Deflazacort Versus Prednisolone In The Treatment Of Idiopathic Nephrotic Syndrome In Children

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Abstract

Background: Nephrotic syndrome is one of the most common renal diseases in children. Nephrotic syndrome is the clinical manifestation of glomerular disease associated with massive proteinuria. The triad of clinical findings associated with nephrotic syndrome arising from the urinary loss of protein are hypoalbuminemia (serum albumin ≤2.5g/dl), edema, and hyperlipidemia (serum cholesterol >200mg/dl). Primary or idiopathic nephrotic syndrome is the most common form and the mainstay of treatment is prednisolone. Approximately 70% of children with steroid sensitive nephrotic syndrome may experience one or more relapse. Patients with relapse of nephrotic syndrome are at greater risk of severe steroid toxicity, as they are exposed to continuous prednisolone therapy to maintain remission.

Objective: To compare the effectiveness and safety profile of deflazacort and prednisolone in the treatment of idiopathic nephrotic syndrome in children.

Materials & Methods: A total 96 children of 2 to 10 years with idiopathic nephrotic syndrome (1st episode or infrequent relapse) were enrolled. Every case was randomized to either deflazacort group (group-I) or prednisolone group (group-II) and accordingly 48 children were equally allocated to group-I and group-II. All patients were followed up monthly during the treatment period and subsequently at 6th month after starting steroid. Data was documented on pre-structured data sheet and analyzed by SPSS version 21.0. Chi square test was done for categorical data and unpaired t-test for continuous data. A probability (p) value of <0.05 was considered statistically significant.

Results: The mean time to achieve remission was (5.6±1.7) days in deflazacort group and (10.2±2.3) days in prednisolone group (p<0.05). Relapse was found in 10(20.8%) patients in deflazacort group and 15(31.3%) in prednisolone group (p>0.05). The remission was 48(100%) in both groups. The mean weight gain was (3.8±1.10) kg in deflazacort group and (6.6±1.20) kg in prednisolone group. The mean height attainment was (2.6±1.10) cm and (1.3±0.70) cm in deflazacort and prednisolone group respectively. The mean weight gain and height attainment were statistically significant (p<0.05).

Conclusion: The mean time to achieve remission was significantly shorter in deflazacort group and deflazacort had lesser side effects than prednisolone. Deflazacort can be used in the treatment of idiopathic nephrotic syndrome in children.

Key words: Nephrotic syndrome, Deflazacort, Prednisolone, Effectiveness, Safety.

Abbreviations:

SPSS: statistical package for the social sciences; kg: kilogram; cm: centimeter; NS: nephritic syndrome; MCNS: minimal change nephrotic syndrome; FRNS: frequent relapse nephrotic syndrome; SDNS: steroid dependent nephrotic syndrome; RME: routine and microscopic examination; HBs Ag: hepatitis B surface antigen; ANA: anti-nuclear antibody; ds: double stranded; DNA: deoxyribonucleic acid; CBC: complete blood count, CS: culture and sensitivity, CXR: chest radiograph; TST: tuberculin skin test

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Introduction

Nephrotic syndrome (NS) is a chronic childhood disorder with a course of relapse and remission. A good number of indoor beds in the pediatric wards are occupied by the patients of NS. It implies both mental stress and economic burden to the families as well as the resource limited health care facilities in our country. Nephrotic syndrome is the clinical manifestation of glomerular disease associated with massive (nephrotic range) proteinuria. Nephrotic range proteinuria is defined as proteinuria ≥1g/m²/24hour or >40mg/m²/hour [1]. The triad of clinical findings associated with NS arising from the large urinary losses of protein are hypoalbuminemia (serum albumin ≤2.5g/dl), edema, and hyperlipidemia (serum cholesterol >200mg/dl) [2]. Globally, the incidence of NS is 1-3 per 100,000 children per year and the annual cumulative prevalence is 16/100,000 in Asian children under 16 years of age [3]. Nephrotic syndrome may be primary or secondary to various systemic diseases and drugs. Primary or idiopathic NS is the most common (90%) form in children and the rest of them has secondary etiology. Glomerular lesions associated with idiopathic NS in children include minimal change NS (most common), mesangial proliferation, focal segmental glomerulosclerosis and membrano-proliferative glomerulonephritis. The prevalence of minimal change nephrotic syndrome (MCNS) is higher in Indian subcontinent but there is no exact data regarding NS in Bangladesh [4]. The pathogenesis of MCNS is unknown but somehow it is related to abnormal T-lymphocyte functions [5]. The characteristic clinical course of MCNS is associated with normal blood pressure, microscopic or no hematuria, highly selective proteinuria and normal C₃ level. It is highly responsive to corticosteroids and has a high tendency to relapse. There are absence of progressive renal deterioration and negative morphological findings by light and immunomicroscopy in MCNS. Predisnolone is the mainstay of treatment for idiopathic NS. Among idiopathic NS (80-90%) respond well to prednisolone therapy [6]. Approximately (70%) of children with steroid sensitive NS may experience relapse, one or more times. Among them (40%) relapse frequently or become steroid dependent that impair their quality of life [7]. Patients with frequent relapse nephrotic syndrome (FRNS) or steroid dependent nephrotic syndrome (SDNS) are at greater risk of severe steroid toxicity, as they are exposed to continuous high-dose prednisolone to induce remission [8, 9]. Important side effects of prednisolone in children include obesity, impaired growth, hypertension, impaired glucose tolerance, osteoporosis, cushingoid symptoms, cataract, and adrenal suppression [10, 11]. Deflazacort is a synthetic glucocorticoid, an oxazoline derivative of prednisolone with anti-inflammatory and immunosuppressive activity [12]. It might act in the same mechanism as prednisolone in NS. It has got fewer adverse effects than prednisolone in children [13]. The adverse effects of deflazacort include oral candidiasis, cataract, dyspepsia, peptic ulcer, impaired glucose tolerance, hypertension, muscle weakness and weight gain. One study in India found that deflazacort in equipotent doses to prednisolone is almost (100%) effective in the treatment of children with idiopathic NS [14]. Broyer et al [16] showed that deflazacort was more effective than prednisolone in limiting relapses in SDNS in children. They also observed that cushingoid symptoms and weight gain was less marked with this drug than with prednisolone. Singhal et al showed that remission rate was comparable in children with idiopathic NS treated with prednisolone and deflazacort although time taken to induce remission was shorter in deflazacort group. They also observed a significant difference in change of mean height on follow up, with prednisolone group gaining lesser height. From this point of view this study was designed to compare the effectiveness and safety of deflazacort to prednisolone in the treatment of idiopathic NS in children.

Materials & Methods:

This was a randomized controlled double-blind clinical trial carried out in the department of pediatrics, Sylhet MAG Osmani Medical College Hospital, Sylhet, Bangladesh from July’2015 to June’2017 involving 96 children of 2-10 years. A detailed history was taken and thorough clinical examination was done to reach the diagnosis of idiopathic NS as well as to rule out any likely secondary causes and complications. During physical examination blood pressure was measured with special attention and plotted in the graph for hypertension. If history and examination suggested then investigations including 24 hours urinary total protein, serum albumin, serum cholesterol and urine for RME were done to confirm the diagnosis. If collection of 24 hours urine was not possible, spot urine protein-creatinine ratio was done as an alternative test to confirm the diagnosis of NS. If the ratio was >2 it was considered diagnostic. In case of suspected secondary NS, HB, Ag, anti-nuclear antibody (ANA) and anti-ds DNA antibody tests were done. Complete blood count (CBC), urine for culture and sensitivity (CS), x-ray chest (CXR) and tuberculin skin test (TST) were done to rule out infections and serum creatinine and serum electrolytes to rule out renal impairment. Children aged 2-10 years with idiopathic NS either 1st episode or infrequent relapse were included. Children with NS <2 years or >10 years, had hypertension, hematuria, impaired renal function (serum creatinine≥1.5 mg/ dl), steroid resistant/ dependant/frequent relapse, secondary NS due to any systemic disorders or drug) were excluded. Purposive sampling was done. Every consecutive case was allocated to either deflazacort group (group-I) or prednisolone group (group-II) randomly by lottery method (by drawing a paper from the container) and accordingly forty-eight patients were equally allocated to group-I and group-II. After diagnosis and infection screening treatment was started. Group-I was treated with oral deflazacort. Initial attack of idiopathic NS was treated with 2.4 mg/kg/day (maximum 72 mg daily) in 3 divided doses daily for 6 weeks followed by 1.8 mg/kg/day (maximum 48 mg) as a single morning dose every alternate day for the next 6 weeks, then therapy was discontinued. Relapse case was treated with 2.4 mg/kg/day in 3 divided doses daily till urinary albumin was nil/trace for 3 consecutive days followed by 1.8 mg/kg/ day as a single morning dose every alternate day for the next...
4 weeks, then therapy was discontinued. Group-II was treated with prednisolone. Initial attack of idiopathic NS was treated with 2 mg/kg/day (maximum 60 mg daily) in 3 divided doses daily for 6 weeks followed by 1.5 mg/kg/day (maximum 40 mg) as a single morning dose every alternate day for the next 6 weeks, then therapy was discontinued. Relapse case was treated with 2 mg/kg/day in 3 divided doses daily till urinary albumin nil/trace for 3 consecutive days followed by 1.5 mg/kg/day as a single morning dose every alternate day for the next 4 weeks, then therapy was discontinued. Renal chart was maintained and vital signs were monitored daily during hospital stay. Urine output was measured in a calibrated plastic bottle. No modification was made in management protocol, clinical practice, equipment and infrastructure in the pediatric units during the study period. A patient once enrolled was not enrolled again in case of relapse and was treated with the same drug used earlier. Bed side urine for albumin (by heat coagulation test) was done daily during hospital stay. If heat coagulation test revealed urinary albumin nil/trace for 3 consecutive days it was considered as the onset of remission. Patient was discharged from the hospital after achievement of urinary remission and resolution of complications, if any. Follow up was done monthly during treatment period and subsequently at 6th month after starting steroid or earlier, if any symptoms like swelling or edema appeared. Visual examination of the face and trunk for cushingoid appearance and measurement of height, weight and blood pressure was done by using stadiometer and pediatric sphygmomanometer respectively at the time of enrollment and subsequently during follow up. To prevent defaulters and to assure compliance the patients were asked to bring back empty tablet blisters. Reminder was given to the patient’s guardian for follow up over telephone. Data were collected by using preformed structured data sheet and presented with appropriate tables, bar diagrams and pie charts. Qualitative data were expressed as frequency and percentage. The Chi-square test was done to analyze the categorical data. Quantitative data were expressed as mean and standard deviation. The student’s t test was done to analyze the continuous data. A probability (p) value of ≤ 0.05 was considered statistically significant. The study protocol was approved by the ethical review committee of Sylhet MAG Osmani Medical College, Sylhet, Bangladesh.

Results
There was no significant difference (p>0.05) of mean age, weight, height and initial attack of NS between the two groups. The male-female ratio was 2.4:1 in deflazacort group and 3:1 in prednisolone group. The difference was not statistically significant (p>0.05) [Table 1]. It was observed that cushingoid appearance was developed in 3(6.25%) patients in deflazacort group and 5(10.4%) patients in prednisolone group. The difference was not statistically significant (p>0.05) [Figure 1]. Hypertension was developed in 4(8.3%) patients in deflazacort group whereas 7(14.6%) in prednisolone group during follow up. The difference was not statistically significant (p>0.05) [Figure 2]. In this study, the mean weight gain was (3.8±1.10) kg in patients of deflazacort group and (6.6±1.20) kg in prednisolone group, the mean height attainment was (2.6±1.10) cm in deflazacort group and (1.3±0.70) cm in prednisolone group and the mean time taken to induce remission was (5.6±1.7) days in deflazacort group and (10.1±2.3) days in prednisolone group. The differences were statistically significant (p<0.05) (Table 2). (Table 3) reveals that remission rate was (100%) in both groups. Relapse was 10(20.8%) in deflazacort group and 15(31.3%) in prednisolone group. Though relapse was more in prednisolone group the difference was not statistically significant (p>0.05).

Table 1: Baseline characteristics of the study population (n=96).
Discussion:
This randomized controlled clinical trial was carried out to compare the effectiveness and safety of deflazacort and prednisolone in the treatment of idiopathic NS in children. The comparison was done in terms of remission rate, time taken to induce remission, number of relapse, development of hypertension and cushingoid appearance, mean weight gain and mean height attainment. The mean age of the patients were (5.4±2.6) years and (5.3±0.45) years in deflazacort group and prednisolone group respectively. The male-female ratio was 2.4:1 in deflazacort group and 3:1 in prednisolone group. There was no significant differences (p>0.05) of mean age, male-female ratio, mean weight, mean height and initial attack or relapse of NS between two groups.

In this study, it

![Image](image1.png)

**Figure 1:** Distribution of the study patients by development of cushingoid appearance.

![Image](image2.png)

**Figure 2:** Distribution of the study patients by development of hypertension.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group-I (n=48)</th>
<th>Group-II (n=48)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain (kg)</td>
<td>Mean±SD</td>
<td>3.8±1.10</td>
<td>6.6±1.20</td>
</tr>
<tr>
<td>Height attainment (cm)</td>
<td>Mean±SD</td>
<td>2.6±1.10</td>
<td>1.3±0.70</td>
</tr>
<tr>
<td>Time taken to induce remission (Day)</td>
<td>Mean±SD</td>
<td>5.6±1.7</td>
<td>10.1±2.3</td>
</tr>
</tbody>
</table>

**Table 2:** Distribution of the study patients by weight gain, height attainment and time taken to induce remission (n=96)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group-I (n=48)</th>
<th>Group-II (n=48)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>Frequency</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>Relapse status</td>
<td>Frequency</td>
<td>10</td>
<td>15</td>
</tr>
</tbody>
</table>

**Table 3:** Distribution of the study population by remission and relapse (n=96)
was found that cushingoid appearance developed in (6.25%) patients in deflazacort group and (10.4%) in prednisolone group (p>0.05). Other studies reported that corticosteroids were associated with numerous side effects like cushingoid appearance which was not statistically significant as well. Broyer et al [15] also showed fewer side effects like cushing syndrome in deflazacort group in their study but the difference was found to be insignificant. So, our finding is consistent with other previous studies. In this study, hypertension was developed in (8.3%) patients in deflazacort group and (14.6%) in prednisolone group. Neves et al [17] found that (10.0%) patients had hypertension treated with deflazacort which was almost similar to our study. Singhal et al found that the number of children with hypertension at the end of treatment and follow up was not different in two groups which was consistent with this study. In another study by Zagury et al [18] hypertension was found in (15.0%) patients treated with prednisolone which was comparable with our study. Singhal et al [14] found the mean weight gain was higher in prednisolone group (1.38±0.56) kg as compared to deflazacort (1.36±0.96) kg which was not statistically significant (p>0.05).Broyer et al reported higher mean weight gain in prednisolone group (3.9±4.1) kg but the difference from deflazacort group (1.7±2.8) kg was not statistically significant. These findings were different from our study where the mean weight gain was (3.8±1.10) kg in deflazacort group and (6.6±1.20) kg in prednisolone group which was statistically significant (p=0.001). On the other hand, Neves et al observed that the mean weight gain in the group treated with prednisolone versus deflazacort was (3.9±4.1) kg and (1.7±2.8) kg respectively which was statistically significant and consistent with our study. The mean height attainment was (2.6±1.10) cm in deflazacort group and (1.3±0.70) cm in prednisolone group which was significantly (p=0.021) higher in deflazacort group. Singhal et al found the mean height increment (2.13±0.50) cm in deflazacort group and (1.3±0.70) cm in prednisolone group which was statistically significant (p>0.05). This finding was consistent with our study. Singhal et al found the mean time taken to induce remission was (10.25±2.41) days and (12.55±1.44) days in deflazacort group and prednisolone group respectively. Time taken to induce remission was significantly shorter (p<0.05) in deflazacort group. In our study, the mean time taken to induce remission was (5.6±1.7) days in deflazacort group and (10.1±2.3) days in prednisolone group which was significantly (p=0.001) higher in prednisolone group. Thus, deflazacort induces earlier remission in patients with idiopathic NS which closely resembled with the previous study. Similar observations were also found by Neves et al and Zagury et al [18]. In this study the remission rate was (100.0%) in both deflazacort and prednisolone groups which was not statistically significant. Broyer et al found that all the children achieved remission in both deflazacort and prednisolone groups. Another study by Singhal et al found that (100%) children from deflazacort group and (91.7%) from prednisolone group achieved remission (p<0.05) which also supported our study. Singhal et al showed that the number of relapse was (9.1%) in deflazacort group and (27.3%) in prednisolone group which was not statistically significant. Broyer et al in their study found that the number of relapse was more in prednisolone group than deflazacort group but this difference was not statistically significant. The investigators concluded that deflazacort was equipotent in comparison to prednisolone in inducing remission and preventing relapse. Similarly, in our study, it was found that the relapse was (20.8%) in deflazacort group and (31.3%) in prednisolone group. The difference was not statistically significant (p>0.05).

Conclusion & Recommendation:

The mean time taken to induce remission was significantly shorter in deflazacort group. Weight gain and growth retardation were significantly higher in prednisolone group. Deflazacort was as effective as prednisolone and had lesser side effects in the treatment of idiopathic nephrotic syndrome in children. Shorter follow-up period of only six months and single center study were the limitations of this study. Deflazacort can be used in the treatment of idiopathic nephritic syndrome in children. Further double-blind multicenter study with long term follow up may strengthen the use of deflazacort in the treatment of idiopathic nephrotic syndrome in children.

References


