target weight reduction in both groups was almost same (Group A in 6.66± 3.710 days and in Group B 6.66± 3.038). There was significant difference in number of infusions in these two groups. Group A required 1.44±0.697 albumin infusion and Group B required 3.11± 1.5 infusions of albumin. It signifies that albumin is more potent than FFP. There were significant cost difference in both the groups (Group A: 4608.00 (\$57.6) taka for albumin whereas Group B: 2177.00(\$ 27.2) taka for FFP). Albumin infusion costs much higher (almost double) than infusion of FFP which is an important issue in developing countries with relapsing illness like NS. Moreover, NS is more common in resource limited countries of Asia including Asian immigrants of Europe¹¹.

No major complications were observed in both the groups. Though some studies stated that acute hypertension, electrolyte imbalance and cardiopulmonary complications due to fluid overload may arise¹². Both the groups were given infusions with strict supervision and monitoring clinical symptoms of fluid overload and we did not observe any complication.

V. CONCLUSION

FFP cost half than albumin and same duration required to reduce edema but with double number of infusion and it is safe in pediatric patients with NS presenting with moderate to severe edema. The cost-effectiveness may place FFP as a better choice especially in developing countries of the world.

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