# Slow Infusion Vs Bolus Injection of Frusemide in Treating Oedema in Nephrotic Syndrome: A Randomised Controlled Trial

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***Abstract - Background - In childhood nephrotic syndrome (NS), oedema is a common problem resulting from urinary loss of albumin and water retention. Bolus injection of frusemide has been judiciously used to treat oedema with variable success rates. In theory, good perfusion and albumin are required for frusemide secretion at the tubular lumen. Thus, in the situation of low glomerular filtration rate and hypoalbuminemia, the efficacy of frusemide might be limited.***

***Objective - To validate the effectiveness of slow infusion of frusemide over bolus injection to control oedema in childhood NS.***

***Methods - A randomized crossover study was conducted, following stratified randomisation, to compare the efficacy between 3 bolus injections of frusemide given 8 hourly at 2mg/kg (total 6mg/kg) vs the same dose infused over 24 hours in NS patients with significant oedema. After 8 hours off medication a cross-over was made. The baseline and 24 hour urine-output and urine-sodium were recorded. The increment of urine-output and urine-sodium after treatment at 24 hours were calculated by using post-treatment minus baseline urine-output/urine-sodium for the corresponding period. The student's t-test was used for statistical analysis.***

***Results - Twenty-two NS patients with hypoalbuminemia (19.2 ± 3.0g/dL) were enrolled. At 24 hours, there were significant differences in the increment of urine-output (0.45 ± 0.38 vs 0.66 ± 0.32L, P < 0.02) and urine-sodium (34.5 ± 27.8 vs 52.0 ± 22.7mEq, P < 0.01) between frusemide bolus and infusion groups respectively.***

***Conclusions - The results indicate that slow infusion of frusemide is superior to the common practice of bolus injection, in enhancing water and sodium excretion and thereby causing diuresis in hypoalbuminaemic NS patients with oedema.***

***Keywords: nephrotic syndrome, frusemide, oedema, bolus injection, continuous administration, intravenous.***

## I. INTRODUCTION

Nephrotic syndrome (NS) is the most prevalent childhood glomerular disorder in which oedema is a cardinal feature. The incidence of NS is 2 to 7 per 100,000 children1. Apart from the decreased quality of life, children with NS are at risk of several complications of the disease which give rise to significant morbidity. Mortality rates up to 2.7%[2] have also been described. A few international guidelines provide guidance for the non-immunosuppressive approaches to these complications which include infections, thromboembolism, oedema and dyslipidemia.

In NS, traditionally it is believed that massive proteinuria leads to hypoalbuminaemia which causes a reduction in plasma oncotic pressure resulting in increased net capillary ultrafiltration leading to the development of oedema3. This is supported by evidence such as reduced intravascular volume, reduced glomerular filtration rate (GFR) and increased plasma renin and aldosterone seen in NS patients4. This hypovolaemic state is associated with symptoms such as tachycardia, abdominal pain, oliguria, cold peripheries and hypotension5. However, another hypothesis, namely the 'overfill hypothesis" states that there is primary sodium retention with resulting intravascular overfilling, with the excess fluid moving to the interstitium, causing oedema3. The proposed mechanism for this phenomenon is that in NS the proteinuria includes plasma proteinases like plasmin which bind to the epithelial sodium channel leading to avid sodium and water retention, leading to oedema. This theory, though not universally accepted forms the basis for the use of diuretics in NS.

While mild oedema is normally managed with fluid restriction and dietary sodium restriction, severe oedema might need pharmacological intervention. Severe oedema places the child at risk serious infections and malnutrition. Oedema of the gastrointestinal tract in a grossly oedematous child may hinder absorption of immunosuppressive medication, delaying remission induction and thus prolonging morbidity. Moreover, severe oedema may restrict the mobility of the child, increasing the risk of thrombosis. Hence control of oedema is considered an important aspect of management in a child with NS. The combination of albumin infusion with a diuretic or administration of diuretics alone when the child is in an euvolaemic state is currently practiced to control oedema6. Frusemide, a loop diuretic, is the most commonly used agent for this purpose. Even though the combination of albumin infusion with a diuretic is far superior in inducing diuresis, the higher morbidity and rare fatality associated with albumin infusion restrict its use. Hence, if an oedematous child has a steady and stable intravascular volume compartment, the use of diuretics

will be the method of choice of most paediatricians. The normal practice in Sri Lankan hospital settings is to administer bolus injections of frusemide. The present study compared the efficacy of intravenous injection of frusemide with slow infusions of the drug.

## II. PATIENTS AND METHODS

This randomized, crossover study was conducted at the Professorial Paediatric Unit, Teaching Hospital Peradeniya, Sri Lanka. Patients with primary nephrotic syndrome presenting with a relapse of the disease were considered for recruitment. Sequential children with NS with hypoalbuminaemia ($19.2 \pm 3.0$g/dL) and showing severe oedema were randomized into two groups following stratified randomisation. Severe oedema was defined as evidence of 3+ or more proteinuria with pitting oedema and ascites with over 20% rise in body weight from the dry weight. Patients with clinical and biochemical evidence of hypovolaemia and patients with evidence of infection were excluded. A total of 22 patients were recruited in to the study.

Group 1 was allocated 12 children who received 3 bolus injections of frusemide, given 8 hourly at 2mg/kg (total 6mg/kg). Group 2 was allocated 10 children who received the same total dose of Frusemide (6mg/kg) administered as an intravenous infusion over 24 hours. After 8 hours off medication a cross-over was done with Group 1 receiving the infusion and Group 2 receiving the bolus injections for the next 24 hours. Serum electrolytes were monitored 8 hourly.

Baseline 24 hour urine-output and urine-sodium excretion were recorded prior to administration of frusemide. The increment of urine-output and urine-sodium after treatment at 24 hours were calculated by using post-treatment minus baseline urine-output/urine-sodium for the corresponding period. The data was analysed with SPSS software using paired-samples *t* test.

## III. RESULTS

All 22 patients completed the study. The age at entry ranged from 4.5 years 10.8 years with a median age of 7.4 years. Fifteen were males and 7 were females. At 24 hours, there were significant differences in the increment of urine-output ($0.45 \pm 0.38$ *vs* $0.66 \pm 0.32$L, $P < 0.02$) and urine-sodium ($34.5 \pm 27.8$ *vs* $52.0 \pm 22.7$mEq, $P < 0.01$) between frusemide bolus and infusion groups respectively. No adverse events were encountered.

## IV. DISCUSSION

Nephrotic syndrome manifests with heavy proteinuria, oedema, hypoalbuminaemia and hyperlipidaemia. Diuretics are the mainstay in the management of oedema. Loop diuretics block the sodium chloride co-transporter in the thick ascending limb of the loop of Henle, which normally reabsorbs about 25% of the filtered Na+ load in the glomerular filtrate. The sodium-potassium-chloride (Na+-K+-2Cl-) co-transporter in the apical membrane of tubular epithelial cells in the thick ascending limb is specifically blocked by Frusemide7.

The required amount of diuretic depends not only on the extent of oedema but also on the patient's response to it. Intravenous administration of loop diuretics is considered in cases of severe oedema whereas mild oedema can usually be managed conservatively. For loop diuretics, intravenous administration is more effective than oral therapy8. Bioavailability of the drug is also a concern. Frusemide, the most commonly used loop diuretic in children, has a pronounced variation in oral bioavailability (10-90%) and in a study by Prandota its oral bioavailability in nephrotic children was observed to be 58%[9]. Frusemide is also highly albumin-bound, hence it is not filtered at the glomerulus. It is secreted into the nephron lumen via an organic transporter at the proximal tubule. In hypoalbuminaemic patients, the binding of frusemide to albumin is hindered, allowing free frusemide to to diffuse in to tissues, ultimately resulting in less secretion into the luminal site of action[10]. Therefore for patients with severe hypoalbuminemia, higher doses of diuretics are required.

Kapur *et al* stated that the underfilled or overfilled status of NS patients should also be taken into consideration by showing that diuretics alone are effective and safe in managing severe oedema in 'overfilled' children, whereas combination therapy of diuretics and albumin is required for 'underfilled' patients. However, this was not a serious concern in the present study since the participants were all at a euvolaemic state. It has been previously demonstrated that a significant portion of normovolemic/euvolemic NS patients could be treated for edema with diuretics alone11.

The bolus therapy group of the present study had lower sodium excretion. This could be explained by the action of bolus frusemide in the body. Though sodium excretion is rapidly increased by bolus therapy, it is at maximum for the first 2 hours and gradually decreases7. The next dose yields 25% lesser natriuretic effect than the first and so on, ultimately resulting in post-diuretic fluid retention and renal sodium retention12. Therefore intravenous infusion appears more advantageous in this context as shown by several studies13,[14,15] also with lesser side effects in patients with acute decompensated heart failure16.

By maintaining an efficacious concentration of frusemide via continuous infusion, inhibition of Na+ reabsorption and higher urine output can be achieved. This is evident by the increased urine output of the continuous infusion group of our study.

## V. CONCLUSION

The significantly higher levels of urine output and urine sodium excretion in the intravenous slow infusion group prove the superiority of this method over the traditional bolus injection commonly used in Sri Lanka. Therefore continuous infusion of loop diuretics could be adapted to manage oedema of euvolemic patients in similar settings, instead of the bolus injections.

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