Original Article

Comparative Trial of Furosemide-Spironolactone Combination and Furosemide-Metolazone Combination in Treating Refractory Edema in Nephrotic Syndrome Patients

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How to cite this article: Gaurav Arya, Shashi Vinod, Akshay Shukla et. al. Comparative Trial of Furosemide-Spironolactone Combination and Furosemide-Metolazone Combination in Treating Refractory Edema in Nephrotic Syndrome Patients. Indian Journal of Public Health Research and Development / Vol. 16 No. 2, April-June 2025.

Abstract

Introduction: Nephrotic syndrome is defined as the presence of nephrotic range proteinuria, hypercholesterolemia, and generalized edema. Proteinuria that is more than 85% albumin is selective proteinuria. Albumin has (-ve) charge, and it is loss of glomerular membrane (-ve) charges could be significant in causing albuminuria.

Objective: Comparison of Furosemide-Spironolactone Combination and Furosemide-Metolazone Combination in Treating Refractory Edema in Nephrotic Syndrome Patients.

Materials and methods: This was a cross-sectional study design of six month from December 2023 to May 2024.

Results: The mean Age of the patients enrolled for the study with the minimum age being 1 year and maximum age being 14 years and the mean age was 5.6 years. It shows that weight loss at day 4 and 5 was significantly higher in group B as compared to group A.

Conclusions: Group B patients having lower mean abdominal girth as compared to group A. Mean Serum electrolyte values like S.Na+, S.K+, S.Ca+ of both the groups were compared and found to be similar thus highlighting that both the combinations had similar effects in the patients with respect to electrolyte abnormalities.

Key words: Nephrotic syndrome, Edema, Furosemide, Spironolactone, Metolazone

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Submission date: June 5, 2024 **Acceptance date**: August 7, 2024 **Published date: March 11, 2025**

Introduction

Nephrotic syndrome (NS) is a common renal disorder with an annual incidence of 1.2 to 16.9 per 100,000children.[1]It is 15 times more common in children than adults.[2]Among children more common male were female with a male to female ratio of 2.6:1.[3] but once adolescence is reached, there is no significant difference between genders.[4]

Nephrotic syndrome is defined as the presence of nephrotic range proteinuria, hypercholesterolemia, and generalized edema. Proteinuria that is more than eighty five percent (85%) albumin is selective proteinuria. Albumin has (-ve) charge, and it is loss of glomerular membrane (-ve) charges could be significant in causing albuminuria. This construct do not permit clear separation of causes of proteinuria, except in minimal change nephropathy, in which proteinuria is selective.[5]

From a therapeutic perspective, nephrotic syndrome may be classified as steroid sensitive, steroid resistant, steroid dependent.[6]Edema, the most important clinical manifestation of nephrotic syndrome. Its pathogenesis is not fully understood and various theories are Underfill theoryand Overfill theory.[7,8]

Infusion of 5% albumin (10-15 ml/kg) or 20% albumin (0.5-1 g/kg) may be used in subjects who does not respond despite two boluses of saline.[9]Very few has been written about the combination of diuretic agents in truly diuretic refractory patients.[10]The prognosis for patients with minimal-change nephropathy is good. Approximately 3% of cases who initially respond to steroids become steroid-resistant.[11]

Both metolazone and spironolactone can be used as add on drugs with loop diuretics like furosemide thus preventing the metabolic complications like hypokalemia. And preventing the development of resistance in cases of refractory edema. There is limited data regarding the comparision of furosemide-spironolactone and furosemide-metolazone combination for treating refractory edema states like nephrotic syndrome in pediatric population. Thus our study aims to compare the efficacy of both the combinations.

Objective: Comparison of Furosemide-Spironolactone Combination and Furosemide-Metolazone Combination in Treating Refractory Edema in Nephrotic Syndrome Patients.

Null hypothesis: There is no difference in between Furosemide-Spironolactone Combination and Furosemide-Metolazone Combination.

Alternative hypothesis: There is difference in between Furosemide-Spironolactone Combination and Furosemide-Metolazone Combination.

Materials and Methods

Study design: We conducted a cross-sectional study to compare the efficacy of oral furosemide-metolazone versus oral furosemide-spironolactone combination therapy in management of edema in nephrotic syndrome. Very few researches mainly on individual drug therapy, has been done.

Place of study: Pediatric ward of Rama Medical College Hospital & Research centre, Kanpur, Uttar Pradesh.

Study Duration: The study period was six month from December 2023to May2024.

Subject selection: Children of age group 6 months to 14 years attending the OPD and IPD in pediatric department with complaint of generalized swelling and decreased urine output were admitted and diagnosed as case of nephrotic syndrome by the following parameter:

1. Bedside urine protein 3+/4+ (significant nephrotic range proteinuria 40mg/m2/24 hour)
2. Hypoalbuminemia (serum albumin <2.5 g/dl)
3. Hyperlipidemia (serum cholesterol >200 mg/dl),

Inclusion criteria:

1. Children diagnosed with nephrotic syndrome according to above mentioned
2. Criteria and not achieving weight loss or diuresis after 2 days of treatment with oral furosemide therapy.
3. Age more than 6 month and less than 14 years.

Exclusion criteria

1. Nephritic syndrome
2. Nephrotic syndrome patient caretakers who refuse to give consent
3. The patients who achieved weight loss or diuresis within 2 days of treatment with oral furosemide therapy.

Sample size: Children admitted in pediatric ward with inclusion criterion during the period of six month (according to the previous six month hospital data of nephrotic syndrome children admission in pediatrics ward data the sample size was 60. During this period maximum numbers of patients are included in the study.

Data Collection: Data including age, gender, residence, height, weight, and blood pressure abdominal girth was recorded. Regular weight recording was done to monitor the decrease or increase of edema. Physical examination was done to detect infections and underlying systemic disorder. This study adds to the current available evidence on comparison of these drugs.

Statistical Analysis

Initially data were entered in MS-excel then transferred it into SPSS 26.0. Descriptive statistics was calculated. T-test was used to compare the mean values and proportions respectively with significance level at $p < 0.05$.

Results

The mean Age of the patients enrolled for the study with the minimum age being 1 year and maximum age being 14 years and the mean age was 5.6 years.

Table 1: Descriptive statistics and distribution of study participants

Characteristics	**N**	**Min.**	**Max.**	**Mean**	**S.D.**	
Age (in years)	60	1.00	14.00	5.61	3.09	
	Group A		**Group B**		**Total**	
Gender	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
N	20	10	16	14	36	24
%	66.7 %	33.3 %	53.3 %	46.7 %	60.0%	40.0%
Age (in years)	5.57	2.81	5.65	3.40	5.61	3.09
Cases	**Number**	**Percentage**	**Number**	**Percentage**	**Number**	**Percentage**
New case	7	23.3%	9	30.0%	16	26.7%
Relapse	23	76.7%	21	70.0%	44	73.3%

The patients were divided into 2 groups with 30 patients in each group. The number of males in Group A and B were 20 and 16 while the number of females being 10 and 14 respectively. The mean Age of group A and B being 5.57 years and 5.65 years respectively. Both the groups had almost equal number of new cases and relapse cases.

Table 2: Comparison between the two groups of study participants

Characteristics	**Group**						**p-value**
	Group A		**Group B**		**Total**		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Age (in years)	5.57	2.81	5.65	3.40	5.61	3.09	0.918
Weight in kgs. at day 1	20.18	6.02	20.03	7.11	19.61	6.54	0.619
Weight in kgs. at day 2	19.71	5.88	19.13	7.21	18.92	6.53	0.806
Weight in kgs. at day 3	19.30	5.90	18.35	6.81	18.32	6.32	0.976
Weight in kgs. at day 4	17.77	5.77	16.08	6.60	17.42	6.15	0.171

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Weight in kgs. at day 5	17.42	5.58	15.64	6.49	17.03	6.01	0.051
SBP in mm hg at day 1	107.67	9.03	104.93	9.82	106.30	9.45	0.266
SBP in mm hg at day 2	100.07	6.49	99.55	6.19	62.32	6.33	0.363
SBP in mm hg at day 3	107.17	8.07	104.33	9.44	105.75	8.82	0.216
SBP in mm hg at day 4	62.67	6.03	60.33	5.98	61.50	6.07	0.138
SBP in mm hg at day 5	105.73	8.10	103.57	8.06	104.65	8.08	0.303
DBP in mm hg at day 1	61.77	6.25	60.07	5.53	60.92	5.91	0.269
DBP in mm hg at day 2	103.87	7.10	102.30	8.04	103.08	7.56	0.427
DBP in mm hg at day 3	60.93	5.53	59.90	5.23	60.42	5.36	0.460
DBP in mm hg at day 4	103.27	6.44	101.87	7.48	102.57	6.96	0.440
DBP in mm hg at day 5	60.77	5.32	59.33	4.44	60.05	4.91	0.262
Abdominal girth in cm at day 1	49.92	4.83	46.10	5.38	48.01	5.42	0.322
Abdominal girth in cm at day 2	49.55	4.91	45.27	5.11	47.41	5.41	0.211
Abdominal girth in cm at day 3	49.07	5.00	45.00	5.03	47.03	5.38	0.237
Abdominal girth in cm at day 4	48.67	4.97	44.70	4.83	46.68	5.25	0.180
Abdominal girth in cm at day 5	48.25	5.00	44.27	4.75	46.26	5.23	0.042

The table 2 describes about the weight loss following the diuretic therapy for 5 days in both the groups. It shows that weight loss at day 4 and 5 was significantly higher in group B as compared to group A (the p-values being 0.17 and 0.05 for day 4 and 5 respectively). Thus it showed that efficacy of frusemide metolazone combination (group B) was more than frusemide spironolactone combination (group A).

The mean systolic and diastolic BP was lower in group B as compared to group A but the results were statistically insignificant. This showed that patients receiving Frusemide-spironolactone(group A) and those receiving frusemide-metolazone combination had almost same SBP and DBP and both the combinations had similar effects in reducing the blood pressure. Mean abdominal girth in both the group A and B the values being lower in group B as compared to group A with the values being statistically significant for day 5, showing that patients in Group B had lower abdominal girth as compared to group A thus indicating better diuretic action of frusemide-metolazone combination as compared to frusemide-spironolactone combination.

Table 3: Distribution of clinical parameters of study subjects

Parameters	**Group**						**p-value**
	Group A		**Group B**		**Total**		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
TLC in /cumm.	308.53	1641.56	8.40	4.07	158.47	1160.79	0.321
LYMPHOCYTES	32.46	4.98	36.15	4.32	34.30	4.99	0.093
POLYMORPHS	53.78	6.12	56.40	6.28	55.09	6.29	0.108
EOSINOPHILS	.75	.34	.66	.25	.71	.30	0.291
S. Cholesterol in mg/dl	300.03	73.07	295.90	52.43	297.97	63.08	0.802
S. Na+ (meq/lt)	139.63	5.18	139.27	4.86	139.45	4.99	0.779
S.K+ (meq/lt)	4.05	.58	4.19	.70	4.12	.64	0.403
S.Ca2+ (meq/lt)	8.51	.89	8.07	.95	8.29	.94	0.073
S. Albumin (g/dl)	2.64	.27	2.69	.30	2.67	.29	0.451
s.urea (mg/dl)	43.82	6.81	44.85	6.21	44.34	6.49	0.544
S. Creatinine (mg/dl)	.75	.25	.83	.23	.79	.24	0.167
pus cells /hpf	4.73	2.75	4.97	2.16	4.85	2.46	0.716

Parameters TLC, DLC, S. cholesterol, S. Electrolytes, S. Albumin, S. Urea, S. Creatinine, Urine Pus cells for both the groups A and B and compares between them for both the Groups. Both the groups were similar in above parameters and the p value was statistically insignificant.

Discussion

The mean Age of group A and B were 5.57 and 5.65 years respectively. The number of new cases and Relapse Cases were almost the same in both the groups . Similar results were seen in other study.[12]

Weight loss following diuretic therapy in both the groups. It showed that group B had higher mean weight loss as compared to group A, especially on days 4 and 5 of the diuretic therapy. Thus, showing that frusemide metolazone combination had better diuretic action than frusemide spironolactone. SimilarlyGhose et al. showed frusemide-metolazone combination better, Paton et al. also showed that metolazone higher efficacy than other thiazide diuretics. [13,14]

Group B had more urine output as compared to Group A particularly in days 4 and 5 of therapy. Marone et al. showed that addition of metolazone to frusemide increased the urine output in patients with refractory edema states.[15]Oimomi et al. also showed that combination diuretic therapy has better diuretic action as compared to single diuretic. The systolic and diastolic blood pressure was reduced in both the groups following diuretic therapy but there was no significant difference in blood pressure in both groups.[16] Paton et al. also showed that metolazone reduces blood pressure in patients receiving it apart from diuretic action.[13]Sica et al. also showed that metolazone, frusemide and spironolactone all have similar effects in reducing blood pressure in patients receiving them.[17]

The Abdominal Girth of both the 2 groups i.e. frusemide-spironolactone group(group A) and frusemide-metolazone group(group B) with group B having lower mean abdominal girth as compared to group A. Similarly Salahuddin M et al.also showed that metolazone-frusemide combination was slightly better than frusemide-spironolactone combination.[18] Cachero SD et al. also stated that addition of metolazone to frusemide increases dieresis in cases with refractory edema.[19] The mean duration of hospital stay was similar in both the groups and frusemide–metolazone combination didn't reduce the duration of hospital stay when compared with the frusemide-spironolactone group.

Conclusion

This study helps in developing protocols for treatment of refractory edema cases in nephrotic syndrome for clinicians improving patient care, prognosis and outcome. Group B patients having lower mean abdominal girth as compared to group A. Mean Serum electrolyte values like S.Na+, S.K+, S.Ca+ of both the groups were compared and found to be similar thus highlighting that both the combinations had similar effects in the patients with respect to electrolyte abnormalities.This study paves way for clinical trials of other combinations for treatment of refractory edema cases in nephrotic syndrome.

Acknowledgement: Weare thankful to healthcare workers of Rama Medical College Hospital & Research centre, Kanpur.

Ethical Clearance: Taken from ethical committee of Rama Medical College Hospital & Research centre,RMCHRC/Ethics/2023/3157-A

Source of Funding: None

Conflict of Interest: NIL

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