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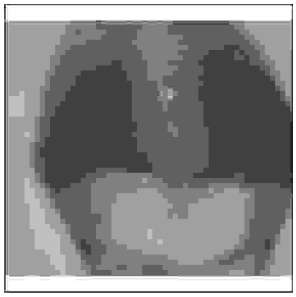
RESISTANT OEDEMA IN NEPHROTICS



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ABSTRACT... Introduction: Hypoalbuminemic nephrotics often have sufficient fluid accumulation to mandate diuretic therapy but are often resistant to diuresis. Furosemide is one of the most effective and least toxic diuretics used in pediatric practice. In children with different diseases who received orally or intravenously 1 to 2 mg/kg doses of furosemide. In a country like Pakistan, such a treatment is not always afforded, albumin being quite costly. **Objective:** To compare the efficacy of albumin furosemide combination infusion to the infusion of furosemide alone in patients of nephrotic syndrome with resistance oedema. **Study design:** Two way crossover study. **Setting:** Paediatric Medicine, Nishtar Medical College, Multan. **Duration:** From January 2004 to June 2005. **Patients and Methods:**10 children. **Results:** There was marked improvement in the symptoms like respiratory distress and oedema in both the groups. Urine output was markedly increased without any significant changes in the BUN, serum creatinine, serum electrolytes and serum calcium. These values were slightly higher in group-I but not statistically significant. No adverse effects like drowziness confusion, hypotension and seizures were observed in any group. **Conclusion:** During the clinical management of resistant oedema in nephrotics, furosemide infusion alone is as efficacious in reducing the oedema as albumin furosemide mixtures without any adverse effects and is much more economical.

Key words: Nephrotic Syndrome, Resistant Oedema, Furoemide, Albumin.

INTRODUCTION

Hypoalbuminemic nephrotics often have sufficient fluid accumulation to mandate diuretic therapy but are often resistant to diuresis. Studies have suggested that hypoalbuminemia itself impairs delivery of effective amounts of diuretic agent into the urine, the site of action[1].

The volume status of such patients, can be difficult to manage, because even large doses of potent diuretics have diminished efficacy and result in complications like electrolyte and acid base disturbances or renal failure[2].

Several potential mechanisms for such diuretic resistance have been suggested and include hypoalbuminemia, diminished GFR, altered pharmacokinetics and pharmacodynamics of loop diuretics[3,4,5,6,7,8].

The overall response to a diuretic is determined by delivery of drug to its site of action, delivery of solute to the site of action, the dynamics of the drug with its receptor and whether or not solute is reclaimed distal to the site of action[4]. Both pharmacokinetic and pharmacodynamic mechanism have been proposed as explanation for the resistance of loop diuretics[3,9,10].

Furosemide is one of the most effective and least toxic diuretics used in pediatric practice. Experimental and clinical data suggest that adrenocorticosteroids and/or endogenous ouabala-like substances may play an import role in its diuretic effect. Also, the drug appears to have anti-inflammatory properties. In children with different diseases who received orally or intravenously I to 2 mg/kg doses of furosemide. A statistically significant positive linear relationship was found between the drug urinary excretion rate and the urine flow rate, especially during the first 6 hours, furosemide inhibits Na reabsorption in the ascending limb of loop of henle, as well as both proximal and distal tubule. This action is independent of any inhibitory effect on carbonic anhydrase or aldosterone. The diuretic effect of furosemide is exerted even when glomerular filteration is markedly impaired. It may promote diuresis in cases which have previously proved resistant to other diuretics. It has no significant pharmacological effect other than on renal function.

It is rapidly absorbed from G.I. tract & the diuretic effect of furosemide is apparent in the first hour following oral administration, peak effect occurs in the first or second hour & duration of action 4-6 hours, but may continue upto 8 hours.

Following I/V administration, diuresis occurs within 30 minutes and duration of action is 2 hours. Urinary excretion is accomplished by glomerular filteration & proximal tubular secretion, and together this account for 2/3" of ingested dose and remainder is excreted in feces[11].

In plasma, furosemide is extensively bound to proteins, mainly to albumin. The albumin-bound fraction of furosemide reaches the proximal tubule cells and is secreted into the tubular lumen. Hypoalbuminemia diminishes the amount of albumin-bound furosemide and diminishes the furosemide delivery to the ascending limb of the loop of Henle[6,7].

A reduction in the amount of pharmacologically active drug and an impairment of tubular reabsorption due to urinary albumin-furosemide binding could ultimately diminish the diuretic effect[5,8]. Absolute or relative hypovolemia in nephrotic syndrome may enhance NaCl reabsorption and contribute to diuretic resistance[5,8,9].

There has long been interest in the use of intravenously administered albumin to enhance diuresis in hypoalbuminemic patients. After salt-poor human albumin became available in 1944, several anecdotal reports suggested that albumin infusions could enhance diuresis in cirrhotic patients[12,13,14,15,16]. Intravenous infusion of albumin in combination with furosemide has been advocated as an effective method of treating edema due to the nephrotic syndrome, but its clinical efficacy is controversial[3,4,10,11,17]. Co-administration of albumin with furosemide may improve furosemide delivery and hence diuretic effect by changing the pharmacokinetics of furosemide.

In a country like Pakistan, such a treatment is not always afforded, albumin being quite costly. Furosemide is of low cost and freely available .it is frequently used as a diuretic to relieve the edema in patients with nephrotic syndrome, it is given as a bolus mi. at 8-12 hourly intervals at a dose of 1-2 mg 1kg. We frequently encounter diuretic resistance in these patients and are then left with a limited choice of medicines, as albumin is not often afforded by the patients.

We decided to use furosemide in the infusion for, as has

been used and recommended in various studies. The present study was undertaken to investigate, whether a combination of albumin and furosemide was more effective as compared to furosemide alone, to treat the resistant edema in nephrotics.

MATERIAL AND METHODS

Ten patients were enrolled after having informed consent. Patients were admitted from January 2004 to June 2005 in the Department of Pediatric Medicine, Unit-I, Nishtar Hospital, Multan, where they remained until the completion of study. These children exhibited generalized edema, and excretion of proteins exceeded 4Omg/m^2/hr. Edematous patients with causes other than nephrotic syndrome e.g. cirrhosis, congestive heart failure, malnutrition, constrictive pericarditis,were excluded from the study. See patient characteristics (Table-I).

Administration of any other diuretics if previously being given, was stopped. These children were kept on I/V injection of furosemide 1-2 mg/kgat 8 hourly interval, odium intake was restricted, initial weight was taken, full blood chemistry panel including CBC, serum electrolytes, serum creatinine, BUN, serum .calcium level, serum .total proteins and albumin levels, urinalysis and 24 hr urinary proteins levels were performed. Thereafter, urine output, serum electrolytes, serum creatinine, serum calcium were measured next morning. Oral fluids were not restricted.

GROUP-I: Received albumin, 20% 1gm/kg in 30-60 minutes, followed by 1 mg/kg/hr of furosemide for 6hrs dissolved in 50m1 of 5% dextrose water.

GROUP-II: Received, only furosemide infusion 1 mgl kg/hr in 50 ml of 5% dextrose water in 6 hours.

All these infusions were started at 8 AM and stopped at 2 PM. Urine was sequentially collected over 24 hours, from 9 AM to 2 PM and 2 PM to 9 AM next morning. BP was measured at 2 hourly interval, urine volume, serum electrolytes, serum creatinine concentration, were measured at the admission, start of infusion etc.

RESULTS

There was marked improvement in the symptoms, like respiratory distress, edema was markedly reduced, with a feeling of well being in both the groups-I and II. Both furosemide, and furosemide with albumin, infusions increased the urine output significantly, as compared to the IN Furosemide bolus injection 8 hourly. However, the volume of urine measured and compared, between frusemide infusion alone, and furosemide after albumin infusion were more in the latter but not statistically significant (Table-II). There was no significant change in the serum electrolyte values of both the groups, neither was there any deterioration in the serum creatinine values. Only one patient had serum creatinine value above normal prior to study, which remained unchanged at completion of the study.

No adverse effects like, hyponatremia, hypokalemia, hypocalcemia, hypotension and hypovolemia were observed during the treatment or in the following 18 hours till completion of the study. In both groups, there were no symptoms like, drowsiness, seizures, confusion, headache, oliguria etc. however mild lethargy & weakness was noticed in two patients .No deafness was observed on the follow up in the following 6 months.

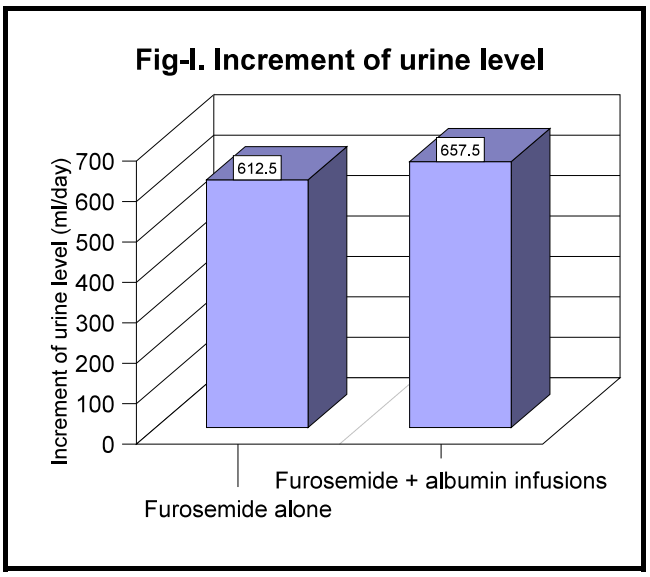
DISCUSSION

In this study, a significant increase in the volume of urine in both the groups was seen, as compared to the administration of furosemide alone, as I/V bolus injection every 8 hours.Though the infusion of albumin and furosemide together may potentiate the diuretic effect of furosemide, this is not as superior a regimen to warrant its use as a preferred choice over furosemide alone, because, persistent proteinuria in these patients again causes the loss of albumin very quickly in urine, warranting the need for re-infusion.

Table-I. Patients Characteristics of Both Groups Before Giving Furosemide + Albumin / Furosemide Infusion.							
Age (Years)	**Sex**	**S. Na+ meq/L**	**S.K + mg/dL**	**S.ca++ mg/dL**	**S. Albumin mg/dL**	**S. Creatinine mg/dL**	**24 hrs urinary protein gms**
GROUP-I							
7	M	134	3.7	9.2	1.8	1.0	2.6
8	F	140	4.4	8.8	2.2	0.6	2.8
9	F	133	3.7	9.0	1.9	0.7	10.5
5	F	139	4.2	9.4	2.1	1.2	5.7
6	M	135	4.8	9.8	2.2	0.8	3.0
GROUP-II							
5.5	M	138	4.2	9.0	2.6	0.8	2.3
7	M	139	3.9	8.8	2.1	0.9	1.4
9	F	137	3.4	7.8	2.2	0.9	1.8
6	M	142	4.3	8.9	2.3	0.8	2.4
8	F	140	4.5	9.4	2.0	0.7	2.5

Table-II. Post-treatment values of both group-I and II				
Pt. No.	**S. Na+**	**S.K+**	**S. Ca++**	**S. Creatinine**
GROUP-I				
1	135	3.4	8.8	1.0
2	134	4.1	8.5	0.6
3	137	3.6	9.2	0.8
4	135	3.7	9.0	1.3
5	132	4.5	10.0	0.7
GROUP-II				
1	137	3.6	9.1	0.8
2	133	3.9	8.9	0.7
3	134	3.3	8.0	0.9
4	135	3.0	9.0	1.2
5	136	4.9	9.6	0.6

Table-III. Average values of both group-I and II					
	24 hrs urine volume ml/dl	S.Na + (Meq/L)	S.K+ (Meq/L)	S. Ca++ (Mg/dl)	S. Creatinine Mg/dl
GROUP-I					
Basal	495.5	136.5	4.0	9.1	0.87
Post-treatment	1107.5	133.75	3.7	8.87	0.92
GROUP-II					
Basal	510	138	3.92	8.6	0.85
Post-treatment	1176.5	134.75	3.45	8.75	0.95



The use of larger doses of albumin would not be practical and would be expensive, secondly it would be necessary to use repeated doses of albumin to produce benefits and this effect does not have a clear cut edge over the administration of furosemide infusion alone[8].

In present study the mean serum albumin level was 2.4 gm/dl, the mean 24 hour urinary volume in group I was approximately 495 ml/day, mean serum creatinine was, -0.85 mg/dl. The mean urinary volume post treatment was 1 107.5 1/day and mean serum creatinine was 0.92 mg/dl. In Group-I the mean pre-treatment urinary volume was 510 ml/ay, serum creatinine was 0.85 mg/dl. While post treatment urine volume and serum creatinine were 1167.5 ml/ay and 0.95mg/dl espectively (Table-III, Fig-1).

However, the results of this study cannot be extrapolated to morbid diuretic resistant patients with more extreme degrees of hypoalbuminemia.

This study showed that albumin pre-infusion increased Diuresis slightly better than furosemide infusion alone. We speculate that albumin preinflision might expand plasma volume, which might therefore have improved the diuretic action of furosemide[8,11,12]. The cross-over study performed by Akcicek et al. demonstrated that potentiation of the furosemide effect by infusion of albumin did not occur[9]. Akicek et al[13] studied the effects of albumin alone, furosemide alone, and the combination in eight hypoalbuminemic patients with nepbrotic syndrome. Albumin alone had negligible natriuretic effects (13±8 mEq/4 h) and had no effect on the response to furosemide.

Fliser et a[14] also studied nine patients with nephrotic syndrome. Their study included dietary equilibration, and they measured the amount of furosemide that reached the urinary site of action. There was no effect on urinary furosemide levels. Albumin increased the response to furosemide by 20%. The mechanism seemed to involve an increase in renal blood flow. Those authors concluded that the effects were statistically significant but likely not clinically relevant.

The study by Inoue et al[2], in analbuminemic rats also reported the effects of an ex vivo mixture of furosemide and albumin in four patients with nephrotic syndrome. All

patients exhibited an increase in urine volume, compared with furosemide alone. No information was provided with respect to the design of this clinical component of their study or the results in terms of sodium excretion.

There are some reports showing that plasma volume expansion, induced by albumin or dextran, caused an increase in urine flow rate but not in sodium excretion in healthy volunteers, and in nephrotic, patients[8,11,12,15]. This is important because an acute rise in blood volume suppresses, vasopressin secretion[16]. The diuretic effect of furosemide is directly related to the amount and rate of the drug excreted in urine. The presence of massive proteinuria and hypoalbuminemia in patients with nephrotic syndrome alters the phannacokinetics of furosemide, the binding of furosemide to plasma proteins decreases in proportion with the reduction of plasma protein levels. At the same time, the volume of distribution is apparently increased.

In a study done by Na KY et al analysis of pharmacokinetic parameters from patients with nephrotic syndrome, total plasma clearance increased slightly, volume of distribution increased and elimination of half life was prolonged. However, there was no significant difference in clearance, volume of distribution and urinary furosemide excretion between furosemide alone and furosemide after albumin infusion. These results indicate that the potentiation of diuresis by albumin pre-infusion is not relevant to the pharmacokinetics of furosemide[17].

A study done by Naga Chalsani et a! on patients with cirrhosis as best clinical model for examination of the principles underlying the potential utility of albumin, furosemide mixtures and their data convincingly demonstrated that co-administration of albumin did not enhance the diuretic response to furosemide. Correspondingly, the pharmacokinetics and pharmacodynamics of furosemide were not altered by concomitant albumin administration. They tested for a relationship between diuretic response & serum albumin and found none[18].

Another study by Bircan et a! on 12 children with minimal change nephrotic syndrome, receiving albuminlfurosemide therapy. They evaluated these children, before, at 2 hours, and 24 hours after therapy. Lipoprotein A, protein C and S. Factor-III, VWF, PT, APTT, AT III, macroglobulin, fibrinogen & antitrypsin, were measured, there was a mild reduction in ATIII and MG in the 2nd hour 7 fibrinogen on the following day, however any serious change leading to thrombotic tendency during alb/furosemide infusion were not recorded, & no absolute correlation has been found between the many biologic abnormalities and the alb/furosemide therapy[19].

Agarwal et al demonstrated that displacement of urinary protein binding with sulfisoxazole in nephrotic patients did not enhance response to furosemide[20]. Urinary protein binding of furosemide is not a major mechanism of diuretic-resistance in nephrotic syndrome[8].

There are several limitations in our study. Firstly, we could not evaluate the exact plasma volume status in these patients. Therefore it was not possible to assess any sequential changes in plasma volume after albumin infusions. Secondly, we did not know the exact underlying renal pathology in these patients, since, each patient with nephrotic syndrome as a diagnosis, does not undergo renal biopsy at the outset of treatment, and it not practically possible to recruit patients with a uniform pathology. Thirdly, 2 out of 10 patients had deranged renal function at the outset, and because abnormal renal function can alter the diuretic action of furosemide, it is possible that our data was confounded by the presence of azotemia. Lastly, the sample size may not have been sufficient for detection of a significant effect.

CONCLUSION

It is concluded that as to the clinical management of patients with nephrotic syndrome it is more reasonable to increase the dose of furosemide (in our study we gave upto >150 mg in6-8 hours) without any adverse effect, than to administer albumin repeatedly and increase the financial burden manifold. Though, in an occasional patient it may be used to overcome the diuretic resistance unresponsive to maximal doses of steroids.

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When losing,
Keep your head high
&
Continue struggle.

Shuja Tahir