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FREQUENCY OF COMPLICATIONS AFTER PROLONGED USE OF STEROIDS IN PATIENTS WITH NEPHROTIC SYNDROME

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ABSTRACT

Introduction: Nephrotic syndrome is one of the most common glomerular diseases that affect pediatric age group. Corticosteroid is first line treatment in patients of nephrotic syndrome but they are associated with wide variety of side effects. Children with nephrotic syndrome can develop growth retardation due to malnutrition caused by prolonged use of corticosteroids. This study described the burden of major side effects as well as data for rationale use of alternative treatment modalities instead of prolonged use of steroids. **Objective:** To determine the frequency of various complications after prolonged use of steroids in pediatric patients with nephrotic syndrome. **Study Design:** Descriptive cross sectional study. **Place & Duration of Study:** Department of Pediatrics, Nishtar Hospital, Multan over a period of six months i.e. March 2019 to September 2019. **Subjects and Methods:** A total of 100 patients of nephrotic syndrome taking steroids for more than six months were enrolled in study. All patients underwent detailed medical history and physical examination followed by required investigations. Data were analyzed in SPSS version 20. Age & disease duration was presented as mean and standard deviation while complications of the treatment were presented as frequency and percentage. **Results:** The mean age of children was 7.14±3.34years. Among 100 patients, 66 were male and 34 were female. Regarding complications, 8 patients had pancreatitis, 11 had liver disease, 68 had Cushing like features, 35 patients had posterior subcapsular cataract, 7 patients had raised intraocular pressure, 19 patients had osteoporosis, and 46 patients had hypertension. **Conclusion:** Most common complication of long term steroids use in children was Cushing features followed by hypertension and posterior subcapsular cataract.

KEYWORDS: Nephrotic syndrome, long term steroids use, complications.

INTRODUCTION

Nephrotic syndrome (NS) is classically defined as massive proteinuria (>40 mg/m2/hr.), hypoalbuminemia (<2.5 g/dL), generalized edema, and hyperlipidemia in most cases).[1] It is one of the most common glomerular diseases that affect children. Nephrotic syndrome has many causes, including primary kidney diseases such as minimal-change disease, focal segmental glomerulosclerosis, and membranous glomerulonephritis. Nephrotic syndrome can also result from systemic diseases that affect other organs in addition to the kidneys, such as diabetes, amyloidosis, and lupus erythematosus. Nephrotic syndrome may affect adults and children of both sexes and of any race. It may occur in typical form, or in association with nephritic syndrome. The latter term connotes glomerular inflammation, with hematuria and impaired kidney function. Renal histology reveals the presence of minimal change nephrotic syndrome in more than 80% of these patients.[2] Estimates on the annual incidence of nephrotic syndrome range from 2-7 per 100,000 children, and prevalence from 12-16 per 100,000. There is epidemiological evidence of a higher incidence of nephrotic syndrome in children from south Asia. The condition is primary (idiopathic) in 95 per cent cases. An underlying disorder that might be identified in less than 5 per cent cases, includes systemic lupus erythematosus, Henoch Schonlein purpura, amyloidosis and infection with HIV, parvovirus B19 and hepatitis B and C viruses1, 3, 4. More than 80 per cent patients with nephrotic syndrome show minimal change disease (MCD) characterized by normal renal histology on light microscopy. The remaining is contributed by focal segmental glomerulosclerosis (FSGS) and mesangioproliferative glomerulonephritis (MesPGN). MCD and FSGS are often considered to represent the same pathophysiological process. Membranoproliferative glomerulonephritis and membranous nephropathy are uncommon conditions in childhood.

The minimal change nephrotic syndrome (NS) usually responds to corticosteroids and proteinuria disappears in 90% of all steroid responsive cases within 21 days. Prednisone is an immunosuppressant used in treatment of

autoimmune disorders. This agent may decrease inflammation by reversing increased capillary permeability and suppressing polymorph nuclear neutrophil (PMN) activity. It may be administered as a single dose in the morning or as divided doses; once-daily dosing is equally effective and greatly improves compliance. A standard regimen for the initial attack is now used almost world-wide, consisting of 4 weeks continuous prednisone (60 mg/m 2 per day) and 4 weeks of intermittent prednisone (40 mg/m 2 on 3 out of 7 days) or alternate day prednisone (40 mg/m 2 per 48 h). The International Study of Kidney Disease in Children (ISKDC) showed that 55% of children relapsed after the initial prednisone regimen within 6 months and that 34% of patients had two or more relapses during the first 6 months. The controlled multicenter study of the Arbeitsgemein schaft suggested that the initial immunosuppressive attack determines the length of benefit from corticosteroid treatment in steroid responsive NS and that an attempt to increase the initial steroid treatment might be justified. Corticosteroids (CS) have reduced the NS mortality rate to around 3%.[3] However, CS have well-recognized potentially serious adverse effects such as cushinoid features, obesity, growth retardation, hypertension, osteoporosis, cataracts, impaired glucose metabolism, dyslipidemia, emotional deprivation, behavioral changes, and avascular necrosis of the femoral head.[4] The best way to avoid complications of CS therapy is to stop unnecessarily extended courses of therapy with high doses of CS.[5] About 12-22% of the children with NS are steroid resistant due to long term use of CS and 70% experience an episode of relapse.[6]

It is noted that there is no single study available at local level, which demonstrates the frequency of various complications after prolonged steroid use in patients with nephrotic syndrome. All available studies have described one or two complications. This cross sectional analysis was designed to describe the burden of major side effects altogether as well as to provide data for rationale use of alternative treatment modalities for patients of nephrotic syndrome instead of prolonged use of steroids to bring breakthrough in better management of nephrotic syndrome and patient's relief from treatment complications.

OBJECTIVE: To determine the frequency of various complications after prolonged use of steroids in pediatric patients with nephrotic syndrome.

PATIENTS AND METHODS

This was a descriptive cross sectional study conducted over a period of six months from March 2019 to September 2019 in department of pediatrics, Nishtar Hospital, Multan. Sample size of 100 cases was calculated with 95% confidence level, 6% margin of error and taking least expected percentage of hypertension i.e. 10% with prolonged treatment of steroid in children presenting with nephrotic syndrome. Non probability consecutive sampling technique was used. Children of age 1 year to 14 years of either gender who had already used steroid for nephrotic syndrome more than 6 months coming for follow-up were included in study while patients who had used treatment modalities other than steroids (on medical record) or children who defaulted follow ups were excluded from the study.

Data Collection & Analysis

After approval from hospital ethical committee & informed written consent from the patient/ guardian of the patients, 100 cases were enrolled in the study from pediatric department of Nishtar Hospital, Multan. Demographic information including name, age, gender, duration of steroid therapy and contact were obtained. Then patients were screened for complications like gastrointestinal complications (through USG and EGD if required), Cushinoid features and hypertension (by clinical examination), ocular problems (by clinical examination and fundoscopy and tonometry) and osteoporosis by using DXA scan and clinical examination (as per operational definition). All this information was recorded by using specially designed proforma. The diagnostic criteria of Nephrotic syndrome considered as edema, proteinuria >3.5gper day or urinary protein/creatinine ratio >2, and serum albumin <2.5 g/dl and hyperlipidemia (cholesterol> 200mg/dl) while prolonged use of steroid like prednisolone does of 2mg/kg per day or 60 mg/m2/day initially for 46 weeks followed by alternate day prednisolone (starting at 40 mg per m2 qod or 1.5 mg/kg qod) for a period ranging from 8 weeks to 5 months, with tapering of dose for >6months. Considering complications, gastrointestinal problems like pancreatitis (inflammation on ultrasonography and amylase level more than 200 mg/dl) or liver abnormality on USG (Inflammation/fibrosis), ocular problem like posterior sub capsular cataract (diagnosed by opacity on slit lamp examination, fundoscopy and visual acuity) and raised intra ocular pressure >21 mm Hg (using tonometry), Cushinoid features like facial puffiness and weight gain (>5kg in one month), Osteoporosis was labelled if T-score ≤ -2.5 on DXA and Hypertension if blood pressure more than 95^{th} percentile for age and gender with sphygmomanometer. Data were entered and analyzed through SPSS version 20.

Quantitative variables like age were presented as mean and standard deviation. Qualitative variable like gender & complications like gastrointestinal complications, cushinoid features, hypertension, ocular problems and osteoporosis were presented as frequency and percentage.

RESULTS

Table 1: Characteristics of children.

Total number of patients	100
Age (years)	7.14±3.34
Male	66
Female	34
Duration of Nephrotic syndrome (months)	12.32±3.77

In our study, 100 children were enrolled with the mean age of 7.14±3.34 years. There were 66 males and 34 females. The mean duration of nephrotic syndrome was 12.32±3.77 months. (Table 1). The most frequent complication was cushinoid features in 68 cases, hypertension was present in 46 cases, posterior subcapsular cataract in 35 cases, osteoporosis 19 cases, liver disease 11 cases, pancreatitis 8 cases and raised intraocular pressure 7 cases. (Fig 1).

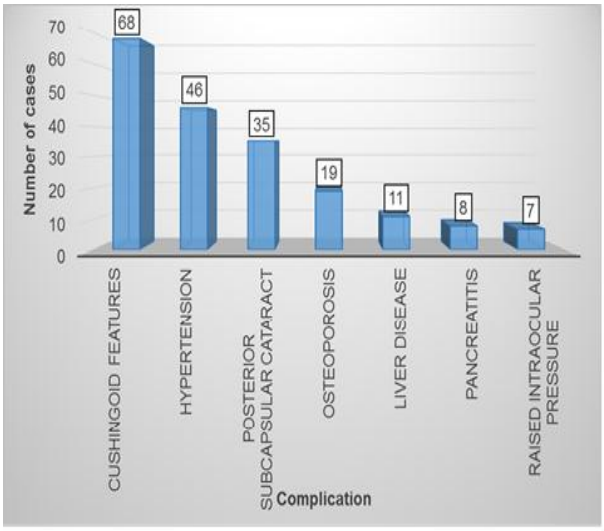

Fig. 1: Complications of prolonged steroid use.

DISCUSSION

In nephrotic syndrome (NS) protein leaks from the blood to the urine through the glomeruli resulting in hypoproteinaemia and generalized edema. While the majority of children with NS respond to corticosteroids, 70% experience a relapsing course. Corticosteroids have reduced the mortality rate to around 3%. However corticosteroids have well recognized potentially serious adverse effects such as obesity, poor growth, hypertension, diabetes mellitus and osteoporosis. This cross sectional analysis precisely presented the list of various complications associated with use of long time steroid use in pediatric patients with nephrotic syndrome. The most common complication remained is cushinoid features i.e. 68% which is quite comparable to reported data of 60% at three months and 70% at the end of six months duration of steroid therapy.[7] Hypertension is found in 46 % while in other studies it ranges from 10 to 40%.[8] The percentage is higher in our population as compared to other studies. It can be possibly attributed to unhygienic food and no proper guidance about balanced diet. A study was conducted in India to estimate the burden of ocular complications like posterior sub capsular cataract and raised intra ocular pressure in children with prolonged use of steroid as treatment of nephrotic syndrome. The proportion of children with posterior sub capsular cataract was 26.8% and raised intra ocular pressure was 10.97%.[9]

One study has reported that after prolonged treatment of nephrotic syndrome with prednisolone (steroid), the relapse rate is lower i.e. 10.4% (n=48 cases) only and it was suggested that prolonged use of steroid for treatment of nephrotic syndrome is beneficial and cause less relapse.[10] But some other studies reported that the frequency of relapse after prolonged use of prednisolone (steroid) was ranged between 31.5-40.9% (n=24-55 cases) which showed that the use of prednisolone (steroid) for prolonged time may not be beneficial more than standard therapy.[11-13] In an autopsy series published by Oppenhiemer, 40% of children with nephrotic syndrome on steroid therapy were found to have evidence of pancreatitis.[14] Cushingoid abnormalities in 88 patients initiating long term systemic corticosteroid therapy found the cumulative incidence rates of these abnormalities to be 61% at 3 months and almost 70% at 12 months. Another study found the rate of cushinoid features to increase linearly with dose: 4.3%, 15.8%, and 24.6% in patients receiving <5 mg/day, 5–7.5 mg/day, and >7.5 mg/day of prednisone (or equivalent), respectively.[15]

Osteoporosis, sometimes even leading to spontaneous fractures, is the most common serious adverse effect of steroid therapy encountered in 30-50% of patients.[15] Of the 269 patients who did report symptoms, 79% experienced pain due to osteonecrosis within 3 years of steroids initiation.[16] The reported incidence of hypertension in patients on long-term steroid therapy varies between 10-40%.[17] The percentage of cataract is 35% while a study in India calculate as 26.8% and intra ocular pressure is 7% while in Indian study it was 10.8%. These eye complications resemble the results of previous studies and strengths result. The pancreatitis is 8% whereas in international study it is as high as 40% this gross difference can be due to poor follow up of patients or many patients might be treated on surgical floor due to which they were missed from data. According to our study results, there is no impact of age, gender and duration of nephrotic syndrome on complications of nephrotic syndrome in pediatrics population.

CONCLUSION

We concluded that most common complication of long term steroids use in children was cushinoid features followed by hypertension and posterior subcapsular cataract. It is important to start with early identification and appropriate treatment for acute complications. Regular examinations and monitoring for chronic complications will improve outcomes for children with nephrotic syndrome.

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