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Original Article

Ocular complications in pediatric nephrotic syndrome treated with corticosteroids

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Abstract

Background Posterior subcapsular cataracts (PSC) and raised intraocular pressure (IOP) are the most common ocular complications of oral steroid administration, particularly following long-term use or treatment with high doses.

Objective To evaluate the association between cumulative steroid dose and duration of treatment with the occurrence of PSC and raised IOP, as well as its associated factors in children with idiopatic nephrotic syndrome (INS).

Methods This cross-sectional study included children aged 4-18 years with INS who received oral steroid therapy for at least six consecutive months. Patients underwent complete eye examinations by an ophthalmologist to evaluate their visual acuity as well as the occurrence of PSC and/or raised IOP.

Results Of 92 subjects, 19.6% had PSC, 12% had raised IOP, and one had a best corrected visual acuity (BCVA) of <6/20. The median cumulative steroid dose was 12,161 (range 1,795-81,398) mg and median treatment duration was 23 (range 6-84) months. There were significant positive associations between cumulative steroid dose as well as treatment duration and the occurrence of PSC, with cut-off points of 11,475 mg and 24 months, respectively, as determined by receiver operator characteristic (ROC) curves. Females were four times more likely to have PSC compared to males (PR 4; 95%CI 1.57 to 13.38; P=0.001). Cumulative steroid dose and duration of treatment were not associated with raised IOP.

Conclusion Cumulative steroid dose of 11,475 mg or higher and/or duration of steroid therapy of 24 months of more were significantly associated with the occurrence of PSC, but not with raised IOP. **[Paediatr Indones. 2024;64:1-9; DOI: 10.14238/pi64.1.2024.1-9**].

Keywords: *poor birth outcome; malaria infection; remote area*

Nephrotic syndrome (NS) is one of the most common chronic diseases in children, caused by increased permeability of the glomerular filtration barrier. The worldwide prevalence of NS is approximately 16 cases per 100,000 children, with an incidence of 2 to 7 per 100,000 children.[1] In Indonesia, the incidence of NS has been reported to reach 6 per 100,000 cases per year, in children aged less than 14 years.[2] Males appear to be more commonly affected than females, with a ratio of 2:1. Idiopathic nephrotic syndrome (INS) is one of the major groups of childhood NS. This clinical condition refers to NS that is not associated with another identifiable systemic disease.[1] Based on recommendations from the *International Study of Kidney Disease in Children* (ISKDC), steroids are the mainstay of treatment in children with NS.[3] However, about one-third of steroid-sensitive children experience relapses and therefore, receive multiple and/or prolonged courses of systemic steroids.[1,3,4]

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The most common ocular complications associated with steroid administration are posterior subcapsular cataracts (PSC) and raised intraocular pressure (IOP) in one or both eyes.[4] Both of these complications contribute to 30% of blindness in children, which, in turn, has serious implications for child growth and development.[5] Several studies have reported PSC and raised IOP in children who received long-term oral steroid therapy.[6-9] However, the association between cumulative steroid dose and duration of treatment has yielded contradictory results in previous studies conducted worldwide.[8] Thus, we aimed to assess for correlations between cumulative steroid dose and duration of therapy with the occurrence of PSC and raised IOP in children with INS. We also aimed to identify factors associated with these complications, as there is currently no existing data on this matter in Indonesia.

Methods

This cross-sectional study was conducted from August 2018 to August 2019 at the Child Health Department and Pediatric Ophthalmology Division of the Ophthalmology Department of Cipto Mangunkusumo Hospital, Jakarta, Indonesia. The study was approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia. There were 199 children diagnosed with idiopathic nephrotic syndrome (INS) during the designated study period. Those aged 4-18 years and who had received steroids for at least six months as the main or adjunctive therapy were considered as eligible and were contacted to participate in the study. Children with congenital cataracts, diabetes mellitus, primary open angle glaucoma (POAG), ocular comorbidities such as trauma, infection, or inflammation, history of topical steroid or miotic use, family history of ocular disease at young age, as well as those with incomplete medical records were excluded from the study. Children who were uncooperative during the complete eye examination, had a history of exposure to high-dose (>2 Gray) and long-term (>2 years) X-ray or gamma-rays, as well as those otherwise indicated for steroid therapy (including those with connective tissue disease, such as juvenile idiopathic arthritis, systemic lupus erythematosus, or Henoch-Schönlein purpura) were excluded. History-taking and physical examinations were conducted prior to ophthalmic examinations. Written informed consent was obtained from all subjects' parents.

The demographic characteristics, diagnosis of INS, details of steroid treatment including age at initiation, type of steroid, cumulative dose, duration of consumption, and additional treatment were obtained from patient medical records (MR). The steroid dose given was calculated to an equivalent dose of prednisone. The cumulative dose and duration of treatment were calculated from the time of steroid initiation to either the time when steroid treatment was stopped or the time of the eye examination. Blood pressure was categorized as normal or hypertension (including elevated blood pressure, stage I, or stage II hypertension) based on the 2017 classification by *American Academy of Pediatrics* (AAP).[10] The diagnosis, management, and type of NS was based on the guidelines from the Nephrology Working Group of the Indonesian Pediatric Society.[11]

Detailed ophthalmologic examination was performed by a pediatric ophthalmologist consultant, including slit lamp biomicroscopic examination, fundoscopy, best corrected visual acuity (BCVA) using Snellen's chart and applanation tonometry using *iCare® Tonometer* to measure IOP, which was documented separately for each eye and expressed in mmHg. Raised IOP was defined greater than 21 mmHg.[12] The BCVA was expressed as a decimal acuity for measuring best corrected vision after use of corrective glasses and classified into two categories: BCVA <6/18 as 'low vision', corresponding to moderate-to-severe visual impairment, and BCVA ≥6/18 as 'normal vision'.[13]

Data were presented as frequencies, percentages, and medians with ranges. The Mann-Whitney test was used to analyze for possible associations between cumulative dose as well as duration of therapy and the occurrence of PSC and raised IOP. If the result was statistically significant, a receiver-operator characteristics (ROC) curve analysis was done to detect a cut-off value to determine the occurrence of PSC or raised IOP. The optimal cut-off value was selected using Youden's index, in which sensitivity + specificity - 1 is at the maximum value.[15] Factors potentially associated with these complications were analyzed by the chi-square, Fisher's exact,

Kolmogorov-Smirnov, and Mann-Whitney tests as appropriate. Data analysis was performed using SPSS version 22.0 (IBM, Armonk, New York). We calculated prevalence ratios (PR) with 95% confidence intervals (95%CI). P values <0.05 were considered to be statistically significant.

Results

A total of 199 patients were identified from electronic health record (EHR) data. Of these, 24 patients were excluded because of secondary NS and history of other illness, while 11 had consumed steroids for <6 months, 14 children were <4 years of age and 38 patients had incomplete data. We also excluded children with whom we lost contact, refused to join, and/or were not cooperative during the ophthalmic examination. We analyzed a total of 92 subjects. The subject recruitment pathway is described in **Figure 1**.

There were 56 males and 36 females. Subjects' median age was 10.1 (range 4-18) years. The median cumulative dose and duration of steroid treatment was 12,161 (range 1,795-81,398) mg and 23 (range 6-84) months, respectively. Steroid-resistant INS was the most common diagnosis. The demographic characteristics of subjects are presented in **Table 1**.

The prevalence of subjects with PSC and raised IOP were 19.6% and 12.0%, respectively. Three (3.2%) subjects had both PSC and raised IOP. One (1.1%) subject had a BCVA of <6/18, which was an indication for surgical intervention. One subject also had exudative retinal detachment that may have been related to his high blood pressure and obesity (**Table 1**).

Children with PSC were generally younger than those without (median age 9.8 and 10.2 years, respectively). However, sex was the only factor significantly associated with the occurrence of PSC, with females four times more likely to have PSC

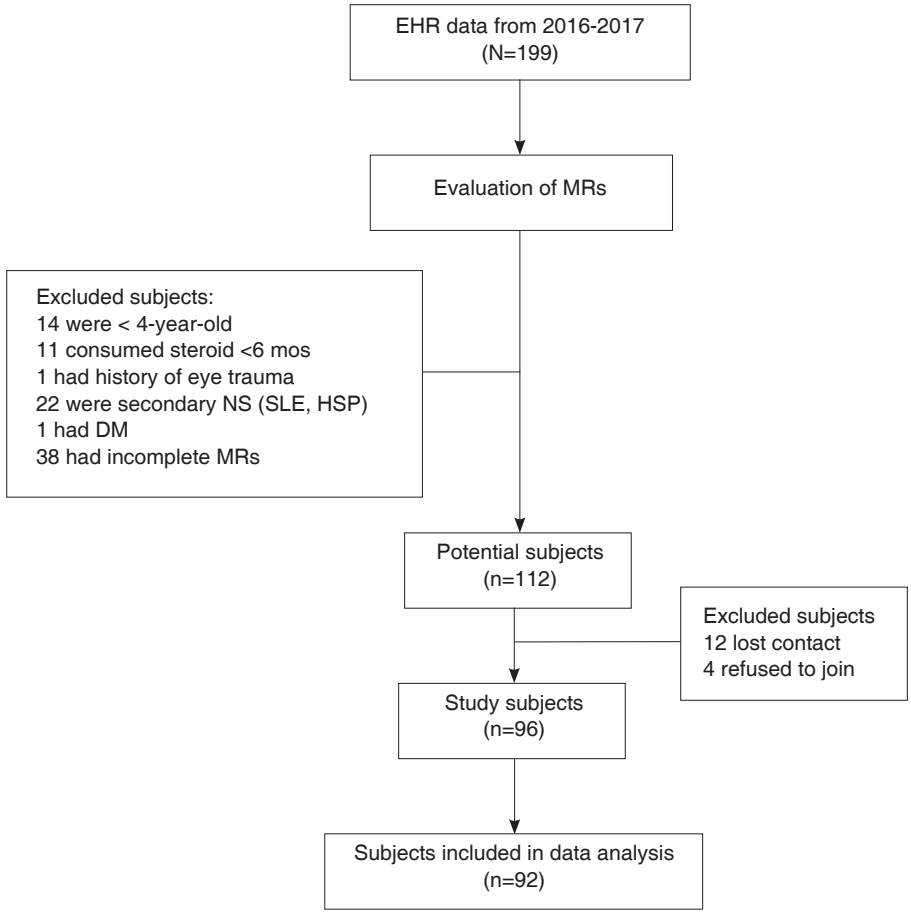

Figure 1. Recruitment of study subjects

Table 1. Demographic characteristics of subjects and occurrence of ocular complications

Characteristics, ocular complications	(N=92)
Median age (range), years	10.1 (4-18)
Sex, n (%)	
Male	56 (60.9)
Female	36 (39.1)
Blood pressure, n (%)	
Normal	58 (63)
Hypertension	34 (37)
Type of NS, n (%)	
SRNS	58 (63)
FRNS	17 (18.5)
IRNS	14 (15.2)
SDNS	3 (3.3)
Median age at starting steroid consumption (range), years	4.7 (1-16)
Type of steroid, n (%)	
Prednisone	83 (90.2)
Methylprednisolone	9 (9.8)
Type of therapy, n (%)	
Steroid only	21 (22.8)
Combined therapy	71 (77.2)
Median cumulative steroid dose (range), mg	12,161 (1,79-81,398)
Median duration of treatment (range), months	23 (6-84)
Ocular complications	
PSC, n (%)	18 (19.6)
Bilateral PSC	7 (7.6)
Raised IOP, n (%)	11 (12)
Bilateral raised IOP	7 (7.6)
Median IOP (range), mmHg	25 (22–28)
PSC + raised IOP, n (%)	3 (3.2)
Steroid-related visual impairment, n (%)	11 (12)
BCVA ≥6/18	10 (10.9)
BCVA <6/18	1 (1)
Exudative retinal detachment, n (%)	1 (1)

NS=nephrotic syndrome; SRNS=steroid resistant NS; FRNS=frequent relapse NS; IRNS=infrequent relapse NS; SDNS=steroid dependent NS; combined therapy=steroid combined with other drugs, such as levamisole, cyclophosphamide, mycophenolic acid, or cyclosporine; PSC=posterior subcapsular cataract; IOP=intraocular pressure; BCVA=best corrected visual acuity.

(PR=4; 95%CI 1.57 to 13.38; P=0.001) (**Table 2**).

All children with raised IOP received combined therapy. Further analysis showed no significant associations between raised IOP and any of the factors (**Table 3**).

The median cumulative steroid dose in children with PSC [16,030 (range 5,766-73,823) mg] was higher than those without PSC [11,156 (range 1,795-81,398) mg]. Moreover, duration of steroid treatment in those with PSC (36 months) was longer than those without (20 months). Further data analysis showed significant association between cumulative dose (P=0.007) as well as duration of treatment (P=0.006) and cataract formation (**Table 4**). In children with raised IOP, the median cumulative dose and duration of steroid treatment were not significantly different compared to children with normal IOP (**Table 4**).

The PSC in our study were detected as early as after eight months of steroid treatment, which highlights the importance of early initiation of ophthalmologic monitoring. These children with PSC were managed with correction of refractory errors using spectacles; one subject with BCVA <6/18 required extraction of PSC. Subjects with raised IOP were prescribed timolol eye drops and were evaluated regularly by an ophthalmologist.

Table 2. Characteristics of subjects with and without PSC

Characteristics	PSC present (n=18)	PSC absent (n=74)	PR (95%CI)	P value
Median age (range), years	9.8 (5.3-18)	10.2 (4-17.7)		0.570^
Sex, n (%)				
Female	13	23 (31.1)	4 (1.576 to 13.381)	0.001
Male	5	51 (68.9)		
Blood pressure, n (%)				
Hypertension	9	25 (33.8)	1.706 (0.750 to 3.878)	0.201
Normal	9	49 (66.2)		
Type of NS, n (%)				
SRNS	12	46 (62.2)	1.172 (0.484 to 2.837)	0.723
SSNS	6	28 (37.8)		
Median age of steroid initiation (range), years	4.9 (1.8-15.5)	4.5 (1-16)		0.318^
Type of therapy, n (%)				
Steroid + cyclosporine	9	39 (52.7)		0.989†
Steroid + non-cyclosporine	6	14 (18.9)		
Steroid only	3	21 (28.4)		

NS=nephrotic syndrome; SRNS: steroid resistant NS; SSNS=steroid sensitive NS including FRNS, IRNS, and SDNS; PSC=posterior subcapsular cataract; non-cyclosporine=levamisole, mycophenolic acid, cyclophosphamide. All statistical analyses were performed using Chi-square test, except ^Mann-Whitney test and †Kolmogorov-Smirnov test

Table 3. Characteristics potentially associated with raised IOP

Characteristics	Raised IOP (n=11)	Normal IOP (n=81)	PR (95%CI)	P value
Median age (range), years	7.5 (4.6–15.1)	10.5 (4–18)		0.073^
Sex, n (%)				
Female	5	31 (38.3)	1.296 (0.427 to 3.935)	0.746*
Male	6	50 (61.7)		
Blood pressure, n (%)				
Hypertension	6	28 (34.6)	2.047 (0.675 to 6.204)	0.318*
Normal	5	53 (65.4)		
Type of NS, n (%)				
SRNS	8	50 (61.7)	1.563 (0.444 to 5.498)	0.741*
SSNS	3	31 (38.3)		
Median age at steroid initiation (range), years	3.2 (1.3-14.7)	5 (1-16)		0.050^
Type of therapy, n (%)				
Steroid only	0	21 (25.9)		0.063
Combined therapy	11	60 (74.1)		

Combined therapy=steroid combined with other drugs, such as levamisole, cyclophosphamide, mycophenolic acid, or cyclosporine. All statistical analysis were performed using Chi-square test, except: *Fisher's exact test; ^Mann-Whitney test.

Table 4. Analysis of cumulative dose and duration of treatment and PSC or raised IO

Variables	PSC			IOP		
	Present	Absent	P value	Raised	Normal	P value
Median cumulative dosage (range), mg	16,030 (5,766-73,823)	11,156 (1,795-81,398)	0.007*	14,124 (4,239-30,579)	12,004 (1,795-81,398)	0.452*
Median therapeutic duration (range), months	36 (8- 61)	20 (6-84)	0.006*	31 (10-61)	21 (6-84)	0.064*

PSC=posterior subcapsular cataract; IOP=intraocular pressure; *Mann-Whitney test.

ROC analysis showed an area under the curve (AUC) between cumulative steroid dose and PSC to be 0.706 (95%CI 0.584 to 0.828; P=0.007). Using a cut-off value of 11,475 mg, cumulative steroid dose had 83.3% sensitivity and 52.7% specificity to predict PSC (**Figure 2a**). **Figure 2b** shows that the AUC between duration of steroid treatment and PSC was 0.708 (95% CI 0.571 to 0.846; P=0.006). The sensitivity and specificity of duration of steroid treatment using a cut-off value of 24 months were 72.2% and 56.8%, respectively. According to Youden's index, the optimal cut-off value to predict PSC was 11,475 mg for cumulative steroid dose and 24 months for treatment duration.

Discussion

Steroid-induced posterior subcapsular cataract (PSC) indicates the presence of an aberrant migration of lens epithelial cells at a central posterior location. Steroids possess glucocorticoid activity that alter protein components of the lens, secondary to protein adduct formation.[16] Many studies have reported cataracts to be a complication of long-term systemic steroid therapy. Of our 92 subjects, 18 (19.6%) had PSC. The prevalence of cataracts was similar to that reported in India (20%),[17] but much lower than that reported in Japan (33.3%).[9] Moreover, this result was higher than in Philippines (13.6%).[6] In the Japanese study, the duration of steroid therapy was longer compared to our study, whereas in the Filipino study, the number of subjects was fewer than in our study.

Steroid-induced raised IOP is secondary to open-angle glaucoma. Raised IOP might be due to the accumulation of extracellular matrix in the trabecular meshwork, which in turn increases aqueous outflow resistance.[18] In our study, the prevalence of raised IOP was 12%, which was similar to a prevalence of 15% reported in a study conducted in Medan, North Sumatera.[19] However, another study in Japan found a higher prevalence of IOP (30.8%).20 The retrospective cohort design of the Japan study, in contrast to our cross-sectional design, may have contributed to the higher prevalence. Studies on IOP in nephrotic children on long-term steroid therapy have been limited worldwide. In addition, the criteria used to define raised IOP can vary, thus making comparisons difficult. In our study, raised IOP was defined as an IOP of >21 mmHg, whereas another study had a cut-off value of >22 mmHg for raised IOP.9

Another ocular complication found in this study was visual impairment. Visual impairment was found in 12% of subjects, and one subject notably had a BCVA of <6/20. This proportion was slightly lower than that reported by a study in Medan (15%).[19] This difference may have been due to differences

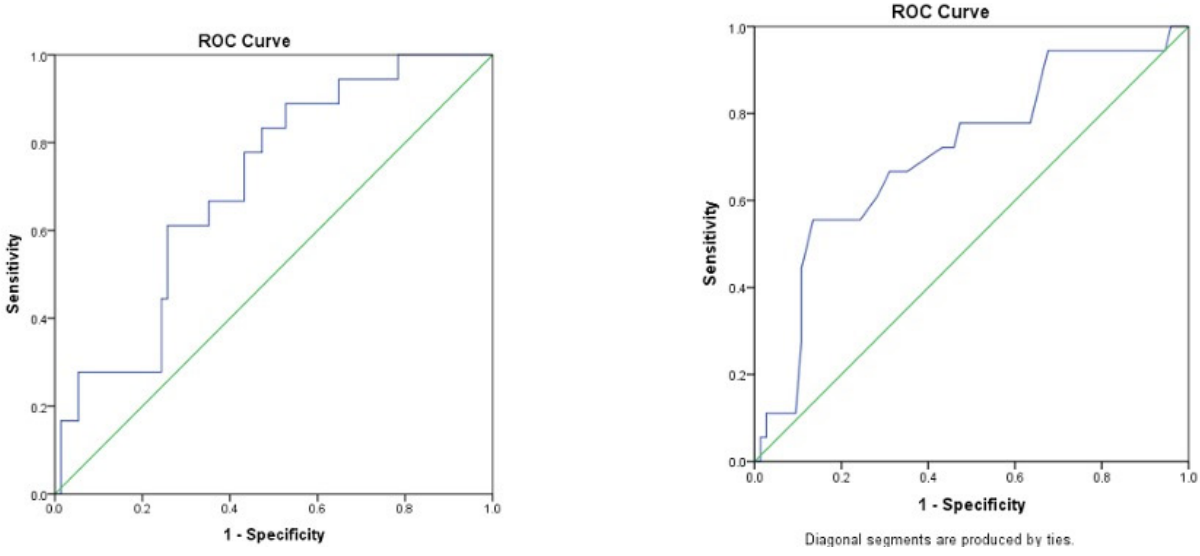

Figure 2. Area under the curve for (a) cumulative dose and (b) duration of steroid treatment to detect the presence of PSC

in sample size as well as the prevalence of subjects with concomitant visual impairments of PSC and raised IOP. In our study, three subjects had all three conditions: PSC, raised IOP, and visual impairment. This may have been related to the fact that steroid initiation occurred very early (1.8 years) in one subject, a long treatment duration of 61 months in one subject, and decreased kidney function in another subject, which was thought to cause more severe steroid side effects.

Many studies have been conducted on the importance of cumulative steroid dose and duration of treatment related to the development of PSC and raised IOP, but with inconclusive results. We found that higher cumulative dose and/or longer duration of steroid therapy led to a higher occurrence of PSC. The results of our study were similar to a previous study in Japan, in which children with PSC had a median cumulative steroid dose of 9,610 (range 2,910-16,650) mg and a median duration of treatment of 25 (range 7-65) months, while those without PSC had a median cumulative dose of 4,680 (range 1,240-21,890) mg and a median duration of treatment of 8 (range 2-35) months.[7] Another study also found a significant difference in cumulative steroid dose between subjects with PSC and those without [17,322 (SD 73) mg/m^2 *vs.* 8,627 (SD 8,208) mg/m^2, respectively], but not in duration of treatment [53 (SD 37) months vs. 48 (SD 37) months, respectively].[14] In contrast to our findings, a study conducted in India found no difference between those with and without PSC in cumulative steroid dose [389.03 (SD 255.89) mg/kg *vs.* 424.1 (SD 258.4) mg/kg, respectively] or duration of treatment [81.2 (SD 69.9) weeks vs. 87.4 (SD 73.2) weeks, respectively] and cataract formation.[8]

In our study, cumulative dose and duration of treatment was not significantly correlated with the occurrence of raised IOP, despite both being higher in children with raised IOP than in those without raised IOP. These results were similar to those reported by a study in India.[8] In contrast, a study in Southeast Asia showed a significant difference between those with and without IOP in duration of treatment [33.33 (SD 18.9) months *vs.* 12.59 (SD 13.9) months, respectively], but not in cumulative dose [8,978.67 (SD 2,952.82) mg *vs.* 5,323.41 (SD 4,824.26) mg, respectively].[19] Our study included subjects who had stopped consuming steroids for a period of time, which may have contributed to the difference in results. Raised IOP occurs during the period of steroid consumption, but IOP will quickly decrease once steroids are withdrawn, and this reduction can occur within days to weeks.[18]

The heterogeneity of studies in terms of sample size, racial backgrounds of the population studied, duration of treatment, and cumulative steroid dose may explain the differences in observed prevalences. In a previous study, there was a significant difference in the distribution of HLA-CW3 antigen between patients with and without PSC among children on steroids following renal transplantation, suggesting the presence of a genetic predisposition to the development of cataracts.[21] Similarly, a genetic basis has been identified for the development of raised IOP, implicating the trabecular meshwork-inducible glucocorticoid (TIGR) gene.[22]

Few studies have reported on demographic characteristics and formation of PSC and raised IOP. The median age of PSC subjects was 9.8 (range 5.3-18) years, which was lower than that in those without PSC [10.2 (range 4-17.7) years]. However, no association was found between age and cataract formation. A previous study noted a lower mean age in children with PSC than in those without (9 *vs.* 11.5 years, respectively), as well as a correlation between age and cataract formation.[8] The difference between results might have been due to the narrower age range in children with and without PSC. Likewise, age at steroid treatment initiation was similar between children with and without PSC, and no correlation was found. In contrast, a study in Hong Kong found a correlation between age at steroid initiation and the occurrence of PSC. In that study, children with PSC had an earlier age of steroid initiation compared to those without PSC (2 *vs.* 5.4 years, respectively).[14]

Further data analysis showed that female sex was associated with PSC in children. A study has reported that females had lower vitamin D levels compared to males, which may be associated with an increased risk of developing PSC.[23] Many other factors may have influenced the results of this study, such as medication adherence, exposure to sunlight, exposure to cigarette smoke, and estrogen levels, which may confound the results of the study.

At present, the contribution of immunosuppressant to cataract formation in children

with INS remains unclear.[6,14] In our study, no association was found between cyclosporine treatment and PSC. Contrastingly, a previous study evaluated the effect of concomitant administration of steroids with azathioprine and/or cyclosporine on the occurrence of steroid-induced cataracts in children who had undergone renal transplantation. In the group receiving combination therapy of all three drugs, the incidence of cataracts was higher than that in the group receiving a combination of only two drugs.[24] There were several differences between studies, including the clinical characteristics of the study population as well as the different types and doses of medications given.

Children with raised IOP had a lower median age at steroid initiation compared to those without raised IOP [3.2 (range 1.3-14.7) *vs.* 5 (range 1-16) years, respectively]. The results showed a trend towards a correlation between age and raised IOP, but this result did not reach statistical significance. Rajeghinezad et al. reported that the lower the age of INS onset and steroid consumption, the higher the possibility of raised IOP.[25] None of the other variables were significantly correlated with raised IOP, possibly due to the small sample size in our study.

The optimal cut-off value to predict cataract formation was 11,475 mg for cumulative steroid dose (83.3% sensitivity, 52.7% specificity) and 24 months for duration of therapy (72.2% sensitivity, 58.8% specificity). We found these sensitivity values to be fairly good to predict the formation of PSC in children with INS receiving long-term oral steroid therapy. To the best of our knowledge, our study is the first to date to report cut-off values for cumulative dose and duration of treatment. Therefore, the results of our study can be used as a reference for future studies. The present study is also the first in Indonesia to assess for correlations between cumulative steroid dose and duration of treatment with the formation of PSC and raised IOP in children aged 4-18 years with INS.

The limitations of our study were related to study design. Cross-sectional designs only measure the outcome once at certain circumstances. However, the exact timing of the onset of ocular complications in affected subjects could not be assessed. In addition, this type of study design will especially affect the measurement of IOP values, as some subjects had stopped steroid treatment at the time of IOP measurement. Intraocular pressure was reported to be reversible when steroid consumption was stopped. Other limitations included not analyzing other possible related factors, such as medication adherence, sunlight exposure, cigarette smoke, vitamin D status, and estrogen levels, which may act as confounders.

A more robust study design is needed to assess the development of steroid-induced PSC and raised IOP. Further studies are also required to determine the interactions between other factors associated with PSC formation, including genetic and environmental factors, such as sunlight exposure, cigarette smoking, vitamin D status, and estrogen levels.

In conclusion, higher cumulative steroid dose and/or longer steroid therapy duration were significantly associated with the occurrence of PSC, with cut-off values of 11,475 mg and 24 months, respectively. This study highlights the importance of serial ophthalmologic evaluations in children with INS prior to steroid administration and at each serial follow-up visit after steroid administration, especially in children who undergo prolonged steroid treatment in order to detect ocular complications as early as possible.

Conflict of interest

None declared.

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