JPPT | Randomized Double-Blind Controlled Study

Comparison of Sequential versus Concurrent Albumin and Furosemide in Pediatric Nephrotic Syndrome Patients: A Blinded Randomized Controlled Clinical Trial

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OBJECTIVE Comparing the effectiveness of sequential and concurrent administration of albumin and furosemide in reducing edema in children with nephrotic syndrome.

METHOD A double blinded randomized controlled clinical trial was conducted in patients diagnosed with nephrotic syndrome between 2 and 15 years of age. The patients were randomly divided into 2 groups of 32 subjects. One group received an admixture of albumin and furosemide, and the other received furosemide immediately after the albumin infusion. The weight loss and urinary sodium concentration results were analyzed in each group.

RESULTS The comparison of the 2 groups demonstrated that the group that received albumin and furosemide sequentially had statistically significant weight loss. There was no significant difference in the amount of urinary sodium, as determined by random spot urine analysis in 9 subjects in each group, and no study drug-associated adverse effects were observed in any patient.

CONCLUSIONS there was a significant difference between weight loss in the 2 groups that received albumin and furosemide simultaneously or sequentially and according to this study, the sequential method of furosemide administration after albumin infusion is the preferred method to reduce edema in pediatric patients with nephrotic syndrome.

ABBREVIATIONS BUN, blood urine nitrogen; GFR, glomerular filtration rate

KEYWORDS albumin; edema; furosemide; loop diuretic; nephrotic syndrome; pediatric

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Introduction

Nephrotic syndrome is characterized by edema, hypoalbuminemia, and proteinuria.[1] The condition is classified into primary and secondary causes, with primary causes being idiopathic or genetic diseases, and secondary causes including infections, medications, immunological diseases, and malignancies.[2,3] In pediatrics, nephrotic syndrome is primarily idiopathic, with Minimal Change Disease (MCD) being the most common subtype. The syndrome may also arise secondary to conditions such as systemic lupus erythematosus or infections like hepatitis and HIV. Hypoalbuminemia contributes to edema by reducing vascular oncotic pressure, allowing fluid to escape into the interstitial space.[4,5]

Edema, a hallmark of nephrotic syndrome in children, can present as periorbital edema, often mistaken for allergies, and may progress to leg edema, abdominal swelling, or significant weight gain if left untreated. Severe edema can lead to complications like pulmonary edema or pleural effusion, and can also negatively impact the quality of life.[6] Studies have shown that children with nephrotic syndrome-associated edema experience increased anxiety, pain, and fatigue, highlighting the importance of effective management.[7]

The primary treatment for nephrotic syndrome includes salt restriction and diuretics.[8] However, when these are insufficient to control edema, albumin infusion is considered.[9] Albumin increases vascular oncotic pressure and facilitates the transfer of fluid from interstitial tissues to the intravascular compartment, which can help reduce edema.[10] Combining albumin with loop diuretics, such as furosemide, has been explored to improve drug efficacy,[9,11,12] especially in hypoalbuminemic patients where the response to diuretics alone is diminished due to decreased drug secretion in the nephron.[13]

This study aims to investigate the optimal method of administering albumin and furosemide to improve edema reduction in pediatric patients with nephrotic

syndrome. While both simultaneous and sequential albumin-furosemide approaches have been used, studies focusing on the most effective administration method in children remain limited.

Material and Methods

Study Population and Study Design. This prospective, parallel, randomized, double-blind interventional clinical trial was conducted in pediatric patients admitted at a single freestanding children's hospital between August 2021 and August 2022 Inclusion criteria for this study were as follows: children ages 2 to 15 years old, admission to hospital for treatment of edema, diagnosis of nephrotic syndrome, and candidate for treatment with intravenous albumin and furosemide. In our treatment protocol, the first line of treatment in steroid-resistant patients is repeated treatment with albumin, diuretics, and fluid restriction, and if the patients do not respond, they are treated with drugs such as tacrolimus, cyclosporine, and mycophenolate. None of our patients were treated with these drugs. Exclusion criteria include renal failure, defined as GFR < 30 mL/min calculated by an onsite patient recruiter using the Schwartz bedside method (2009)[14]; hepatic failure, defined as child-Pugh class B and C; patients who received diuretics within 30 days prior to participation; patients who lose weight in a manner other than urine (such as diarrhea and vomiting due to gastroenteritis); patients who received albumin and furosemide more than 1 dose during the first 24 hours of the study; patients undergoing renal dialysis or anuria for 24 hours after the intervention; and patients receiving rituximab before the intervention.

A power analysis was performed to determine the number of patients for enrollment: difference between 2 independent means with alpha 0.05 and beta 0.8 and in 2 groups of 64 people. The selected 128 patients were divided into 2 random groups (n = 64). Randomization was carried out in 32 quadruple blocks using the block randomization method. One group received a mixture of albumin and furosemide simultaneously, and the other group received albumin and furosemide, respectively (after the albumin infusion was finished). Albumin 20% infused intravenously 0.5 to 1 g/kg/dose over 30 to 60 minutes and furosemide (20 mg/2 mL) administered with dose of 1 mg/kg/dose intravenously over 30 minutes. The double dummy method was used for blinding the study; each patient was assigned a unique nonsequential code and 2 identical syringes marked with codes and numbers 1 and 2. In 1 group, syringe 1 contains 4 mL of sterile normal saline; syringe 2 contains 40 mg of furosemide in 4 mL, and vice versa in the other group. According to the protocol, syringe 1 is injected into an albumin 20% vial, and syringe 2 is injected intravenously at the end of the infusion at a dose of 0.1 mL per kg based on the volume of prepared syringes. After 50% sampling, the codes are opened, and an interim analysis is performed in the middle of the study. If it is significant ($p < 0.05$), the end of the study is announced. By the end of the study, the code-breaking process is performed in 2 stages. In the first stage, the results are divided into 2 groups and analyzed, and in the second stage, it is determined which intervention was conducted in which group.

Data and Specimen Collection. Body weight was measured before and after drug administration for all patients in the same manner in both groups. All patients were weighed using the same scale for both pre- and post-administration measurements, and the scale was calibrated weekly by the hospital's medical engineering department to ensure accuracy. Vital signs, demographic information, and routine patient clinical tests, including serum sodium and potassium, BUN, and serum creatinine, are recorded before and after the intervention were obtained from our clinical laboratory. Urine sodium was randomly sampled at 6-hour intervals during the 24 hours following study medication infusion. Urine was collected in 4 separate 6-hour time blocks throughout the 24-hour period. Total sodium excretion was calculated by measuring the sodium concentration in each sample and multiplying it by the corresponding urine volume. The cumulative total sodium excreted over the 24-hour period was then calculated by summing the sodium content from all 4 intervals. Moreover, the duration of hospitalization and the patient's outcome was recorded. Patients underwent a standard clinic visit with their physician on day 28 following discharge. Additionally, patients received weekly calls from trained pharmacists for interviews. A trained pharmacist evaluated for possible adverse drug reactions during and after administration. Any adverse reaction related to medications and method of administration such as any nausea and vomiting, blue lips, dizziness, pulse rate, body temperature, chest pain, hypersensitivity, pale skin, flushing sweating, swelling in the legs and ankles, blood pressure and rate of breathing was recorded to assess the safety of the administration methods. A project manager coordinated the budget, human resources, and study time.

Statistical Analysis. All statistical analyses were performed using SPSS statistical software (version 26). After data collection, quantitative data were described using mean and SD. Also, independent-test and T-test statistical analysis were used to compare the sequential versus combined groups. The significance level (p value) was considered less than 0.05. The linear regression method was used to investigate the effect of intervening factors.

Results

In our study, initially 128 patients were selected, and block randomization was performed on 128 subjects. After 50% sampling, the codes were opened, and due

to the significance of the results, the end of the study was announced. Finally, out of 85 patients, 68 patients were included in our study.

The Supplemental Figure shows inclusion and exclusion of patients in the intervention. The participants in this study were divided into simultaneous administration and sequentially administration groups, with 58.1% males and 41.9% females.

Table 1 indicates the demographic information of the patients and our study findings.

A T-test of 2 independent samples with equal variance was performed to investigate the intervention conducted on patients' weight difference percentage [(W2-W1)/W1] and urine sodium. according to the analytical results, there was a significant relationship between the injection time of furosemide relative to albumin and weight loss (reduction of edema) in children with nephrotic syndrome (p = 0.0151). A t-test comparing urinary sodium excretion after the intervention revealed no significant relationship between the timing of furosemide and albumin administration and the amount of urinary sodium excreted (p = 0.337). Thus, the timing of administration did not influence the effectiveness of sodium excretion in children with nephrotic syndrome.

The relationship between serum albumin concentration and serum creatinine concentration was investigated. A correlation test revealed a weak positive correlation between the initial concentrations of serum albumin and serum creatinine (correlation coefficient = 0.273, p = 0.057).

Additionally, sex was found to significantly affect both serum albumin and serum creatinine concentrations. Males had lower serum albumin (2.20 g/dL) and serum creatinine (0.53 mg/dL) concentrations compared with females, who had higher values (serum albumin = 2.44 g/dL, serum creatinine = 0.80 mg/dL). Due to the significant relationship between sex, serum albumin, and serum creatinine, these variables were not included in the same statistical model to avoid confounding.

In terms of weight difference percentage before and after the intervention, no significant impact was observed from the initial concentration of serum creatinine (p = 0.463) or serum albumin concentration (p = 0.783). Similarly, sex did not significantly affect the weight difference before and after the intervention, with a p value of 0.497 for gender's effect on weight change.

The vital signs of the patients in this study were monitored during the drug infusion. None of the patients had side effects or infusion reactions. The pharmacist who evaluated the side effects was blinded. The pharmacist operated under the supervision of the

Table 1. Demographic Information and Patient Data

Parameters	Simultaneous Group				Sequential Group				p value	
	Mean Pre-intervention	Mean Post-intervention	SD Pre-intervention	SD Post-intervention	Mean Pre-intervention	Mean Post-intervention	SD Pre-intervention	SD Post-intervention	Sig. (2-tailed) Pre-intervention	Sig. (2-tailed) Post-intervention
Age, yr	4.56	NA	3.83	NA	5.98	NA	3.36	NA	0.28	NA
Body weights, kg	20.25	19.95	15.03	14.85	22.63	22.63	10.46	10.19	0.46	0.56
Serum albumin, g/dL	2.20	NA	0.34	NA	2.40	NA	0.28	NA	0.112	NA
Initial serum creatinine, mg/dL	0.60	NA	0.32	NA	0.71	NA	0.55	NA	0.569	NA
Initial BUN, mg/dL	19.64	NA	9.25	NA	20.54	NA	12.53	NA	0.835	NA
Initial serum sodium, mEq/L	132.42	NA	3.57	NA	133.73	NA	3.19	NA	0.367	NA
Urine sodium, mEq/L	36.00	57.625	21.16	42.42	10.10	77.9	2.96	43.75	0.165	0.337

BUN, blood urea nitrogen; NA, not applicable

attending pharmacist. If any issues had arisen during the process (though none did), the blinded pharmacist was required to report them to the attending pharmacist. Also, patients' vital signs were checked every 6 hours for 48 hours after receiving the medicine, and none of the patients had any side effects caused by the medications.

Discussion

This study showed that sequential administration of albumin and furosemide improves the efficacy of this combination by investigating the optimal method of administering albumin and furosemide to children with nephrotic syndrome presenting with edema and hypoalbuminemia. Albumin and furosemide can be prescribed in 2 different ways when patients meet the clinical need for receiving these drugs. One method is the simultaneous administration of albumin and furosemide, mixed before injection. Another method is to administer furosemide after the completion of the albumin infusion. This study helps to determine the optimal method to reduce edema and increase the efficacy of furosemide in patients with nephrotic syndrome. Despite the high frequency of the use of albumin and furosemide in children with nephrotic syndrome, the therapeutic experience of the best method to reduce edema in pediatrics is limited.[15]

This study examined the effect of sex, serum creatinine, and serum albumin concentration on the patient's body weight reduction before and after the intervention. Moreover, in this study, to eliminate a possible influence of albumin infusion duration on weight loss, as discussed in some articles, albumin infusion was done over 1 hour after a complete examination of vital signs by hospital staff and the project manager. Furthermore, there are relatively few studies that have investigated the effects of age and sex on the serum albumin concentration in these patients. Among the studies that have been conducted, the findings are inconsistent. One study reported no difference in serum albumin concentration between sex and age.[16] The data of Manolio et al,[17] which were studied in the age range of 18 to 30 years, did not show any correlation between concentration of albumin and age or sex. All these studies were done in adults, and there was no detailed study on this factor in pediatrics. In our study, a significant relationship was observed between sex and serum albumin, and sex with serum creatinine, and to remove interfering factors, the relationship of each of these factors on weight was examined separately.

Some hypotheses exist for pathophysiological mechanisms of edema in nephrotic syndrome, including volume depletion and overfill. Considering that the cause of edema and the pathophysiology of nephrotic syndrome in children and adults may be different,[18,19] the effectiveness of the administration methods of these drugs (albumin and furosemide) in these 2 groups may also be different. As a result, separate investigations should be conducted for children and adults. Unlike adults, children often have more severe hypoalbuminemia and edema, requiring hospitalization and IV administration of albumin.[20] There are various reasons why albumin is commonly used in children, including decreased serum oncotic pressure due to hypoalbuminemia, resistance to diuretics, and reduced diuretic effectiveness when administered to patients with nephrotic syndrome,[1,21–23] and reluctance to treat patients with diuretics alone due to concerns about dehydration and an increase in the risk of thromboembolism.[17,22,24]

In 2012, Phakdeekitcharoen and Boonyawat[25] compared the effects of furosemide and the combination of albumin and furosemide in 24 adults (66.4 ± 12.8 patient years) with chronic kidney disease and hypoalbuminemia. The administrated dose for furosemide was less than 40 mg. Clinical endpoints measured 6 and 24 hours after administration included urine volume, sodium, potassium, blood pressure, calculated GFR, and the albumin serum concentration. According to the results of their study, albumin combined with furosemide compared with furosemide alone produced a beneficial effect on diuresis and natriuresis in the short term (6 hours). Additionally, the researchers stated that their results support the hypothesis that albumin may assist in delivering furosemide to the site of action and increase renal blood flow in hypoalbuminemia patients.[25]

Some clinical trials have been published on using albumin and furosemide to treat edema in patients with nephrotic syndrome in adults and children to determine whether such a combination is beneficial in these patients.[26] Due to differences in selection criteria, trial design, and clinical endpoints, no definitive recommendation has been made regarding using albumin and furosemide.[27] It seems beneficial to consider the creation of the experiment according to the doses and the administration methods for these 2 drugs. Both albumin and furosemide administration methods have been studied; receiving albumin and furosemide simultaneously or albumin infusion before furosemide. The timing of albumin administration is related to the time of furosemide administration. Albumin shows maximum intravascular volume-increasing effects within 30 to 60 minutes after administration. Based on the work of Na et al,[28] albumin administration before furosemide can facilitate diuresis more effectively than furosemide alone and should be considered as a treatment option in diuretic-resistant patients.[8,28] Furthermore the peak effect of intravenous administration of furosemide is approximately 30 minutes[29] and the peak effectiveness of these 2 drugs can overlap with each other.

According to an article published in 2003 by Elwell et al, which reviewed several studies from 1996 to 2002,[26] furosemide and albumin are sometimes combined simultaneously or separately, depending on

Table 2. T-test Interventions Performed on the Weight Difference Percentage of Patients*

Interventional Groups	Number	Mean	SE	SD	CI (conf. 95%)	Approximate Interval
Simultaneous group	32	0.009333	0.009202	0.035638	−0.0104	0.029069
Sequential group	32	0.048625	0.01193	0.047721	0.023196	0.074054
The 2 groups in total	64	0.029613	0.008289	0.04615	0.012685	0.046541
The difference between the 2 groups		−0.03929	0.01521		−0.0704	−0.00818

* p = 0.0151; degree of freedom = 29; t = −2.5833

the administration technique. The optimal method of administering these 2 drugs is controversy, and after rigorous search, 3 reports were found that furosemide and albumin were mixed before administration.[1,30,31] Interestingly, an investigation compared the efficacy of premixed furosemide and albumin with infusions of these 2 drugs separately but simultaneously into the contralateral forearms of similar subjects. They found no significant difference between these methods.[31] Although mixing the 2 drugs may have no clinical advantage over simultaneous infusion, furosemide stability in a premixed furosemide/albumin mixture has been demonstrated. The combination of 60 mg of furosemide with 50 mL of 25% human albumin solution is chemically stable and free of microbial contamination when protected from light and stored at room temperature for up to 48 hours.[32] The studies described here did not report any side effects associated with this combination. However, these studies were underpowered and were not designed to assess the incidence of rare or unusual adverse reactions.

According to the studies and the results presented, the need for a controlled clinical trial with appropriate samples was felt. To check whether other factors such as sex, concentration of creatinine before the intervention, and concentration of albumin before the intervention affected this response, the effect of each of these factors on weight loss was also analyzed. According to our results of the relationship, these 3 confounding factors could not be investigated in the same model. Therefore, the relationship between these factors and weight loss before and after the intervention was analyzed separately. According to our results, sex, serum creatinine concentration, and the initial serum albumin concentration did not affect the weight loss before and after the intervention or the relationship between the intervention and weight loss (Table 2).

Weight loss is considered a measure of the reduction of edema in patients; therefore, we investigated the difference in weight before and 24 hours after the intervention for both groups receiving albumin simultaneously with furosemide and the group receiving furosemide following albumin infusions. It was demonstrated that children receiving albumin and furosemide sequentially experienced more weight loss and, therefore, more significant edema reduction.

Also, the amount of urinary sodium, which indicates the effectiveness of furosemide in patients, was examined in 18 of these patients (9 patients in each group), and the results demonstrated no significant difference in the amount of urinary sodium in the 2 groups. This negative finding could very well reflect the small sample size, the use of a spot urine sample combined with the random timing of obtaining the spot sample post study drug administration.

No adverse reactions were reported during the study period. This may be related to the short duration of the intervention, and the patients included in the study were indicated to receive albumin and furosemide.

Limitations

Urine spot sodium testing has limitations as an indicator of total sodium output. It can be influenced by factors such as hydration status, urine concentration, and timing of collection. In pediatric patients, particularly younger children, obtaining a reliable sample may be challenging, and variability in urine output can further affect accuracy. Thus, spot urine sodium should be interpreted with caution, especially in pediatric populations.

Conclusion

There was a significant difference between weight loss in the 2 groups that received albumin and furosemide simultaneously or sequentially. Because weight reduction is the most basic clinical parameter in assessing the edema reduction in pediatrics, we employed this metric to assess it in these patients. According to this study it seems that sequential administration of furosemide after infusion of albumin is more effective and sequential injection of these 2 drugs can be the preferred method to reduce edema in pediatric patients with nephrotic syndrome.

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