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REVIEW

STEROID THERAPY FOR CHILDREN WITH IDIOPATHIC NEPHROTIC SYNDROME: IS A SHORT-TERM OR LONG-TERM TREATMENT PLAN MORE EFFECTIVE?

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ABSTRACT

Idiopathic nephrotic syndrome is one of the most common glomerular diseases in childhood. Corticosteroids are the first line of treatment for this disease. Although the majority of patients respond to steroids, recurrences of idiopathic nephrotic syndrome are quite common. Therefore, it is important to determine the most appropriate duration of treatment because of relapses and possible steroid side effects. In this review, the literature is summarized by evaluating the difference between the short (2 to 3 months) and long (>3 months) durations of steroid therapy in terms of relapses and steroid side effects. In most of the studies, it has been seen that the two-to-three-month treatment protocol is sufficiently efficient. Nowadays, most prefer 2-3 months of steroid treatment to achieve good disease control and avoid steroid-related side effects. Yet, studies with larger patient groups on this subject need to be carried out.

Keywords: Nephrotic syndrome, children, steroids, therapy

INTRODUCTION

Idiopathic nephrotic syndrome is a kidney disease that is common in childhood and occurs because of a damaged glomerular filtration barrier (1). Although it may differ depending on ethnicity and region, it affects between 1.15 and 16.9 per 100,000 children worldwide each year (2). Genetic ancestry is also important in the incidence of the disease and the patient's response to treatment (3). This disease is defined by nephrotic-level proteinuria, hypoalbuminemia, and generalized peripheral edema (2). At the same time, due to increased hepatic lipoprotein synthesis, hyperlipidemia is also observed (4).

The two most common histopathologic findings of idiopathic nephrotic syndrome in children are minimal change disease and focal segmental glomerulosclerosis (5). Minimal change disease accounts for 70-90% of idiopathic nephrotic syndrome cases in children older than one year (6, 7). Most of the cases are idiopathic (primary nephrotic syndrome) and have a very good prognosis (7, 8). However, it can develop secondary to conditions such as infection, neoplasia, allergy, drug use, human immunodeficiency virus, systemic lupus erythematosus, and type 1 diabetes mellitus (8).

Focal segmental glomerulosclerosis, on the other hand, is less common than minimal change disease. However, it may have further negative long-term consequences and can progress to end-stage renal disease due to its resistance to treatment (4).

Corticosteroids, which are the most important and first-line drugs in the treatment of idiopathic nephrotic syndrome, can cause various side effects with long-term use. It increases susceptibility to infection due to immunosuppression. It may also cause many side effects, such as central obesity, moon face (a round face), buffalo hump (due to unusual fat accumulation on the back), hyperglycemia, and hypertension. In addition, if steroid treatment is stopped suddenly, a serious clinical picture called "adrenal crisis" may occur due to the lack of cortisol production in the adrenal gland (9).

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This review aims to determine the duration of treatment that will be most effective and cause the fewest side effects, considering the recurrence rates of the disease and possible side effects of corticosteroid use.

In this literature review, we will discuss the pathogenesis of idiopathic nephrotic syndrome and try to evaluate randomized controlled trials (RCTs) and meta-analyses on this subject between 2012 and 2022. The results of the studies were evaluated in terms of the number of relapses and side effects of steroids after short-term (2-3 months) and long-term (>3 months) steroid use in children with idiopathic nephrotic syndrome.

Pathogenesis

The exact pathogenesis of childhood nephrotic syndrome is not fully understood, but recently, immune system dysregulation has been the focus, and many other diverse factors, such as genetic factors and environmental factors, are thought to play a role in podocyte dysfunction (10). Infections have also been suggested to play a role in disease onset or recurrence (11).

In recent years, it has been stated that the presence of autoantibodies against the protein called nephrin, which is expressed on the surface of podocytes and has a critical role in preventing proteinuria, is important in minimal change disease (12, 13). It is thought that "diffuse podocytopathy," which is seen frequently in children with nephrotic syndrome, is caused by the damage of podocytes due to an autoimmune response (14, 15).

There are various theories regarding immune system dysregulation in the pathogenesis of idiopathic nephrotic syndrome. According to the "T-cell theory," upregulation of CD4+ T helper cells and downregulation of CD8+ cytotoxic T-cells creates an imbalance resulting in increased Th2, and this plays a role in the pathogenesis of the nephrotic syndrome. The fact that immunosuppressants (corticosteroids, cyclosporine, and cyclophosphamide) that suppress T-cell function are beneficial in the treatment and that patients go into remission due to impaired T-cell function in some cases of measles supports this hypothesis. The demonstration that anti-CD20 B-cell targeted therapies (e.g., rituximab) are effective in children with frequent relapses or steroid-dependent nephrotic syndrome supports the "B-cell theory." It has also been suggested that circulatory factors play a role in the pathophysiology, especially in patients with focal segmental glomerulosclerosis (10).

Genetic factors also play an important role in the development of nephrotic syndrome. There is a single gene mutation associated with podocytes in 30% of steroid-resistant cases (10). This is mostly seen in the steroid-resistant condition that emerges in the first three months of life, which is called congenital nephrotic syndrome (CNS) rather than idiopathic nephrotic syndrome cases. For example, the absence of nephrin protein due to the *NPHS1* gene mutation causes Fin-type nephrotic syndrome, which is an important subtype of CNS (12). In addition, it has been suggested that the human leukocyte antigen-DQ and HLA-DR regions are associated with steroid-sensitive nephrotic syndrome (SSNS) cases (10).

Clinical and Laboratory Findings

Idiopathic nephrotic syndrome is clinically characterized by generalized edema, nephrotic-range proteinuria (>40 mg/m^2/h or urine protein to creatinine ratio (Up/Uc) >2 mg/mg in the first-morning specimen or urine protein 3-4+ with dipstick/boiling test), hypoalbuminemia (<3 g/dL), and hyperlipidemia with an increase in total and low-density lipoprotein (16, 17). Thromboembolic events may also accompany the disease (18).

Generalized edema is the most important finding of idiopathic nephrotic syndrome in children, especially in minimal change disease (19). It increases with standing, especially during the day, and is in the form of soft edema that leaves pitting. In these patients, acid accumulation in the abdomen, scrotal, penile, or labial edema may develop (5).

Two hypotheses, namely "underfilling" and "overfilling," have been proposed for edema formation. In both of these hypotheses, proteinuria resulting from kidney damage lowers oncotic pressure by causing a decrease in serum albumin. Therefore, intravascular fluid shifts into the interstitial space and the increase in interstitial fluid causes edema. According to the "underfilling" hypothesis, blood pressure decreases due to decreased plasma and blood volume, and the renin-angiotensin-aldosterone system is activated. There is an increase in the plasma volume, which supports the increase of interstitial fluid and, therefore, the formation of edema. According to the "overfilling" hypothesis, there is an increase in sodium retention due to kidney damage and, therefore, in plasma volume. As a result, increased plasma volume combined with the loss of albumin leads to increased edema (20).

Although edema is the main finding of nephrotic syndrome, patients may present with complications of nephrotic syndrome, such as thromboembolic events (pulmonary embolism, deep vein thrombosis, etc.), spontaneous bacterial peritonitis, cellulitis, and abdominal pain due to intestinal wall edema or hypoperfusion (5).

Even though some patients with nephrotic syndrome may have nephritic features (hypertension, hematuria, and decreased kidney function), these findings are not expected in minimal change disease (5, 16). Therefore, persistent hematuria suggests different diseases , such as infection-related glomerulonephritis, complement C3 glomerulopathy, or systemic lupus erythematosus, and additional investigations are required (16).

On physical examination, edema is the predominant finding. During the examination, syndromic conditions and complications of nephrotic syndrome (thromboembolism, peritonitis, and cellulitis) should be investigated (5).

Diagnosis and Kidney Biopsy

According to International Pediatric Nephrology Association (IPNA) recommendations, depending on the age and clinical

characteristics of the cases, different approaches are used for diagnosis (2).

Kidney biopsy is not routinely performed in the diagnosis of SSNS in children aged 1-12 years with typical symptoms because of its limited prognostic and clinical utility. However, there are several situations where a biopsy is indicated. If the patient has atypical features such as macroscopic hematuria, low C3 levels, acute kidney injury not related to hypovolemia, sustained hypertension, arthritis, and/or rash, which are not routinely seen in nephrotic syndrome, a kidney biopsy is initially performed to elucidate the etiology (2).

In patients presenting with typical nephrotic syndrome findings, an age-based approach is preferred for the diagnosis. If the patient is older than 12 years of age, two different strategies are considered on a case-by-case basis: performing a kidney biopsy or initiating corticosteroid therapy directly without a biopsy. Steroid treatment is started initially in the patient group between the ages of 1 and 12 years. In patients aged 3-12 months, there are three different options for diagnosis: Genetic testing (the primary choice), starting treatment without a biopsy, or performing a kidney biopsy. If the patient is younger than three months of age, has extrarenal features, or has a family history that suggests hereditary and syndromic steroid-resistant nephrotic syndrome, genetic testing is primarily preferred to clarify the CNS (2).

As mentioned in IPNA recommendations, kidney biopsy is also suggested in patients with persistent microscopic hematuria in populations where glomerular diseases such as IgA nephropathy are prevalent (2).

Treatment

Steroids have been the cornerstone of treatment, as most children with idiopathic nephrotic syndrome achieve remission after 4-6 weeks of daily prednisone or prednisolone therapy (21, 22). Particularly, minimal-change disease responds favorably to corticosteroid therapy (7).

To summarize the treatment algorithm generally, corticosteroid therapy (prednisone/prednisolone) is started at the first stage (2, 21). If relapses are frequent (≥2 relapses in the first 6 months following remission of the initial episode or ≥3 relapses in any 12 months) or if significant steroid toxicity has occurred, low-dose alternate-day steroids or steroid-sparing drugs (levamisole, mycophenolate mofetil, etc.) can be given to reduce dependence on steroids and minimize the side effects of steroid therapy (16, 21). In addition, it is also crucial to refer the patient to a pediatric nephrologist who can provide individualized treatment recommendations (21).

There are two different treatment protocols specified in the IPNA recommendations for patients with the first episode of idiopathic nephrotic syndrome. The first of these suggestions is four weeks at 60 mg/m^2 or 2 mg/kg (maximum dose of 60 mg/day), followed by alternate-day prednisone/prednisolone at 40 mg/m^2 or 1.5 mg/kg (a maximum dose of 40 mg on alternate days) for four weeks. The other suggestion, which is stated to be a "grade A strong recommendation", is six weeks at 60 mg/m^2 or 2 mg/kg (a maximum dose of 60 mg/day), followed by alternate day prednisone/prednisolone at 40 mg/m^2 or 1.5 mg/kg (maximum dose of 40 mg on alternate days) for six weeks (2).

Since the Kidney Disease: Improving Global Outcomes 2021 Guidelines, 8-12-week treatment plans of prednisone/prednisolone are recommended instead of a 24-week regimen in minimal-change disease. It is recommended to establish a treatment plan in which patients are given 60 mg/m^2/day or 2 mg/m^2/day in the first half and 40 mg/m^2/day or 1.5 mg/kg/day in the second half of the treatment period (23).

Although minimal change disease is steroid-sensitive, relapses are very common in these cases (7). Approximately 70-80% of the patients experience at least one relapse during follow-up (2). Repeated steroid therapies can cause toxicity after a while (24). Due to the side effects of glucocorticoid therapy such as obesity, hypoglycemia, cataracts, and hypertension, a treatment plan should be considered to minimize steroid toxicity (25, 26). Therefore, it is important to investigate the efficiency of long- and short-term treatments for nephrotic syndrome.

DURATION OF TREATMENT, EFFECTIVENESS, AND CORTICOSTEROID SIDE EFFECTS

In an RCT conducted by Yoshikawa et al. (27) in 2015 involving 246 children from 90 centers in Japan, patients were treated with corticosteroids for 2 or 6 months, then followed for 24 months for relapse. The time to first relapse and the side effects that may be seen due to steroids are similar for both groups receiving 2 or 6 months of treatment. Therefore, it was recommended that the prolongation of the treatment period was not clinically significant.

A similar result was found in another RCT in England, which was published in 2019 and included 237 children aged 1-14 years during the first episode of SSNS. In this study by Webb et al. (28), the efficiency of 8- and 16-week treatment plans was compared in patients divided into two groups. Afterwards, they were followed for 24 months to observe recurrence and side effects, and no significant difference was found between the two groups in terms of time to first relapse. Concerns about side effects were also not supported in the long-term steroid group. A possible weakness of this study is the possible exclusion of young children who cannot take the trial drug, which is provided as a crushable tablet (28).

In the study conducted by Sinha et al. (29) in 2015, the effectiveness of the 3- and 6-month treatment processes was investigated. A total of 181 patients were included in this study conducted in northern India, 92 of whom received 6-month treatment and 89 of whom were in the 3-month treatment group. At the end of the one-year follow-up, the number of relapses was 1.54 in the 3-month treatment group and 1.26 in the 6-month group. Since these values were not statistically significant, it was concluded that the 3-month treatment provided sufficient efficiency. The strengths of the study are

that it was designed as a anonymous, placebo-controlled, multicenter study and has a low risk of selection, performance, and selective reporting bias. The main limitation is that it is not stratified for key variables that may affect disease severity, such as age and gender (29).

In another study implemented by Kainth et al. (30) in 2021, the duration of continued steroid treatment after remission was compared. A total of 117 patients participated in this prospective study, 55 of whom were on the short regimen and 62 on the standard treatment regimen. Both randomly allocated groups received prednisolone 60 mg/m^2 until remission. One of the groups was given a short regimen of 40 mg/m^2 for two weeks after remission, while the other group was given a 4-week standard regimen. As a result of the study, the relapse rates in the short regimen group were similar to those in the other group; therefore, the short treatment was not inferior. Although the number of participants in the two groups is not equal, which is a limitation of the study, it has been stated that this situation did not cause a statistical difference (30).

One hundred twenty patients were included in the study conducted by Al Talhi et al. (31) in 2018, and prednisolone treatment was given for 3 months to one group and 7 months to the other. The follow-up period was two years. As a result of this study, it was observed that the risk of relapse was significantly lower in the patient group that received 7 months of treatment (31). The reason why the result of this study conducted in Saudi Arabia differs from the others may be due to the limited number of patients participating in the study and the differences in patients due to factors such as genetic predisposition and living conditions.

In an RCT involving 69 centers in the Netherlands, it was investigated whether the duration of steroid treatment or the cumulative dose was important. Hundred and fifty children aged 9 months to 17 years were included in the study. In this study, prednisolone treatment was given to one group for 3 months and to the other group for 6 months, but the total cumulative doses received by both groups were kept equal. As a result, the fact that there was no significant difference between the two groups in terms of relapse rate showed that the important factor was the cumulative dose (32).

In the study conducted by Geng et al. (33), a similar result was obtained. This prospective, non-RCT included 89 new-onset primary nephrotic syndrome cases between December 2017 and May 2019. One of the groups was given 2 mg/kg/day prednisone treatment for 4 weeks and the other for 6 weeks. Then, both groups were treated every other day with 2 mg/kg prednisone for 4 weeks, and the doses were gradually reduced until drug withdrawal. When the recurrence rates in the two groups were evaluated, it was observed that the amount of recurrence was significantly higher in the first 3 months in the group that received a total of 8 weeks of treatment. At one-year follow-up, there was no significant difference between the 8- and 12-week regimens. As a result of this study, it was recommended to give a 12-week regimen in total, especially considering the recurrence difference in the first 3 months (33). For this reason, considering various studies, treatment of nephrotic syndrome in children should be planned for at least three months (34, 35).

Studies on the duration and efficiency of corticosteroid therapy in patients with idiopathic nephrotic syndrome are summarized in Table 1, along with their aims and results.

According to the meta-analysis published by Schijvens et al. (36), when the two- and three-month treatment regimens were compared, the group who received steroid treatment for two months experienced 51% more recurrences than those who received three-month treatment.

Table 1: Studies on the duration and efficiency of corticosteroid therapy and their results.

Study, year	Country	Types of studies	Number of participants	Duration of the follow-up period	Aims of studies	Results of studies
Yoshikawa et al. (27), 2015	Japan	RCT	246	24 months	Evaluation of 2 and 6 months of corticosteroid treatment in terms of relapse and side effects.	Since the relapse rates were similar in both groups, it is recommended that there is no need to extend the treatment.
Webb et al. (28), 2019	England	RCT	237	24 months	Evaluation of 8- and 16-week treatment plans in terms of time to first relapse in patients with their first episode of SSNS.	There was no significant difference between the two groups in terms of time to first relapse.
Sinha et al. (29), 2015	North India	RCT	181	12 months	Evaluation of recurrence rates of 3 and 6-month corticosteroid treatments.	Since the difference between the two groups was not statistically significant, it was stated that the 3-month treatment regimen was sufficient.
Kainth et al. (30), 2021	India	RCT	117	12 months	Comparison of recurrence rates in groups receiving short-term therapy (2 weeks) and standard therapy (4 weeks) after remission.	It has been demonstrated that the short-term regimen is not inferior to the standard regimen.
Al Talhi et al. (31), 2018	Saudi Arabia	RCT	120	24 months	Comparison of recurrence rates in patients treated with prednisolone for 3 or 7 months.	It was found that the relapse rate was lower in the group that received 7 months of treatment.

Table 1: Continued.

Study, year	Country	Types of studies	Number of participants	Duration of the follow-up period	Aims of studies	Results of studies
Teeninga et al. (32), 2013	Netherlands	RCT	150	32-60 months (median: 47 months)	Investigation of the difference between the relapse rates of the 3- or 6-month treatment regimens given by keeping the total cumulative dose constant.	Since there was no significant difference between the recurrence rates of the 3- and 6-month regimens, it was mentioned that the important parameter in terms of relapse was the cumulative dose.
Geng et al. (33), 2022	China	Non-RCT	89	12 months	Comparison of relapse rates in the first 3 months and after 1 year of 8- or 12-week corticosteroid regimens.	A higher rate of recurrence was seen in patients who received an 8-week treatment regimen in the first 3 months. Based on this, it is recommended that the treatment be arranged for at least 12 weeks.

RCT: Randomized controlled trial, SSNS: Steroid-sensitive nephrotic syndrome

Although long-term treatment is recommended in some studies, the Cochrane Database showed that three months of corticosteroid treatment was sufficient for children with nephrotic syndrome (35, 37).

CONCLUSION

On this subject, the lack of stratification such as ethnicity, gender, and genetic predisposition in RCTs causes limitations. In addition, standardized studies involving more patients will be useful in determining the most efficient protocol for the treatment plan.

We tried to evaluate the current literature for ideal duration of steroid treatment for idiopathic nephrotic syndrome. Nowadays, a 2- to 3-month steroid regimen seems sufficient for disease control and to avoid potential steroid-related side effects. On the other hand, it should be noted that the duration and intensity of steroid therapy in childhood NS should be weighed against the benefits and risks. The intensity of the disease, response to initial treatment, risk of recurrence, and presence of complications should be determined, and the patient should be monitored in close contact with a pediatric nephrologist.

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