RESEARCH ARTICLE

A Study of Drug Utilization Pattern in Pediatric Patients of Nephrotic Syndrome at a Tertiary Care Teaching Hospital

Aniruddha Prajapati*, Chandresh Dumatar, Chetna Desai

Department of Pharmacology, B.J. Medical College, Gujarat University, Ahmedabad, Gujarat, India

ABSTRACT

Introduction: Nephrotic Syndrome (NS) is the most common glomerular disorder of childhood with significant morbidity and mortality. As data regarding drugs utilization in various types of NS in children are scarce in India, study was conducted to evaluate drug utilization pattern for pediatric patients of various types of NS at a tertiary care teaching hospital.

Methods: This cross-sectional, observational study was conducted at Department of Paediatrics, Civil Hospital, and Ahmedabad over a period of 24 months. All pediatric patients of NS admitted at pediatric ward who fulfil the inclusion criteria were enrolled. Demographic details, disease characteristics, details of drug treatment were recorded in a pretested Case Record Form (CRF).

Results: Data of 84 patients were analyzed. Male to female ratio of 2.23:1 with the maximum incidence was in the age group of 4-6 years (58.3%). The mean age of the patients was 6.3 ± 2.4 years. Most common clinical presentation was periocular oedema followed by facial puffiness and pedal oedema. Supplementary drugs (multivitamin, iron-folic acid, calcium, zinc) (97.6% patients) were most commonly prescribed drugs followed by antimicrobials (85% patients) and steroids (79% patients). 3rd generation cephalosporin were most common prescribed antimicrobials. Immune modulators used were tacrolimus and cyclophosphamide in frequent relapsing and steroid resistant NS.

Conclusion: This study showed that in this hospital, majority of patients were prescribed steroids along with other antimicrobials. This prescribing pattern seems appropriate as per recent guidelines of KDIGO.

Keywords: Paediatric, Nephrotic syndrome, Drug utilization study, Cyclosporine, Tertiary care

Correspondence:

Aniruddha Prajapati, Department of Pharmacology, B.J. Medical College, Gujarat University, Ahmedabad, Gujarat, India, Tel: 923012222861; E-mail: ani8491prajapati@gmail.com

INTRODUCTION

Nephrotic Syndrome (NS) was known since days of the "Hippocrates". He first observed that when bubbles settle on the surface of urine, they indicate the disease of the kidneys. Richard Bright was first to put altogether the triad of generalized oedema, proteinuria, and kidney disease, as presenting features of nephrotic syndrome [1]. NS is a clinical syndrome defined by massive proteinuria responsible for hypoalbuminemia, with resulting hyperlipidaemia, oedema, and various complications. It is caused by increased permeability through the damaged basement membrane in the renal glomerulus that may be primary with a disease-specific to the kidneys or secondary to congenital infections, diabetes, systemic lupus erythematosus, neoplasia, or certain drug use. The estimated annual incidence of NS in children is two to seven new cases per 100,000 children. There is epidemiological evidence of a higher incidence of nephrotic syndrome in children from South Asia [2].

The classic NS presentation is oedema. In the early phase, it is located in the face in the morning on waking with puffiness of the eyelids. Without treatment, they become more pronounced, diffuse and lead to anasarca with ascites, hydrocele or pleural effusion, may also be revealed by a complication such as hypovolemia, infection (pneumonia and peritonitis due to Streptococcus pneumoniae), deep-vein or arterial thromboses, and pulmonary embolism [3].

Earlier, mortality rates due to NS in children was high, as dietary modification and law salt diet with some weak mercurial diuretics of little action were only provision for treatment. But availability of corticosteroid and antibiotics in 20th century has changed treatment outcome and prognosis of the disease. Since the introduction of corticosteroids, the overall mortality of NS has decreased dramatically from over 50% to approximately 2%-5%. Despite the improvement in survival, NS is usually a chronic, relapsing disease and most patients experience some degree of morbidity [4].

There are certain challenges even with corticosteroid such as development of steroid resistance, steroid dependence and complications due to side effects of corticosteroids particularly in growing children. To encounter this problem, various steroid-sparing agents such as cyclophosphamide, cyclosporine, levamisole, mycophenolate mofetil, rituximab etc. have been successfully used particularly in relapsing and steroid resistance cases. Despite having this treatment, rarely, some patients may face renal failure and require renal transplant as last option [5]. As data regarding drugs utilization in various types of NS in children are scarce, study was conducted to evaluate drug utilization pattern for paediatric patients of various types of NS at a tertiary care teaching hospital.

METHODOLOGY

Study design

It was a cross sectional, observational study carried out over a period of 24 months from September 2019 to August 2021.

Ethical approval

The study protocol was approved by Institutional Ethics Committee (IEC) of Civil Hospital, Ahmedabad of B.J. Medical College and Civil Hospital, Ahmedabad after submission of protocol of the study (EC/Approval/40/15).

Setting and participants

Study was conducted at B.J. Medical College and Civil Hospital, Ahmedabad. All pediatric patients admitted at pediatric ward with age of 1-12 years who have been diagnosed with NS and were willing to sign written informed consent and/or assent form for the study were included.

Data collection and management

Patients were enrolled in the study after obtaining written informed consent and assent (if patient is above 7 years of age), which was translated in vernacular language (Gujarati and Hindi). Demographic details, disease characteristics, details of drug treatment were recorded in a pretested Case Record Form (CRF).

Received: 20-Apr-2022, Manuscript No. Jbclinphar-22-61279; **Editor Assigned:** 22-Apr-2022, Pre QC No. Jbclinphar-22-61279 (PQ); **Reviewed:** 12-May-2022, QC No. Jbclinphar-22-61279; **Revised:** 23-May-2022, Manuscript No. Jbclinphar-22-61279 (R); **Published:** 01-Jun-2022. DOI: 10.37532/0976-0113.13(3).163.

Cite this article as: Prajapati A, Dumatar C, Desai C. A Study of Drug Utilization Pattern in Pediatric Patients of Nephrotic Syndrome at a Tertiary Care Teaching Hospital. J Basic Clin Pharma 2022;13(3):163-166.

RESULTS

A total of 84 patients of paediatric NS were enrolled over 24 months period and analysed according to following characteristics:

Demographic details

NS was more common in male with male to female ratio of 2.23:1 with the maximum incidence was in the age group of 4-6 years (58.3%). Age wise distribution of study population is described in Table 1. The mean age of the patients was 6.3 ± 2.4 years. Data showed that 66.9 % patients were from rural area and 33.1 % patients were from urban area. 85.7% patients were having history of hospital delivery and 9.6% patients were having history of home delivery whereas birth histories of 4.7% patients were not known to their relative. 80.9% patients were born at full term whereas 14.3% patients were born preterm.

Table 1: Age wise distribution of patients (n=84).

Age group	Total No. of patients (n=84)	Male (n=58)	Female (n=26)
< 1 year (Infant)	1 (1.2%)	1	-
1-3 years (Toddler)	20 (2.4%)	12	8
4-6 years (Pre-school)	50 (58.3%)	36	14
7-12 years (School-age)	13 (16.7%)	9	4

Out of 84 patients of NS, immunization histories of 4 patients were unknown. Among these 80 patients, 2 patients were unimmunized (child of 12-23 months of age who has not received DPT3), 12 patients were partially immunized (child who had missed any vaccine to be given under NIS till one year of age) and 66 patients were fully immunized respective to their age as per the national immunization schedule.

Clinical presentation and diagnosis of the patients

Out of 84 patients, 28 patients presented with complain of peri-ocular oedema followed by co-presentation of facial puffiness with pedal oedema in 18 patients then facial puffiness in 14 patients and pedal oedema in 12 patients. 8 patients had peri-ocular oedema with pedal oedema as chief complain. Only 2 patients were having chief complain of anasarca and rest 2 patients had other complains such as respiratory tract infection and urinary tract infection.

All patients from present study showed presence of albumin in their urine sample which confirmed diagnosis of nephrotic syndrome. 28.5% patient were having anemia in present study which imply burden of malnutrition in study population. 16.7% patient was having leucocytosis in blood reports which suggest presence of infection in patients. 28.6% patient had hypoproteinaemia, 11.9% patient had deranged serum level of sodium, potassium and 4.7% patient had hypercholesterolemia which correlates with pathophysiology of nephrotic syndrome.

Treatment of nephrotic syndrome in paediatric patients

Various drugs used for treatment are analysed in Table 2. The patients diagnosed with SSNS were prescribed prednisolone at the dose of 2 mg/kg/day as standard therapy. Among SDNS patients, 84.6% were treated with corticosteroid as main therapy, 11.5% had received levamisole and tacrolimus as steroid sparing agents while only 3.9% had received concomitant therapy of corticosteroid and levamisole. Out of 22 patients diagnosed with FRNS, 77.7% had received corticosteroid as primary treatment and 22.3% were given concomitant therapy of corticosteroid with immunomodulatory (mycophenolate mofetil and levamisole). In present study, 2 patients were diagnosed with SRNS out of which, 1 patient was given tacrolimus and other was given cyclophosphamide.

Table 2: Analysis of treatment in different types of NS.

Drug Groups	No. of Patients received treatment			
	SSNS* (n=34)	SDNS* (n=26)	FRNS* (n=22)	SRNS* (n=2)
Prednisolone	34	23	22	-
Antimicrobial	32	20	17	3
Supplementation	33	25	22	2
Diuretics	4	12	18	2
Antihypertensive	1	2	3	2
Immunomodulators	-	4	5	2
Antiepileptic	1	-	2	-
Hypolipidemic	-	1	1	-

Note: *SSNS: Steroid Sensitive NS, *SDNS: Steroid Dependent NS, *FRNS: Frequent Relapsing NS, *SRNS: Steroid Resistant NS

Drugs used for supplementation such as multivitamin, zinc, iron, folic acid, calcium were prescribed in 97.6% patients. Antimicrobials were prescribed in 85% patients in which most commonly used antimicrobials were 3rd generation cephalosporin's in 52.7% patients, amoxicillin+clavulanic acid in 19.4% patients, metronidazole in 8.3% patients, albendazole in 6.9% patients, piperacillin+tazobactam in 5.5% patients, levofloxacin and vancomycin, each in 2.8% patients and meropenem in 1.4% patients. Among these, 80% of antimicrobials were administered *via* parenteral route while only 20% of antimicrobials were given by oral route.

Diuretics were prescribed in 42.8% patients such as furosemide, metolazone and combination of furosemide and spironolactone (lasilactone). Antipyretic agent (paracetamol) was given in 51.2% patients and antiemetic agents (ondansetron and domperidone) were given in 21.4% patients. Antihypertensive agents (enalapril and amlodipine) were used in 9.5% patients and antiepileptic (valproic acid) was used in 3.6% patients.

4.7% patients were given albumin, dextromethorphan and antihistamines each. 2.4% patients were treated with atorvastatin and dicyclomine each. One patient was a known case of Eisenmenger syndrome so treatment of sildenafil and digoxin for the condition was given. The analysis of prescription according to WHO core prescribing indicators was described in Table 3.

Table 3: Analysis of prescriptions as per WHO core prescribing indicators.

Prescribing indicator	Value
Total number of prescriptions	84
Total number of prescribed drugs	477
Average number of drugs prescribed per prescription	5.67
Total number of drugs prescribed by systemic route	162
Total number of drugs prescribed by oral route	315

DISCUSSION

NS is a chronic kidney disease that is relatively common in children with higher incidence in Asian, African-American and Arab children. In India the incidence is 90-100/million population [2]. Without treatment, NS in children is associated with a high risk of death, most commonly from infections [6]. Various findings from present study are discussed here.

Demographic details

The results of present study showed that the mean age of the study population (n=84) was 6.3 ± 2.4 years with male to female ratio of 2.23:1. Out of these 84 patients, maximum number of patients belonged to 4-6 years of age group (n=50). These findings correlate with results of one study conducted at Kerala, in which, mean age of the patients (n=81) was 7.6 ± 3.8 years with maximum no. of patients belonged to

5-10 years of age [7]. These finding also match up with the results of a study conducted at Thiruvananthapuram which showed that prevalence is high in males 62.1% [8].

It is advisable to have vaccination against pneumococcal, influenza and varicella infection as per KDIGO [12]. In our study, 2.5% were unimmunized and 15.3% were partially immunized. So specific attention needs to be given to immunization in children suffering from NS.

Clinical presentation and diagnosis of the patients

Clinical presentation of NS in various studies was compared in Table 4. Our study showed anemia (28.5%), hypo-proteinemia (28.5%), leukocytosis (16.7%), hyperbilirubinemia (11.9%), raised serum sodium (7.1%) and potassium levels (4.7%), raised serum level of urea and creatinine (5.6%) and hypercholesterolemia (4.7%) in patients of pediatric NS. Similar findings were reported in a study done in Pakistan (n=176). It showed hypoproteinemia (4.53 ± 0.81 g/dl), hypoalbuminemia (2.0 ± 0.58 g/dl), hypercholesterolemia (369.93 ± 114 mg/dl) and nephrotic range proteinuria [9]. So, hyperlipidemia in NS is not related to intake of exogeneous fat but it shows inverse relationship with albumin level, when plasma albumin level falls, free form of fatty acids which remain bound with albumin would rise and result into hypercholesterolemia.

Table 4: Comparison of clinical presentation of NS in various studies.

Present study (n=84)	Study conducted by K. N. Moorani, 2019 [9] (n=176)	Study conducted by K. S. Sahana, 2014 [10] (n=47)
Peri-ocular oedema + facial puffiness 33.3%,	Oedema 88%	Facial puffiness + swelling of limbs 76%,
Pedal oedema 21.4%,	Hypertension 9.2%	Abdominal distension 21%,
Facial puffiness in 16.7%,	Gross haematuria 2.8%	Genital swelling 3%
Pedal oedema in 14.3%,	-	-
Peri-ocular oedema + pedal oedema 9.5%,	-	-
Anasarca 2.4%,	-	-
Systemic infection 2.4%	-	-

Treatment of nephrotic syndrome in pediatric patients

There are various guidelines for treatment of pediatric nephrotic syndrome among these, KDIGO guidelines are widely acceptable as it is governed by an international board and is managed by the National Kidney Foundation of the United States (KDIGO, 2012).

New onset NS (SSNS): As per KDIGO guidelines, the standard dosing regimen for the initial treatment of nephrotic syndrome is daily oral prednisone/prednisolone 60 mg/m2 /day or 2 mg/kg/day (maximum 60 mg/day) for four or six weeks [12]. In present study of 84 patients, there were 34 patients of new onset NS which were given prednisolone at the dose of 2 mg/kg/day as standard therapy. This is in conformance with recent treatment guidelines of KDIGO. Corticosteroid was prescribed in form of tablet prednisolone as per weight of the child in all the 34 patients of SSNS.

SDNS and FRNS: For children with frequently-relapsing nephrotic who develop serious corticosteroid-related adverse effects and for all children with steroid-dependent nephrotic syndrome, KDIGO recommend that corticosteroid-sparing agents to be prescribed, rather than no treatment or continuation with corticosteroid treatment alone. Patients should ideally be in remission with corticosteroids prior to the initiation of steroid-sparing agents such as levamisole, azathioprine, cyclosporin, MMF (mycophenolate mofetil), rituximab, or CNIs (calcineurin inhibitors such as cyclophosphamide, tacrolimus). Cyclophosphamide and levamisole may be preferable steroid sparing therapies in frequently-relapsing nephrotic syndrome. MMF, rituximab, cyclophosphamide, and CNIs may be preferable steroid-sparing therapies in children with steroid-dependent nephrotic syndrome [12]. In present study of 84 patients, it is observed that 26 were diagnosed with SDNS. Out of these 26 patients, 22 patients (84.6%) were treated with corticosteroid as main therapy, 3 patients (11.5%) had received immunomodulatory as steroid sparing agents while only 1 patient (3.9%) had received concomitant therapy of corticosteroid and immunomodulatory. Our study had also included 22 patients diagnosed with FRNS. Out of these, 17 patients (77.7%) had received corticosteroid has primary treatment and 5 patients (22.3%) were given concomitant therapy of corticosteroid with immunomodulatory.

SRNS: KDIGO recommend using cyclosporine or tacrolimus as initial therapy for children with steroid-resistant nephrotic syndrome [12]. In present study, 2 patients were diagnosed with SRNS among which 1 patient was given tacrolimus and other had received cyclophosphamide as main treatment.

Usage of other drugs: In present study, most commonly prescribed antimicrobials were 3rd generation cephalosporin's (52.7%), amoxicillin+clavulanic acid (19.4%), metronidazole (8.3%), albendazole (6.9%), piperacillin+tazobactam (5.5), levofloxacin (2.8%), vancomycin (2.8%) and meropenem (1.4%). These findings are consistent with that of a study conducted at Kerala which showed that cephalosporin's were the most commonly used antibiotics (47.8%), mostly third and fourth generation cephalosporin's were used, followed by combination of amoxicillin with clavulanic acid (39.1%) and Azithromycin (13%). As paediatric patients of NS are more prone to get infection due to reduced serum concentration of immunoglobulin, impaired ability to make specific antibodies, decreased levels of alternative complement pathway and immunosuppressive treatment, use of anti-microbial agents are necessary to reduce morbidity and mortality among children suffering from NS [11].

Among diuretics, drugs prescribed in our study were furosemide (61.1%), metolazone (22.2%) and combination of furosemide and spironolactone (16.7%). These result correlate with findings of a study conducted in Kerala in which combination of frusemide and spironolactone (76.9%) were frequently prescribed, followed by frusemide (23.1%). These studies draw out a conclusion that diuretic therapy is beneficial, particularly in children with symptomatic oedema.

All patients of our study had received supplementary drugs such as multivitamin (41.2%), calcium (20.6%) and combination of iron+folic acid (19.2%), folic acid (10.8%), vitamin D (5.9%) and zinc (2.3%). A study conducted at Kerala, 2020 also drew the same inference by having treatment with vitamin D in 6.3% patients and calcium in 12.3% patients. As malnutrition is very common among paediatric population, NS itself can cause malnutrition by causing proteinuria and treatment with corticosteroids and immunomodulatory may result into growth impairment of a child by depleting calcium level from body, provision of multivitamins are very necessary along with standard treatment of the disease.

In our study, antihypertensive used were enalapril (5.6%) and amlodipine (3.6%). These findings are different from a study carried out at Kerala which showed that losartan (14.8%) followed by enalapril (13.6%) and combination of amlodipine with nifedipine (7.4%) were commonly prescribed antihypertensive [7]. Some contributing factors are known to cause acute and episodic elevations in blood pressure in a child suffering from NS such as fluid shifts, sodium retention, and medication side effects.

Hyperlipidaemia was treated rarely with lipid lowering agents because the symptoms decrease according to remission. Only patients with

persistent high cholesterol levels were treated. In present study, atorvastatin was given to 2 patients (2.4%). Similar results were obtained in a study done at Kerala in which atorvastatin was given in 4 patients (4.2%) [7].

Strength and limitations of present study: Present study had included patients diagnosed with all clinical types of NS (SSNS, SDNS, FRNS, SRNS) at Civil Hospital, Ahmedabad which gave an idea about burden of paediatric NS in Gujarat. The treatment given in different clinical types of NS was compared with guidelines of KDIGO, 2012. Present study showed that our institution adhered with standard treatment guidelines. We had also analysed study population as per their growth parameters and immunization status and the conclusion was reached that special attention is required for nutrition and vaccination in children suffering from nephrotic syndrome.

In concern with the limitations of present study, outcome of the drug therapy in study population was not studied as it was a cross-sectional study. Adverse drug reactions were not recorded. Renal biopsy was not performed at our hospital. So, patients who were diagnosed to develop chronic kidney diseases were transferred to Institute of Kidney Disease and Research Centre, Ahmedabad. These patients were not included in our study.

CONCLUSION

It can be concluded from present study that nephrotic syndrome is more common in male children at age of 4-6 years and presented with oedema and facial puffiness as major complain. Diagnosis of nephrotic syndrome was made according to definition given by KDIGO. Drug treatment provided in different clinical types of nephrotic syndrome was in concurrence with guidelines of KDIGO, 2012 particularly for using corticosteroids and immunomodulatory. Present study showed that, special attention needs to be given to the children suffering from nephrotic syndrome with regard to their nutrition and immunization status.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SOURCE OF FUNDING

Nil

ACKNOWLEDGEMENTS

We would like to thank Dr. Jolly Vaishnav, Head of the Department of Paediatrics who gave the permission to conduct this study in Paediatrics department.

REFERENCES

1. Cameron JS., Trompeter RS, Hicks J et al. Long-term outcome for children with minimal-change nephrotic syndrome. The Lancet. 1985; 325(8425):368-370.
2. McCloskey O, Maxwell AP. Diagnosis and management of nephrotic syndrome. The Practitioner. 2017;261(1801):11-15.
3. Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. The Lancet, 2018;392(10141):61-74.
4. Katsuno T, Masuda T, Saito S et al. Therapeutic efficacy of rituximab for the management of adult-onset steroid-dependent nephrotic syndrome: A retrospective study. Clin Exp Nephrol. 2019;23(2):207-214.
5. Xia ZK. Interpretation of guidelines for the diagnosis and treatment of steroid resistant nephrotic syndrome. Chin j pediatr. 2017; 55(11): 810-812.
6. Greenbaum LA, Benndorf R, Smoyer WE. Childhood nephrotic syndrome—current and future therapies. Nat Rev Nephrol. 2012; 8(8):445-458.
7. Ansam, Priya Nair S, Jayakrishnan SS et al. World Journal of Pharmaceutical and Medical Research. 2020;6(9):141-149.
8. Kiron SS, Saritha M, Uthup S et al. A prospective study of management of nephrotic syndrome in pediatrics in a tertiary care teaching hospital in Thiruvananthapuram Inventi Journals. 2010.
9. Moorani KN, Hotchandani HM, Zubair AM et al. and Veerwani N.R. Immunosuppressive therapy in children with primary nephrotic syndrome: single center experience, Karachi, Pakistan. BMC nephrology, 2019;20(1):1-8.
10. Moorani KN, Hotchandani HM, Zubair AM et al. Immunosuppressive therapy in children with primary nephrotic syndrome: single center experience, Karachi, Pakistan. BMC Nephrol. 2019;20(1):1-8.
11. Sahana KS. Clinical profile of nephrotic syndrome in children. J Evol Med Dent Sci. 2014;3(4): 863-871.
12. Anderson DC, York TL, Rose G et al. Assessment of serum factor B, serum opsonins, granulocyte chemotaxis, and infection in nephrotic syndrome of children. Journal of Infectious Diseases. 1979;140(1):1-11.
13. Lombel RM, Gipson DS, Hodson EM. Treatment of steroid-sensitive nephrotic syndrome: new guidelines from KDIGO. Pediatric nephrology. 2013 Mar;28(3):415-26.