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Nutritional status and laboratory characteristics of nephrotic syndrome in children undergoing steroid and non-steroid therapy at Dr. Zainoel Abidin Hospital, Banda Aceh

Status nutrisi dan karakteristik laboratorium sindrom nefrotik pada anak yang menjalani terapi steroid dan non-steroid di Rumah Sakit Umum Daerah Dr. Zainoel Abidin, Banda Aceh

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Abstract

Nephrotic syndrome (NS) is a clinical condition characterized by massive proteinuria, hypoalbuminemia, edema, and hypercholesterolemia. Frequently relapsing NS, steroid-dependent NS, and steroid-resistant NS are categorized as problematic owing to treatment difficulties. These patients require prolonged high-dose steroid therapy or immunosuppressants, resulting in significant side effects. This study evaluated the nutritional status and laboratory characteristics of NS in children undergoing steroid and non-steroid therapies. This study is the first to assess the nutritional status and laboratory characteristics of children with difficult-to-treat NS who received steroid and non-steroid therapy at RSUDZA Banda Aceh. A cross-sectional study was conducted at the outpatient clinic and pediatric ward of Dr. Zainoel Abidin General Hospital, Banda Aceh, in 2019, which was a limitation because it was conducted during the Covid-19 pandemic so that the number of research subjects was limited, which could have caused bias in the study. Statistical analyses included the chi-square test or Fisher's exact test for categorical variables and the independent sample t-test or Mann-Whitney test for numerical variables, with a 95% significance level ($p < 0,05$). A total of 60 children aged 2–18 years participated in this study, with 29 receiving steroid therapy and 31 receiving non-steroid therapy. Urine protein levels and relapse incidence differed significantly between the groups ($p < 0,001$). However, the serum albumin, urea, creatinine, calcium, and total cholesterol levels were not significantly different. No significant differences were observed in the laboratory characteristics between the steroid and non-steroid therapy groups. However, the non-steroid group exhibited a better urine protein status and fewer relapses, indicating potential therapeutic advantages.

Keywords: Nephrotic syndrome, difficult-to-treat nephrotic syndrome, laboratory characteristics, steroids, non-steroids, immunosuppressant therapy

Abstrak

Sindrom nefrotik (SN) adalah kondisi klinis yang ditandai dengan proteinuria masif, hipoalbuminemia, edema, dan dalam beberapa kasus, hiperkolesterolemia. SN yang sering kambuh, bergantung steroid, dan resisten steroid dikategorikan sebagai SN bermasalah karena tantangan dalam pengobatannya. Kondisi ini memerlukan terapi steroid dosis tinggi jangka panjang atau imunosupresan yang berisiko menimbulkan efek samping signifikan. Penelitian ini mengevaluasi status nutrisi dan karakteristik laboratorium SN pada anak yang menjalani terapi steroid dan non-steroid. Studi ini merupakan studi pertama yang menilai status nutrisi dan karakteristik laboratorium anak SN yang sulit diobati yang mendapat

terapi steroid dan non steroid di RSUDZA Banda Aceh. Studi potong lintang dilakukan di poliklinik rawat jalan dan bangsal anak Rumah Sakit Umum Dr. Zainoel Abidin, Banda Aceh Tahun 2019, yang menjadi keterbatasan karena dilakukan saat pandemi Covid-19 sehingga jumlah subjek penelitian terbatas yang dapat menimbulkan bias pada penelitian. Analisis statistik menggunakan uji Chi-Square atau uji Fisher untuk variabel kategorikal serta uji t-independen atau uji Mann-Whitney untuk variabel numerik, dengan tingkat signifikansi 95% ($p < 0,05$). Sebanyak 60 anak berusia 2–18 tahun berpartisipasi, terdiri dari 29 anak dengan terapi steroid dan 31 anak dengan terapi non-steroid. Protein urin dan kejadian kekambuhan berbeda secara signifikan antar kelompok ($p < 0,001$). Namun, kadar albumin serum, urea, kreatinin, kalsium, dan kolesterol total tidak menunjukkan perbedaan signifikan. Tidak terdapat perbedaan signifikan dalam karakteristik laboratorium antara kedua kelompok terapi, tetapi kelompok non-steroid menunjukkan perbaikan status protein urin serta penurunan kekambuhan, yang mengindikasikan potensi manfaat terapi.

Kata Kunci: Sindrom nefrotik, sindrom nefrotik sulit diobati, status nutrisi, karakteristik laboratorium, steroid, non-steroid, terapi imunosupresan

Introduction

Nephrotic syndrome (NS) is a kidney disorder characterized by severe proteinuria, massif hypoalbuminemia, edema, and hypercholesterolemia (Trautmann et al., 2023). The incidence of NS in children in the United States and England is estimated to be 2–7 new cases per 100,000 children per year, with a prevalence ranging from 12 to 16 cases per 100,000 children. (Valavi et al., 2023). In Indonesia, the reported incidence is approximately 6 per 100,000 children per year in those younger than 14 years (Uwaezuoke, 2015).

Frequently relapsing NS, steroid-dependent NS, and steroid-resistant NS are often classified as problematic NS due to their challenging treatment and the necessity for prolonged, high-dose steroid therapy or immunosuppressants, which carry the risk of significant side effects (Nilawati, 2012; Valavi et al., 2023). Immunosuppressant therapy is considered a second-line treatment for frequently relapsing NS (≥2 relapses in 6 months or ≥4 relapses within 12 months) or steroid-dependent NS (relapse during corticosteroid treatment or within two weeks of discontinuation) (Downie et al., 2017). Long-term steroid use is associated with adverse effects, necessitating the exploration of alternative therapies that provide effective treatment with minimal side effects, thereby reducing morbidity and mortality (Trihono et al., 2023).

Despite the effectiveness of corticosteroids as the primary treatment for NS, prolonged use has been linked to various complications, including growth retardation, hypertension, osteoporosis, and increased susceptibility to infections (Uwaezuoke, 2015). Additionally, some children develop steroid resistance, requiring more aggressive therapeutic approaches that often include immunosuppressants such as cyclosporine, mycophenolate mofetil, and cyclophosphamide (Downie et al., 2017). However, these agents also pose risks, including nephrotoxicity and bone marrow suppression, making it crucial to evaluate their impact on laboratory parameters and overall patient outcomes (Uwaezuoke, 2015).

Understanding the laboratory characteristics of children receiving steroids versus non-steroid therapy is essential to optimize treatment strategies and minimize long-term complications. Laboratory parameters, such as urine protein, serum albumin, urea, creatinine, total cholesterol, and calcium levels, can provide critical information on the efficacy and safety of different therapeutic approaches. At Dr. Zainoel Abidin General Hospital, Banda Aceh, Indonesia, immunosuppressants have been widely used in difficult-to-treat NS cases. Given the risks associated with long-term steroid use, this study aimed to compare the nutritional status, laboratory characteristics, and incidence of relapse of children with NS receiving steroid and non-steroid therapy at Dr. Zainoel Abidin General Hospital.

Methods

This cross-sectional study was conducted at the Dr. Zainoel Abidin General Hospital, Banda Aceh, Indonesia. This study was approved by the

Committee of Research Ethics, Faculty of Medicine, Syiah Kuala University and Dr. Zainoel Abidin General Hospital, Banda Aceh. The study participants were pediatric patients treated at the outpatient clinic and pediatric ward of the hospital for four months. Eligible participants were children aged two–18 years who had been diagnosed with nephrotic syndrome (NS) and had been undergoing treatment for more than six months. Patients with comorbid conditions such as atopy or tuberculosis, and those with complications of chronic kidney disease were excluded from the study.

Subjects were selected using a consecutive sampling technique from all available patients with NS until the minimum required sample size of 96 subjects (or all eligible patients within the study period) was achieved. The sample size of the study was calculated using the unpaired categorical analytical research sample size formula. Participants who met the inclusion criteria were divided into two groups based on their treatment regimens. All participants underwent demographic data collection, anthropometric examination, clinical assessment, and laboratory investigations, including urine protein, urea, creatinine, albumin, total cholesterol, and calcium levels. Routine clinical and laboratory evaluations were conducted by a Pediatric Nephrology Consultant from the Division of Nephrology, Section/KSM of Child Health Department, Dr. Zainoel Abidin General Hospital, Banda Aceh.

All collected data were systematically recorded on a data collection sheet, coded, and entered into a computerized worksheet using SPSS version 24 for statistical analysis. Descriptive statistics are presented in the form of frequency tables. Prior to the analysis, the Shapiro-Wilk test was performed to assess the normality of the data distribution. The basic characteristics of the research subjects, as well as the NS characteristics, were analyzed using the chi-square test. If the Chi-square test assumptions were not met (i.e., when more than 20% of the expected values in the contingency table were less than five), Fisher's exact test was applied. Laboratory characteristics were compared using the nephrotic syndrome, relapse frequency, urine protein levels, serum albumin, and total cholesterol sample t-tests for normally distributed data, whereas the Mann-Whitney U test was used for non-normally distributed data for serum urea, serum creatinine, and serum calcium samples.

Result and Discussion

A total of 298 participants were initially included in this study. Of these, 234 subjects were excluded based on the study criteria: 186 were repeat patients with multiple visits to the polyclinic, 27 had been diagnosed with nephrotic syndrome (NS) for less than six months, 5 had congenital NS, 9 had comorbidities, and 7 had end-stage renal failure. Additionally, four participants declined to participate. As a result, 60 subjects were enrolled in the study (Figure 1).

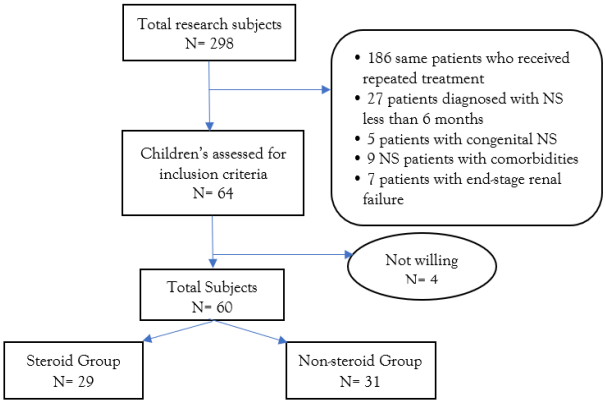

Figure 1. Enrollment of study subjects

Table 1. Baseline characteristics of children with nephrotic syndrome receiving steroid and non-steroid therapy

Characteristics	Steroid (n = 29)	Non-Steroid (n = 31)
Age; n (%)		
2 - <5 years	3 (10,3)	5 (16,1)
5 - 11 years	13 (44,9)	15 (48,4)
12 - 16 years	10 (34,5)	8 (25,8)
>16 - ≤18 years	3 (10,3)	3 (9,7)
Sex; n (%)		
Male	22 (75,9)	24 (77,4)
Female	7 (24,1)	7 (22,6)
Nutritional status; n (%)		
Malnutrition	7 (24,1)	9 (29,0)
Normal	18 (62,1)	19 (61,3)
Overweight	2 (6,9)	3 (9,7)
Obesity	2 (6,9)	0 (0,0)
Height; n (%)		
Normal	16 (55,2)	20 (64,5)
Stunted	13 (44,8)	10 (32,3)
Severely stunted	0 (0,0)	1 (3,2)

Among the 60 enrolled subjects, 29 were assigned to the steroid group and 31 to the nonsteroid group. The subjects were aged between 2 and 18 years and were recruited from

a dr. Zainoel Abidin Hospital, Banda Aceh. There were no statistically significant differences between the steroid-treated and non-steroid-treated groups in terms of age, sex, nutritional status, or height. The baseline characteristics of the study population are shown in Table 1.

Clinical Characteristics

Among the subjects in the steroid group, the most common diagnosis was relapsing NS (15 subjects, 51,7%), whereas in the non-steroid group, the majority of subjects were diagnosed with steroid-resistant NS (14 subjects, 45,2%).

The incidence of relapse during therapy showed that 14 subjects (48,3%) in the steroid group experienced at least two relapses within six months, whereas all subjects in the non-steroid group had fewer than two relapses within the same period (100,0%). Proteinuria status was also significantly different between the groups. In the steroid group, 20 subjects (69,0%) had positive urine protein levels (≥+2), whereas in the non-steroid group, all 31 subjects (100,0%) had either negative or trace levels of urine protein (Table 2).

Table 2. Characteristics of nephrotic syndrome patients based on treatment group

Characteristics	Steroid (n = 29)	Non-Steroid (n = 31)	p-value
Nutrititional Status	18 (62,1)	19 (61,3)	
Nephrotic syndrome; n (%)			<0,001a
Steroid-dependent	14 (48,3)	6 (19,3)	
Frequently relapsing	15 (51,7)	11 (35,5)	
Steroid-resistant	0 (0,0)	14 (45,2)	
Relapse frequency; n (%)			<0,001a
≥2 times/6 months	14 (48,3)	0 (0,0)	
<2 times/6 months	15 (51,7)	31 (100,0)	
Urine protein levels; n (%)			<0,001a
Positive (≥+2)	20 (69,0)	0 (0,0)	
Negative/trace	9 (31,0)	31 (100,0)	

*Analysis performed using the chi-square test.

Laboratory Characteristics

The biochemical parameters analyzed in both treatment groups included serum albumin, urea, creatinine, calcium, and total cholesterol levels. The results of the laboratory tests are summarized in Table 3.

Table 3. Laboratory characteristics of nephrotic syndrome patients based on therapy group

Laboratory Parameter	Steroid (n = 29)	Non-Steroid (n = 31)	p-value
Nutrititional Status	18 (62,1)	19 (61,3)	
Serum albumin (g/dL), mean (SD)	2,30 (0,49)	2,58 (0,64)	0,061a
Serum urea (mg/dL), median (min-max)	26,00 (9,00-123,00)	24,00 (10,00-88,00)	0,900b
Serum creatinine (mg/dL), median (min-max)	0,40 (0,26-1,94)	0,44 (0,20-1,71)	0,929b
Serum calcium (g/dL), median (min-max)	6,70 (5,80-8,60)	6,90 (5,80-9,40)	0,099b
Total cholesterol (mg/dL), mean (SD)	516,24 (96,53)	466,13 (108,36)	0,064a

a : Analysis performed using an independent sample t-tes
b : Analysis performed using the Mann-Whitney test
SD : standard deviation

This study is the first to compare laboratory characteristics in children with nephrotic syndrome (NS) receiving steroid and non-steroid therapy at RSUDZA Banda Aceh, The assessed parameters included urine protein levels and serum albumin, total cholesterol, calcium, urea, and creatinine levels as modalities for therapeutic evaluation in NS management. These assessments aim to prevent the progression to steroid-resistant nephrotic syndrome (SN), glomerular damage, glomerulosclerosis, and tubulointerstitial damage, ultimately reducing the risk of end-stage renal failure.

The study involved 60 pediatric NS patients aged 2-18 years, divided into steroid and non-steroid therapy groups. Among them, 22 males (75,9%) were in the steroid group and 24 (77,4%) were in the non-steroid group, with male-to-female ratios of 3,1:1 and 3,4:1, respectively. These findings align with those of previous studies reporting a higher prevalence of NS in males, with ratios ranging from 2:1 to 3:1 [8-11]. While gonosomes do not appear to play a direct role in NS, mutations in autosomal dominant or recessive genes are believed to contribute to glomerular filtration barrier damage (Kari et al., 2012).

Most study subjects were aged 5-11 years (44,9% in the steroid group and 48,4% in the non-steroid group), followed by those aged 12-16 years age range (34,5% and 25,8%, respectively). These results are consistent with findings indicating that NS is more common in children older than six years. However, variations in age distribution have been reported, likely due to differences in classification and study populations (Husein Albar, 2019).

Three problematic NS diagnoses were identified: frequently relapsing (43,3%), steroid-dependent (33,3%), and steroid-resistant (23,3%). These results align with the ISKDC report, which stated that frequent relapses occur in up to 50% of patients with relapsing NS (Wati et al., 2016). Regarding nutritional status, 62,1% in the steroid group and 61,3% in the non-steroid group had normal weight, consistent with previous studies reporting similar trends (Adrian Umboh, 2013; D Kandou Manado Valentine Umboh et al., 2019). Obesity and overweight were observed in 6,9% of the steroid group and 10% of the non-steroid group, reflecting the known long-term effect of glucocorticoid therapy on weight gain and central obesity (McCaffrey et al., 2016).

Stunting was observed in 44,8% of the steroid group and 32,3% of the non-steroid group, which is commonly associated with prolonged steroid use (McCaffrey et al., 2016).Steroids suppress growth hormone secretion and IGF-1 mRNA expression, inhibit bone growth, and cause osteodystrophy. Studies have shown that NS patients on steroids may experience significant growth retardation, with those aged 12-16 years being up to 10 cm shorter than expected (Boyer et al., 2023; Li et al., 2024).However, alternate-day steroid regimens have been linked to better growth outcomes compared to prolonged daily therapy, supporting the use of steroid-sparing agents in NS management (Li et al., 2024).

Proteinuria was detected in 69,0% of the steroid group (+2 proteinuria) and was absent or present at trace levels in all non-steroid group patients, suggesting a more favorable response to non-steroid therapy. Studies have reported varying proteinuria levels, likely due to differences in classification techniques (Juliantika et al., 2017). Massive proteinuria leads to hypoalbuminemia, a crucial indicator in NS monitoring, as it contributes to anasarca edema and hypovolemia due to intravascular fluid extravasation (Pardede & Rahmartani, 2016).

Serum albumin levels were lower in the steroid group [2,30 (0,49 SD)] than in the non-steroid group [2,58 (0,64 SD)]. Previous studies have reported similar trends, with decreased albumin levels resulting from increased glomerular filtration and subsequent protein loss (Nilawati, 2012). The compensatory increase in hepatic albumin synthesis is insufficient to counteract the loss, leading to sustained hypoalbuminemia and exacerbating proteinuria (Valavi et al., 2023).

Hypoalbuminemia also stimulates hepatic lipoprotein synthesis, which leads to hypercholesterolemia. Reduced lipoprotein lipase activity further impairs lipid metabolism, resulting in elevated free fatty acids and dyslipidemia (Adrian Umboh, 2013; Juliantika et al., 2017). In this study, mean total cholesterol levels were higher in the steroid group [516,24 (96,53 SD)] than in the non-steroid group [466,13 (108,36 SD)]. All subjects exhibited hypercholesterolemia, consistent with findings that frequently relapsing NS patients tend to have elevated cholesterol levels (Juliantika et al., 2017). Monitoring serum cholesterol is crucial in preventing complications, as increased plasma lipid levels are associated with a higher relapse risk in NS (Boyer et al., 2023; Trihono et al., 2023).

Cholesterol levels inversely correlate with serum albumin levels; lower albumin levels lead to increased cholesterol synthesis as a compensatory hepatic response (Primashanti, 2019). This correlation has been documented in patients with NS, with no significant differences between the steroid-sensitive and steroid-resistant groups (Mamesah et al., 2016).

Hypoalbuminemia influences hypocalcemia in NS, because calcium is primarily bound to serum proteins, especially albumin, and total

serum calcium levels are significantly affected by protein levels (Garniasih et al., 2016). Albumin serves as the main transport and storage medium for plasma calcium, with approximately half of the total plasma calcium being albumin bound. Protein binding to calcium occurs via EF-hand proteins, which have high-affinity calcium-binding sites. The EF-hand structure is prevalent in many calcium-binding proteins, including albumin (Husein Albar, 2019).

In this study, the average serum calcium level was lower in the steroid therapy group than in the non-steroid group [6,7 (5,8–8,6) vs. 6,9 (5,8–9,4)]. The literature suggests that hypocalcemia is a common feature in patients with NS, although some studies have reported normal serum calcium levels. Glucocorticoids contribute to hypocalcemia by reducing gastrointestinal calcium absorption and increasing urinary calcium excretion via decreased renal tubular reabsorption, leading to a negative calcium balance (Vorum et al., 1995).

Garniasih et al. (2016) found a correlation between serum albumin and total serum calcium levels in children, in which a decrease in total serum calcium was accompanied by a decline in ionized calcium levels. Similarly, Freundlich et al. (1986) reported a weak negative correlation between serum albumin and ionized calcium levels, as well as a very weak positive association between ionized calcium levels and proteinuria severity. Additional factors influencing ionized calcium levels included the duration of proteinuria before treatment and the patient's initial diagnosis, which were statistically correlated with ionized calcium levels in their study (Freundlich et al., 1986).

As shown in Table 3, the mean urea and creatinine levels were lower in the non-steroid therapy group than in the steroid therapy group. The literature indicates that approximately 30–40% of children with idiopathic NS experience elevated blood urea and serum creatinine levels due to hypovolemia. A reduction in glomerular filtration rate (GFR) in NS is attributed to hypovolemia and glomerular injury caused by the underlying pathology. Chronic kidney disease (CKD) may develop in some patients, particularly those with steroid-resistant NS (SRNS), although it remains rare in steroid-sensitive cases (Bhimma, 2014).

Creatinine levels in NS increase because of glomerulopathies that impair renal filtration. A study by Lowenborg EKM et al (1999). found that NS patients with histological changes had lower GFR, and a reduction in GFR increased the risk of SRNS by 14-fold. Conversely, low creatinine levels may result from increased protein catabolism of muscle origin as a compensatory response to massive proteinuria, a condition known as a negative nitrogen balance. Elevated urea levels in patients with NS may stem from increased hepatic urea production or dietary intake. While serum creatinine levels in patients with NS are not significantly high, urine volume remains low, making GFR a crucial parameter in assessing disease progression toward terminal renal failure (Manalu, 2019).

This study had several limitations that should be acknowledged. First, the cross-sectional design limits the ability to establish causality between the treatment regimens and laboratory outcomes. Longitudinal studies with larger sample sizes are required to assess the long-term effects of different NS therapies. Second, the study was conducted at a single center, which may limit the generalizability of the findings to a broader population. Multicenter studies involving diverse demographic and clinical settings would provide a more comprehensive understanding of the treatment outcomes. Finally, while this study focused on laboratory parameters, future research should incorporate clinical outcomes, quality of life assessments, and long-term renal function to provide a more holistic evaluation of NS management strategies.

Conclusion

This study demonstrates that non-steroid therapy in children with nephrotic syndrome (NS) at Dr. Zainoel Abidin General Hospital offers better proteinuria control and fewer relapses than steroid therapy. Despite no significant differences in serum albumin, urea, creatinine, or calcium levels between the groups, steroid therapy was linked to persistent proteinuria and steroid dependence.

Additionally, there was no correlation between nutritional status and nephrotic syndrome in patients receiving either steroid or nonsteroid therapy. These findings underscore the potential of immunosuppressant-based

therapy, while highlighting the importance of individualized treatment to minimize risks and enhance patient outcomes.

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