ORIGINAL ARTICLE

Medication Adherence in Patients with Nephrotic Syndrome

AMALLIA NUGGETSIANA SETYAWATI[1,2], OMEGA MELLYANA[2], M. HERU MURYAWAN[2]
[1]Department of Biochemistry, Faculty of Medicine, Diponegoro University
[2]Department of Pediatrics, Faculty of Medicine, Diponegoro University
Correspondence to Amallia Nuggetsiana Setyawati, email amallia.setyawati@fk.undip.ac.id

ABSRACT

Background: Pediatric nephrotic syndrome (NS) are universally treated according to defined protocols. Medication adherence is important part of patient management to reach clinical goals.
Aim: To identify whether the medication book intervention may improve outcome in patients with Nephrotic syndrome.
Method: This randomized study involved 47 pediatric patients with NS in a pediatric nephrology outpient clinic or ward. However, 3 subjects were not included in the analysis. Both groups received education by the attending doctors. A diary-book was given to intervention group for medication reminder. The treatment outcome, proteinuria was assessed after 2 months.
Result: The remission status between intervention (n=22) and control group (n=20) were not different (p=0.346). In term of medication adherence (MMAS-8) showed average of 7.04+0.15 and 7.25+1.6 (p=0.353). There were 22 subjects who were included in the intervention group, the average compliance filling was 83.22+0.80% in the remission group while in the proteinuria (unresponsive) was 80+2.04%.
Conclusion: There was no significant difference of the use of medication diary-book in for parents of NS. However, the average compliance filling is slightly higher in remission status patients in intervention group**.**
Keyword: Nephrotic syndrome, medication diary-book book, remission status

INTRODUCION

Medication monitoring is considered the first step toward self-care and recognition[1]. A proper self-monitoring increased body awareness and therefore enhanced a better communication with doctors. Human biopsychosocial health care is engaged with emotional and somatic mindfullnes[2].

Among the most common pediatric kidney disease, it is Nephrotic syndrome (NS). The disease's characters are commonlysensitive to resistant with steroid treatment. The management of NS requires outpatient follow-up and family engagement[3]. Frequent relapses are common in NS. The complexity of NS increases as it requires a thorough parental home-based management intaking the drugs with lowering doses and alternate day-intakeprotocol. In a standard follow-up period, the disease requires medical care for relapses or deficient response to steroids[4].

The practice of non-adherence may cause of treatment failure in pediatric chronic conditions. There were several reasons for not taking the medication as advised by the doctor e.g.; forgetting to take the medication, being away from home, school schedule, exhaustion from long term treatment, drug shortage (delay to the outpatient care visit) were barriers found to be associated with a low adherence. The involvement of family education in combination with self-regulation, may benefit patients with chronic disease. Mutual understanding of the motives of parents and caregivers is important for children with chronic conditions and may improve outcomes[5].

METHOD

This research was conducted from July 2018-July 2019. This research was conducted at inpatient ward and outpatient care of Pediatric Nephrology.This was an experimental research with randomized controlled trial performed with systematic sampling.Research subject was nephrotic syndrome cases who were coming to the inpatient ward and outpatient care of nephrology clinic Dr. Kariadi hospital and meeting the inclusion and exclusión criteria, as follow; (inclusión criteria):Sensitive steroid NS (initial attack and relapse), following the treatment protocol recommended by the pediatric nephrologist recommended by working group of pediatric nephrology, age at onset: ≥1.0 to < 18 years, written informed consent. We did not involve subjects who did not wish to participate in the study. NS due to specific kidney disease (such as Henoch-schoenlein purpura, acute glomerolunephritis, lupus erythematosus, or associated with hepatitis B or C), participation in another trial, and children with congenital forms of NS were excluded from the study. A structured medication diary-book consisted of part I. The patient logbook which contained individual data (age, date of birth, gender, initial date of diagnosis), part II. NS introduction (definition, clinical characteristic, management, complication, part III: Medication check list, and parental home care for patient (daily monitoring of symptom and drugs taken). Parental counselling of NS consists of overview of Nephrotic Syndrome, treatment of Nephrotic Syndrome, psychosocial and dietary issues with NS, the advantages of immunosuppressive treatments and outcomes known for patients with steroid dependent NS.

The collected data is checked for the completeness and correctness of the data. Further data is coded, tabulated and inserted into the computer. Nominal data such as patient's gender, patient's transportation time, patient's diagnosis, parental education of both father and mother, and socioeconomic status (BPS category) are described as frequency distributions and percentages. While numerical data such as current patients 'age, age at onset, transportation time, compliance percentage, and MMAS-8 expressed as mean and standard deviation. Data were analysed using computer with SPSS 17.0 program (1) Comparison of proportion of each subject group compared

with using Pearson Chi-Square test for categorical data and Shapiro wilks for numeric data (2) Compare mean test to compare the MMAS-8 from each group, using Mann-whitney test (3) Two-sided Fischer's exact test was applied to evaluate remission status for intervention and control group (4) Average difference test to compare mean duration of NS between 2 groups using independent t test (5). Stastically, it is considered to be significant if the difference with p<0.05, 95% confidence interval and 80% power. Every NS patient who met the sample criteria had been asked for parental/ guardian consent using written informed consent. This research had been granted approval by the ethics committee accordingly.

RESULT

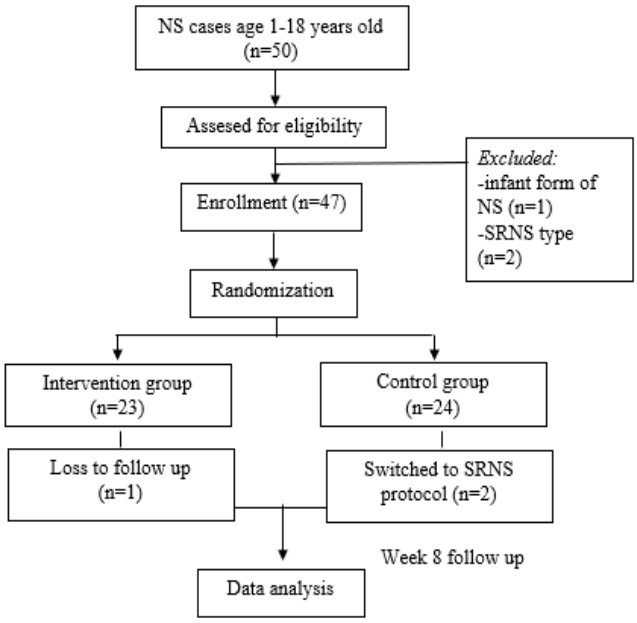
Research subject characteristic**.** During the research period (July 2018- 2019) there were 47 NS patients age 1-18 years old at RSUP Dr. Kariadi Semarang who met the inclusion criteria. There were subjects who were excluded during the study follow up due to protocol change. Below, it is described the research flow of the study subjects.

Table 1: Characteristics of study patients

Variable	**Intervention** (n=22)	**Control** (n=20)	***P***
Age, mean	8-year 5 month + 10 month	9-year 1 month + 1 year 1 month	0.22±
Age at diagnosis	6-year 6 month ± 10 month	5-year 8 month ± 10 month	0.32±
Albumin, at onset	2.08 ± 0.8	2.1 ± 0.9	0.20±
Hematuria, at onset	5/22(22.7%)	5/20 (25%)	0.863*
Hyperlipidemia, at onset	18/22(81.8%)	15/20(75%)	0.591*
Infection			
-Respiratory track	6	4	0.849*
-Dermatological	1	2	
-Urinary tract	1	2	
-Caries dentine	4	6	
-Absent	8	8	
Gender, n (%)			
Male	15	13	0.827*
Female	7	7	
Transportation time			
-1 hour	10	7	0.289*
-2-3 hours	12	11	
->3 hours	0	2	
Diagnosis			
Initial attack	7	3	0.201*
Relapse	15	17	
Parent's education level			
Father			
-High (>senior high school)	13	11	0.789*
-Low	9	9	
Mother			
-High	11	9	0.746*
-Low	11	11	
Health insurance			0.23*
-BPJS	18	19	
-Jamkeskot	1	1	
-Self pay	3	0	
Socioeconomic status			
BPS	5	4	0.830*
Poor (<10 points)	17	16	
Adequate (>10 points)			

±Shapiro-wilks
*****Pearson Chi-Square
Education level low (<junior high school) high (>junior high school)

Fig. 1: The CONSORT flow of study diagram chart (enrollment, intervention allocation, follow-up, and data analysis)



Regarding to the gender, age, transportation time, parental education, education economic background, there were no significant difference. More males were included in the study. There were 9 patients who were coming from poor SES background (23%).

During study course 42 parents received a verbalexplanation, subsequently 22 patients did not receive any intervention. At the time of analysis (August 2019), twenty-two patients who were coming from the intervention and twenty patients were in the control group. The remission status in the control group was 19/20 patients and, in the intervention, group was 18/22 patients. The exact 2-sided significant Fischer's exact test showed *p value* of 0.346.

Table 2: Remission status between control and intervention group

	Remission status	
	Yes	**No**
Control (n=20)	19	1
Intervention (n=22)	18	4

*P value 0.346 *Fischer's exact test*

The MMAS-8 was applied to evaluate the medication adherence between intervention and control group. The Shapiro walk distribution analysis showed P=0.00 and subsequently Independent samples Mann-Whitney U test was performed to identify significance, the result was with p value of 0.353.

Table 3: MMAS-8 and remission status

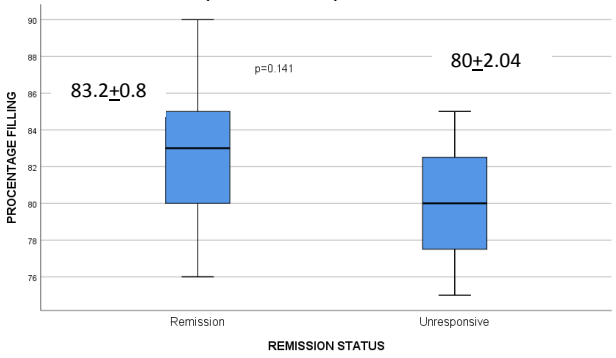
	Group	
	Intervention	**Control**
MMAS-8	7.04±0.15	7.25±1.6

P value 0.353 *******Independent samples Mann-Whitney U test*

There were 22 subjects who were included in the intervention group, the average percentage filling was

83.22±0.80% in the remission group while in the proteinuria (unresponsive) was 80±2.04%. The means comparison between groups showed *p value* of 0.141.

Fig. 2: Compliance in filling the medication book (%), remission status n=18 and unresponsive n=4, p=0.141



DISCUSSION

In our study, between control and intervention group was determined by rotating cycle nephrology resident. The groups both received information regarding to the disease, dietary, and medication to take. The possible identified confounding factors that may influence the remission status such as age at diagnosis, albumin at onset, haematuria at onset, hyperlipidemic at onset, concomitant infection, and gender have been elucidated. The treatment protocol used is in concordance with Indonesia Pediatric Nephrology Working Group[6].

Regular medication taking and be present for scheduled hospital appointments are the aims of medication diary-book provision.There are also sheets for parents to freely write down any additional information, such as reasons for not taking the medication.Sense of parents' control over the wellbeing of their child could have been added with medication diary-books[7]. Fundamentally, this may improve compliance with prescribed treatment. A study identified that the non-compliance manner to steroid therapy can be accountable for multiple relapses[5].

This randomized research assessed the efficacy of using an NS treatment outcome using medication diary-book. This study assessed the use of a medication diary-book on NS patients' treatment outcome. Medication diary-book-books may improve parents/patients and health facilities treatment's plan.[5]However, the use of the diary-book might be a problem for low-educated mothers[8].

The mean age of patients at diagnosis confirms to the known epidemiology of NS in western countries. In our study concluded that the male patients were 2:1 This was consistent with the reported incidence of INS being 6.49 cases/100,000 children per year, with no clear correlation with the geographic region. The male: female ratio was 1.9 and about 50 per cent of children were diagnosed < 5 years of age[6].

Socioeconomic status is considered to be one of the nonmodifiable individual influences adherence include demographic variables such as age, gender, race, socioeconomic status and cognitive ability. Most of the cases which are included in the study are coming from adequate socioeconomic status based on the National Statistic Bureau (BPS) criteria system. There were no significant differences in basic characteristic data of the patients (age, gender, transportation-time, economic background, parental education history between the intervention and the control groups).Forty-two parents received a verbal explanation, subsequently 20 patients did not receive any intervention. At the time of analysis (August 2019), twenty-two patients who were coming from the intervention and twenty patients were in the control group.

It was concluded for no significant difference between the control group and in the intervention groupin the remission status. The exact 2-sided significant Fischer's exact test showed *p* value of 0.346. Shotened time for first recurrence and concomitant infection during recurrences will predict regular recurrences in the future. Such predictors can be useful in treating patients, in closer evaluation and in developing better treatment protocols and relapse-specific interventions.[7] Although the unisgnificant difference result, it shows an important result that the communication to patient and or caregiver in both groups are considered to be sufficient for patient's compliance. Parents often remember when to give the medication by looking at the medication log provided by Dr. Kariadi hospital, notes on handphone, calendar and medication label. The diary use has been found to be very similar between patients/parents. This may be explained by the effort provided by the parents of chronic disease patients who tend to be more compliant[9]. As a percentage of the Indonesian population is analphabetic,some parents may have not been able to fill in the diary, however they seek for assistance to guide during the filling. Furthermore, parents may have not well understood the instructions, or the instructions to fill in the diary were unclear or not always the same. The overestimation is very common and it has been shown that there is an average 30% surplus of diary entries. Certain factors that may lead to its unreliability, including the possibility the patient the falsified rise in patient adherence rate and inability to return the diary at the appointed time.[7]The plausible explanation for these findings is that patients who have started to take medication are aware of the importance and the benefits of therapy and are thus compliant to their diary and therapy. In another chronic CKD study which involved 558 CKD patients, suggested that less adherence was linked to increased drug frequency, but not with the number of medical problems needing treatment.[10] Reinforcement improves compliance. It is important to check the diaries. The reliability of all the entrances in the diaries remain in question. There is a possibility that the parents did not fill the medication diary-book as scheduled. It is thus doubtful whether parents have written down the truth/real intake of medication. Parents knowing, they had an appointment, out of guilt/shame/fear may have filled many marks before the appointment to make good impression on the doctor during their visits. Written marks may not mean taken medication, but unwritten marks may not mean untaken medication either.

Adherence in taking the medication is fundamental in the management of NS. The MMAS-8 was not different between group intervention (7.04±0.15) and control (7.25±1.6) with *p* 0.353.

The parental education system may have led to the state of remission. The initiative aims to make clear the essence of the disease and the need for all people, particularly low educational background families.This may be explained that the parental education program which aims to make parents know the disease's nature and the treatment's goal comprehensible for all families, might have contributed to the remission status. There is a consideration that families with a low background in education may require more time to comprehensively understand the messages. There are several studies which indicate that repeated education based on patient or parent cognitive abilities increased the awareness and care's outcomes[11].

The attitudes, motives, social and economic factors, levels of physical / cognitive disability of the patient; particular drug treatment issues; the medical condition being treated; and the health care system in which the patient receives care may affect medication adherence[12]. In this study the MMAS-8 was applied to evaluate the medication adherence between intervention and control group. The Shapiro walk distribution analysis showed P=0.00 and subsequently Independent samples Mann-Whitney U test was performed. MMAS-8 score for intervention was 7.04±0.15 and control 7.25±1.6, *p* =0.353. In a study that included a total of 45 patients with pediatric nephrotic syndrome, it was concluded with 30 patients adhered to the prednisolone regimen and 15 were non-adherent to the regimen. Upper respiratory tract infections were the most prevalent infections, observed in 31%. Non-adherence was observed in 33.3% of the patients according to the MMAS-8. Trate of relapse was significantly different in comparison with the adherent group. Thus, it may lead to frequent hospitalizations. Subsequently, it may have some considerable cost burden on the parents. The most common reason for non-adherence was found to be a busy school schedule for the child, followed by symptoms resolving and the child feeling better. In a study, the relapse rate per patient in the non-adherent group was twofold higher than in the adherent group, signifying a need to improve adherence through intensive patient counselling and education[13]. The cause of remission is drug intake in accordance with doctor's recommendations. In our study, most of the patients and parents say that they can easily contact their attending pediatric nephrologists by WhatsApp and or SMS. Suggesting that there is a positive reinforcement in the medication programme.

There were 22 subjects who were included in the intervention group, the average percentage filling was 83.22±0.80% in the remission group while in the proteinuria (unresponsive) was 80±2.04%. The means comparison between groups showed *p value* of 0.141.

There were several limitations identified in our study: (1) The reported consumption of medicines in the diary log does not necessarily indicate that the drug was actually taken, (2) The contamination effect of providing medication-diary book(3) We did not examine all the histopathology in our subjects, as known that there is a risk of histological features associated with poor prognosis (4) Some mothers of pediatric NS patients created their own medication book or self-reminder (handphone, notes on calendar) to maintain the intake of prescribed medication.

This confirms that medication diary-book may be a reminder method to improve medication adherence. There is not any significant difference in remission status and MMAS-8 in the study group patients. Therefore, the improvement of medication diary-bookwhich includes the tailoring of medical education to the specific characteristics of each patient.

CONCLUSION

Although, there was no significant difference of the use of medication diary-book in for parents of NS. However, the positiveness of average compliance filling is slightly higher in remission status patients in intervention group.

REFFERENCE

1. Fouda MA, Youssef DM, Elseifi OS, Frere NO. Biopsychosocial model versus biological model in managemen of childhood nephrotic syndrome, single center experience, Egypt. Indian J Med Res 2015;2:6:1-13.
2. Kanbara K, Fukunaga M. Links among emotional awareness, somatic awareness and autonomic homeostatic processing. J BioPsychoSocial medicine. 2016;10(1):16.
3. MacHardy N, Miles PV, Massengill SF, Smoyer WE, Mahan JD, Greenbaum L, et al. Management patterns of childhood-onset nephrotic syndrome. J Pediatric Nephrology. 2009;24(11):2193-201.
4. Borges K, Sibbald C, Hussain-Shamsy N, Vasilevska-Ristovska J, Banh T, Patel V, et al. Parental health literacy and outcomes of childhood nephrotic syndrome. J Pediatrics. 2017;139(3):e20161961.
5. Ducharme FM, Zemek RL, Chalut D, McGillivray D, Noya FJ, Resendes S, et al. Written action plan in pediatric emergency room improves asthma prescribing, adherence, and control. J American journal of respiratory. 2011;183(2):195-203.
6. Albar H. Tata laksana Sindrom Nefrotik Kelainan Minimal pada Anak. J Sari Pediatri. 2016;8(1):60-8.
7. Sitaresmi MN, Mostert S, Gundy CM, Ismail D, Veerman AJ, cancer. A medication diary- book for pediatric patients with acute lymphoblastic leukemia in Indonesia. J Pediatric blood. 2013;60(10):1593-7.
8. Sitaresmi MN, Mostert S, Schook RM, Veerman AJ. Treatment refusal and abandonment in childhood acute lymphoblastic leukemia in Indonesia: an analysis of causes and consequences. J Psycho- Oncology. 2010;19(4):361-7.
9. Eiser C. Effects of chronic illness on children and their families. J Advances in Psychiatric Treatment. 1997;3(4):204.
10. Blydt-Hansen TD, Pierce CB, Cai Y, Samsonov D, Massengill S, Moxey-Mims M, et al. Medication treatment complexity and adherence in children with CKD. J Clinical Journal of the American Society of Nephrology. 2014;9(2):247-54.
11. Hazarika M, Mishra R, Saikia BJ, Bhuyan C, Nyuthe C, Sarma A, et al. Causes of Treatment Abandonment of Pediatric Cancer Patients–Experience in a Regional Cancer Centre in North East India. J Asian Pacific Journal of Cancer Prevention. 2019;20(4):1133-7.
12. Diong SC, Syed SZ, Rasat R, Wan IW. Parental knowledge on nephrotic syndrome and disease relapse in children. J Med J Malaysia. 2019;74(4):289.
13. Panda BK, Sharma J, Srivastava P, Mishra A, Practice. Paediatric nephrotic syndrome: prednisolone treatment adherence and short-term outcomes. J European Journal of Hospital Pharmacy: Science. 2013;20(6):346-50.