

INTERVENTION TO IMPROVE MEDICAL ADHERENCE IN PEDIATRIC KIDNEY TRANSPLANT RECIPIENTS

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Abstract

Background: Adolescent age at transplantation has long been recognized as a risk factor for graft failure, and a major contributor might be medical nonadherence. Many interventions have been applied to improve adherence in adults. However, there is limited data about intervention in pediatric kidney transplant recipients.

Objectives: The study aimed to study the improvement of medical adherence in pediatric kidney transplant recipients after receiving the intervention and to evaluate the associated factors to medical non-adherence

Methods: A single-center randomized controlled trial was conducted on pediatric kidney transplant recipients at Phramongkutklao Hospital, aged below 21 years, with at least one year post-transplantation and without acute rejection within three months. Randomization was 1:1. The intervention included educational sessions with individual booklets, telephone calls, or video call visits every two weeks, with regular assessment of adherence. Adherence was assessed using the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS) and the coefficient of variation (CV%) of tacrolimus level.

Results: Thirty-three patients were eligible: 17 for intervention and 16 for control. The mean age was 15.7 ± 3.12 years. Nonadherence prevalence at baseline was 30.3% by questionnaire and 40.7% by %CV. After one year, the total number of non-adherents decreased to 21.2% using the questionnaire and 15.4% using %CV, but there was no difference between the intervention and control groups. After performing a multivariate analysis to evaluate the factors associated with medical nonadherence, no factor was significantly associated. However, some factors, such as the total number of prescribed drugs, tended to be significant ($p = 0.071$ and 0.331 using univariate and multivariate analysis, respectively).

Conclusion: The prevalence of medical nonadherence in pediatric kidney transplant recipients is higher than in adults. Medical nonadherence is complex; interventions must be individualized and done with a multidisciplinary team.

Keywords: medical nonadherence, pediatric kidney transplantation, BAASIS questionnaire, intervention, %CV

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Introduction

Medical nonadherence has a significant impact on kidney transplant patients, including allograft rejection and loss. The 2022 Annual Report of Organ Transplantation in Thailand revealed that graft survival of pediatric patients below 18 years old at 1, 5, 10, and 15 years was 95.4%, 80.8%, 59.2%, and 44.9%, respectively. Causes of graft failure were chronic allograft nephropathy (34%), nonadherence (15%), and graft rejection (14%).⁽¹⁾ Adolescent age at transplantation has long been recognized as a risk factor for graft failure. Data from USRDS from 1928 to 2009 demonstrated that graft failure peaked at 6.6 per 100 person-years among 19-year-olds, and nonadherence was proposed to be a major contributor.^(2,3) In 2010, the estimate of nonadherence among patients aged 10 to 19 was as high as 31.8%.⁽⁴⁾

When patients lose graft function and return to dialysis therapy, their mortality rate increases significantly compared to patients awaiting transplantation.⁽⁵⁾ Thus, nonadherence should be considered to prolong graft and patient survival.

Many interventions have been applied to improve medical adherence. A study from Foster et al.⁽⁶⁾, which was a randomized trial of a multicomponent intervention to promote medication adherence: The Teen Adherence in Kidney Transplant Effectiveness of Intervention Trial (TAKE-IT) has been conducted with the use of a 3-month interval coaching technique and reminder intervention such as text message, e-mail, or visual cue and the use of electronic monitoring to monitor adherence. After applying these interventions, the participants in the intervention group had significantly greater odds of taking medications than those in the control group (Odds ratio 1.66, 95% CI 1.15-2.39).

Due to technological advancement and limitations of medical expenses, Schmid et al.⁽⁷⁾ have attempted to apply telemedicine to improve medical nonadherence in adult kidney transplant recipients and revealed that telemedicine could reduce medical nonadherence significantly (17.4% V.S. 56.5%, $p = 0.013$). Furthermore, Data from Andrew et al.⁽⁸⁾, who have been gathering multiple case studies of telemedicine in adult kidney

transplantation in Australia, demonstrated that telemedicine could reduce medical expenses, traveling expenses, and loss of time with similar satisfaction to in-person visits.

Studies about adherence and interventions to improve medical adherence in pediatric kidney transplant recipients are scarce. Therefore, we conducted this study to find an intervention that can improve medical adherence in pediatric kidney transplant recipients and practically conduct it.

Methods

Study design

A randomized controlled trial was conducted on pediatric kidney transplant recipients at the Division of Pediatric Nephrology, Phramongkutklo Hospital, Bangkok, Thailand. The Institutional Review Board, Royal Thai Army Medical Department approved the study (No. IRBRTA 302/2566, Code: R009h/66). Written informed consent was obtained from all participants and parents for those aged < 18.

Study population

Eligible pediatric kidney transplant recipients aged below 21 who were at least one year post-transplantation, had functioning grafts and could be followed up by telemedicine were participants. Participants were excluded for acute rejection within three months.

Study overview

Participants were recruited, and the baseline characteristics of participants and parents were obtained by interviewing and reviewing medical records. All participants answered the Basel Assessment of Adherence to Immunosuppressive Medications Scale, BAASIS⁽⁹⁾, a self-report questionnaire to assess baseline nonadherence. Then, participants were randomly assigned to either an intervention or control group using blocks of four methods with adjusting with the factors previously described to impact the adherence: age group (aged < 17 years or ≥ 17 years) and baseline nonadherence.⁽¹⁰⁾ (**Figure 1**)

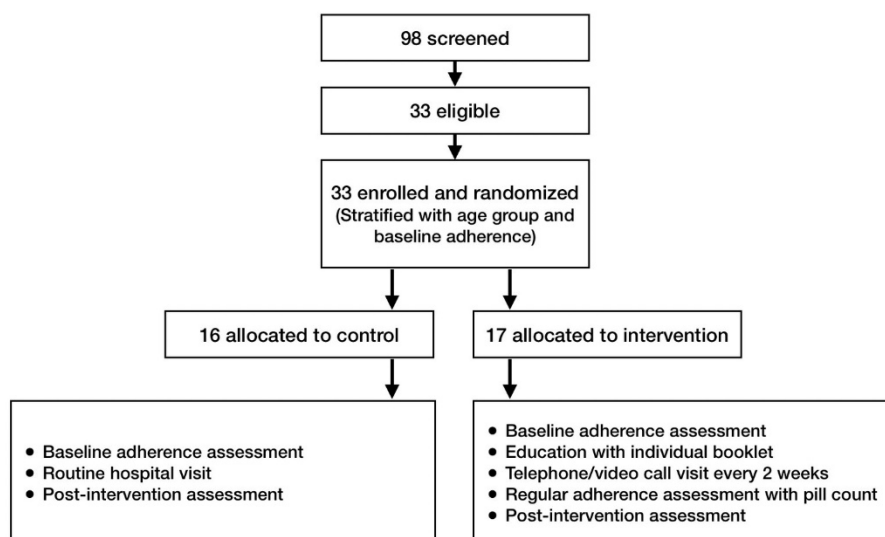


Figure 1. Timeline of the study procedure

Adherence assessment

This study used the BAASIS questionnaire and the coefficient of variation (CV%) of tacrolimus level.⁽¹¹⁾ The BAASIS questionnaire was developed to assess adherence to immunosuppressive drugs in transplant recipients and has been used worldwide.

At enrollment, all participants answered the BAASIS questionnaire and were evaluated CV% for tacrolimus level ($< 30\%$ = adherence, $\geq 30\%$ = nonadherence) to assess baseline medical nonadherence. Then, In the intervention group, the patients were done the adherence assessment by pill count technique⁽¹²⁾ ($< 80\%$ = nonadherence, $\geq 80\%$ = adherence) at every visit a telephone call or video call by medical personnel. At the end of the study (1 year after eligibility), all participants answered the BAASIS questionnaire and were evaluated CV% for tacrolimus level to assess the study outcome.

Intervention

At the first visit, the patients and their parents were instructed (re-educated) for 10 minutes by the medical personnel about the importance of immunosuppressive drugs and other aspects of medicines, such as how to store the drugs and factors that may affect the level of drugs. Then, medical personnel provided them with individual booklets consisting of information about immunosuppressive drugs and made an appointment to

perform telephone call or video call visits, which were done every 2 weeks until the end of the study (one year after eligibility).

Medical personnel conducted telephone or video call visits within 15 minutes. The objectives of each visit were to verify the types and doses of prescribed immunosuppressive drugs, assess patients' adherence by pill count technique, and consult patients about problems or doubts that could hinder their medical adherence.

Control condition

Patients in the control group were scheduled for hospital visits at the same intervals as usual. Each follow-up session lasted about 15 minutes and discussed general signs and symptoms, laboratory results, and prescribed drugs.

Outcome measurement

The primary outcome of this study was to study the improvement of medical adherence in the pediatric kidney transplant recipients who received the intervention. The secondary outcomes were to evaluate the associated factors that may affect medical nonadherence.

Statistical analysis

Statistical analysis was performed with SPSS Statistics version 23. Descriptive statistics were obtained, such as mean, standard deviation (SD),

frequencies, median, and interquartile range (IQR). Categorical variables were analyzed with the chi-square test, and the Mann–Whitney U-test was used for continuous variables. All analyses were performed at 95% CI, with two-sided $p < 0.05$ being statistically significant. Univariate and multivariate logistic regression models were used to evaluate the associated factors concerning medical nonadherence.

Results

Baseline characteristics

We screened 98 patients who have had kidney transplants at our center. We identified 33 eligible patients and actively followed up at our center. After randomization with stratification according to age group and baseline adherence, 17 patients were assigned to the intervention group and 16 to the control group. Twenty-one patients were male (63.6%). The mean age during the study was 15.7 ± 3.12 years, and the mean age of transplantation was 11.21 ± 3.31 years. The mean period of transplantation was 4.03 ± 2.28 years, and the mean period of dialysis before transplantation was 2.73 ± 1.89 years. The type of

kidney transplantation mainly was deceased donors (27 patients, 81.8%). The median number of drug types was 8; all patients had three types of immunosuppressive drugs. Almost every patient except one patient had been in the first transplantation period. Baseline characteristics were similar between the two groups except for the education and previous history of rejection (**Table 1**).

The patients in the control group were mainly uneducated (5 patients, 31.3%), whereas those in the intervention group were mostly in high school grades (11 patients, 64.7%). The number of patients with a history of rejection in the control group was less than in the intervention group (6.3% VS 41.2%, $p = 0.019$).

Ten patients had baseline nonadherence by the BAASIS questionnaire (30.3%) and were equally assigned to both groups. In patients who used tacrolimus as their immunosuppressive regimens, we calculated %CV and found that 11 out of 27 patients (40.7%) had baseline non-adherence by %CV. Five patients were assigned to the control group, and six were assigned to the intervention group.

Table 1. Baseline characteristics between the control group, intervention group, and total

	Control		Intervention		Total		<i>p</i> -value
	n	%	n	%	n	%	
Sex							0.188
Male	12	75.0	9	52.9	21	63.6	
Female	4	25.0	8	47.1	12	36.4	
Age group							0.881
< 17 years	9	56.3	10	58.8	19	57.6	
≥ 17 years	7	43.8	7	41.2	14	42.4	
Type of transplantation							0.935
Deceased donor	13	81.3	14	82.4	27	81.8	
Living related	3	18.8	3	17.6	6	18.2	
Number of transplantation							0.325
1 time	16	100.0	16	94.1	32	97.0	
2 times	0	0.0	1	5.9	1	3.0	
Education							0.049*
Uneducated	5	31.3	1	5.9	6	18.2	
Primary school	4	25.0	1	5.9	5	15.2	
High school	4	25.0	11	64.7	15	45.5	
University	3	18.8	4	23.5	7	21.2	

Table 1. Baseline characteristics between the control group, intervention group, and total (Cont.)

	Control		Intervention		Total		<i>p</i> -value
	n	%	n	%	n	%	
Previous rejection							0.019*
No	15	93.8	10	58.8	25	75.8	
Yes	1	6.3	7	41.2	8	24.2	
Family income (baht/month)							0.269
< 10000	3	18.8	1	5.9	4	12.1	
10001-30000	10	62.5	9	52.9	19	57.6	
30001-50000	3	18.8	7	41.2	10	30.3	
≥ 50000	0	0.0	0	0.0	0	0.0	
Caregiver							0.295
Yes	15	93.8	17	100.0	32	97.0	
No	1	6.3	0	0.0	1	3.0	
Marital status of parents							0.201
Married	10	62.5	14	82.4	24	72.7	
Single parents	6	37.5	3	17.6	9	27.3	
Immunosuppressive frequency							0.325
OD	4	25.0	2	11.8	6	18.2	
BID	12	75.0	15	88.2	27	81.8	
Immunosuppressive regimen							0.232
Pred+MMF+Tac	12	75.0	14	82.4	26	78.8	
Pred+MMF+CSA	0	0.0	1	5.9	1	3.0	
Pred+MMF+mTOR inh	2	12.5	1	5.9	3	9.1	
Pred+Tac+mTOR inh	1	6.3	1	5.9	2	6.1	
Pred+AZA+CSA	1	6.3	0	0	1	3.0	
Baseline adherence by BAASIS questionnaire							0.909
Adherence	11	68.8	12	70.6	23	69.7	
Nonadherence	5	31.3	5	29.4	10	30.3	
Baseline adherence by %CV							
Adherence	8	61.5	8	57.1	16	59.3	
Nonadherence	5	38.5	6	42.9	11	40.7	

	Control	Intervention	Total	<i>p</i> -value
Age (year)				0.471
Mean±SD	15.31±3.24	16.06±3.05	15.7±3.12	
Median(min-max)	16(10-20)	16(11-21)	16(10-21)	
Period of transplantation (year)				0.554
Mean±SD	4.31±2.5	3.76±2.11	4.03±2.28	
Median(min-max)	4(1-9)	3(1-9)	3(1-9)	
Period of dialysis (year)				0.636
Mean±SD	2.63±1.63	2.82±2.16	2.73±1.89	
Median(min-max)	2(1-7)	2(1-10)	2(1-10)	

Table 1. Baseline characteristics between the control group, intervention group, and total (Cont.)

	Control	Intervention	Total	<i>p</i> -value
Age at transplantation (year)				0.160
Mean±SD	10.63±2.92	11.76±3.65	11.21±3.31	
Median(min-max)	10(6-16)	13(5-17)	11(5-17)	
Total number of drug types				0.832
Mean±SD	8.44±2.13	8.12±2.09	8.27±2.08	
median(min-max)	8(6-13)	8(5-12)	8(5-13)	
Total number of immunosuppressive drugs				1.000
Mean±SD	3±0	3±0	3±0	
Median(min-max)	3(3-3)	3(3-3)	3(3-3)	

*Chi-square test and Mann-Whitney U test, $p < 0.05$

Pred = Prednisolone, MMF = Mycophenolate, TAC = Tacrolimus, CSA = Cyclosporin, MTOR inh = Mammalian target of rapamycin inhibitors, AZA= Azathioprine

Primary outcome: medical nonadherence

We evaluated the adherence at one year after eligibility in both groups and found that seven patients (21.2%) were defined as medical non-adherence by the BAASIS questionnaire. Four out of 26 patients (15.4%) were defined as medical nonadherence by %CV. Both measurements improved adherence at 1 year, but there was no difference in medical nonadherence improvement between the intervention and control groups (**Table 2**) ($p = 1.000, 0.303$).

Satisfaction

After we performed the intervention on patients in the intervention group, we provided a satisfactory survey to patients and their parents. In their opinion, the questions included overall satisfaction with telephone or video call visits, satisfaction with the frequency of visits, satisfaction with the booklets, and the importance of adherence assessment. The full score was 30. The mean score in our patients was 28.63±1.41. The median score was 29. We also performed the open-ended question to ask patients and their parents about the hindrance to medical adherence in their opinion. Some patients replied that the number of prescribed drugs affects their adherence.

Associated factors to medical nonadherence

We studied the factors associated with medical nonadherence by comparing baseline

adherence with other baseline characteristics using the BAASIS questionnaire. We found that no factor was statistically associated with non-adherence by univariate or multivariate analysis (**Tables 3 and 4**). However, factors such as the number of drug types had a trend toward significance ($p = 0.071$ using univariate analysis, 0.331 using multivariate analysis).

Discussion

The prevalence of medical nonadherence in this study was 30.3%, according to the BAASIS questionnaire, which was similar to the previous study⁽⁴⁾ but higher than that of a prior study in Thailand. Wangpradit et al.⁽¹³⁾ studied the prevalence of nonadherence among adult kidney transplant patients using the BAASIS questionnaire and found that the prevalence was only 24%. There is no data on nonadherence to the BAASIS questionnaire among pediatric kidney transplant patients in Thailand. This data emphasizes that adherence in pediatric and adolescent patients is worse than in adults.

Another method that we used to measure adherence was %CV. The result of medical non-adherence by %CV was 40.7%, which was higher than the data from our center in 2019, which was 35.9%. As we know, the %CV can be affected by many factors, such as time to collect the blood, errors in the laboratory, and drug interaction.⁽¹¹⁾ Therefore, these results might vary from time to

Table 2. Comparing medical adherence between control and intervention group

	Baseline adherence by %CV								<i>p</i> -value
	Adherence				Nonadherence				
	Control		Intervention		Control		Intervention		
	n	%	n	%	n	%	n	%	
Adherence at one year									NA
Adherence	6	100	8	100	4	80	3	50	0.303
Nonadherence	0	0	0	0	1	20	3	50	

	Baseline adherence by BAASIS questionnaire								<i>p</i> -value
	Adherence				Nonadherence				
	Control		Intervention		Control		Intervention		
	n	%	n	%	n	%	n	%	
Adherence at one year									0.484
Adherence	9	81.8	11	91.7	3	60	3	60	1.000
Nonadherence	2	18.2	1	8.3	2	40	2	40	

* Chi-square test, *p* < 0.05

Table 3. Associated factors to medical nonadherence using univariate analysis

	Adherence		Nonadherence		<i>p</i> -value	Crude Odds ratio	95%CI
	n	%	n	%			
Sex							
Male	14	66.7	7	33.3	0.617	1.500	0.306-7.361
Female	9	75.0	3	25.0			
Age group							
< 17 years	12	63.2	7	36.8	0.346	2.139	0.44-10.391
≥ 17 years	11	78.6	3	21.4			
Type of transplantation							
Deceased donor	18	66.7	9	33.3	0.433	2.500	0.253-24.719
Living related	5	83.3	1	16.7			
Number of transplantation							
1 time	22	68.8	10	31.3	NA	NA	NA
2 times	1	100.0	0	0.0			
Education							
Uneducated	3	50.0	3	50.0	0.433	2.500	0.253-24.719
Primary school	4	80.0	1	20.0			
High school	11	73.3	4	26.7			
University	5	71.4	2	28.6			
Previous rejection							
No	19	76.0	6	24.0	0.174	3.167	0.601-16.692
Yes	4	50.0	4	50.0			

Table 3. Associated factors to medical nonadherence using univariate analysis (Cont.)

	Adherence		Nonadherence		<i>p</i> -value	Crude Odds ratio	95%CI
	n	%	n	%			
Income (baht/month)							
<10000	3	75.0	1	25.0		1	
10001-30000	14	73.7	5	26.3	0.957	1.071	0.089-12.831
30001-50000	6	60.0	4	40.0	0.600	2.000	0.15-26.734
Caregiver							
No	0	0.0	1	100.0	NA	NA	NA
Yes	23	71.9	9	28.1			
Marital status of parents							
Married	17	70.8	7	29.2		1	
Single parent	6	66.7	3	33.3	0.817	1.214	0.235-6.271
Immunosuppressive frequency							
OD	3	50.0	3	50.0	0.257	2.857	0.464-17.583
BID	20	74.1	7	25.9		1	
Immunosuppressive regimen							
Pred+MMF+Tac	18	78.3	8	80.0		1	
Pred+MMF+CSA	1	4.3	0	0.0		NA	NA
Pred+MMF+mTOR inh	1	4.3	2	20.0	0.246	4.500	0.355-57.106
Pred+Tac+mTOR inh	2	8.7	0	0.0		NA	NA
Pred+AZA+CSA	1	4.3	0	0.0		NA	NA
*Logistic regression, <i>p</i> < 0.05							
	Adherence		Nonadherence		<i>p</i> -value	Crude Odds ratio	95%CI
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)			
Age (year)							
Mean±SD	15.74±3.32		15.6±2.76		0.905	0.985	0.774-1.255
Median (min-max)	16(10-21)		16(11-20)				
Period of transplantation (year)							
Mean±SD	4.04±2.06		4±2.87		0.959	0.991	0.712-1.38
Median(min-max)	4(1-9)		3(1-9)				
Period of dialysis (year)							
Mean±SD	2.87±2.1		2.4±1.35		0.514	0.854	0.531-1.373
Median(min-max)	2(1-10)		2(1-5)				
Age at transplantation (year)							
Mean±SD	11.13±3.43		11.4±3.2		0.827	1.026	0.817-1.288
Median(min-max)	11(5-17)		11(7-16)				
Total number of drug types							
Mean±SD	7.83±1.9		9.3±2.21		0.071	1.443	0.969-2.149
Median(min-max)	8(5-13)		9.5(6-12)				
Baseline %CV							
Mean±SD	24.05±11.32		36.96±17.31		0.049*	3.611	1.242-20.32
Median(min-max)	20.8(9.1-50)		34.25(14.9-63.5)				

Table 4. Associated factors to medical nonadherence using multivariate analysis (Cont.)

	Adherence		Nonadherence		<i>p</i> -value	Adjusted Odds ratio	95%CI
	n	%	n	%			
Age group							
< 17 years	12	63.2	7	36.8	0.202	5.335	0.408-69.743
≥ 17 years	11	78.6	3	21.4		1	
Previous rejection							
No	19	76.0	6	24.0		1	
Yes	4	50.0	4	50.0	0.481	2.882	0.151-54.88
Immunosuppressive regimen							
OD	3	50.0	3	50.0	0.419	2.674	0.246-29.097
BID	20	74.1	7	25.9		1	
Total number of drugs							
Mean±SD	7.83±1.9		9.3±2.21		0.331	1.249	0.798-1.956
Median(min-max)	8(5-13)		9.5(6-12)				
Baseline %CV							
Mean±SD	24.05±11.32		36.96±17.31		0.145	2.501	0.602-20.722
Median(min-max)	20.8(9.1-50)		34.25(14.9-63.5)				

*Logistic regression, *p* < 0.05

time. However, in other aspects, the prevalence of nonadherence by %CV was higher than that of the BAASIS questionnaire. The plausible causes aside from the sensitivity of %CV could be information bias and recall bias. The patients and their parents were asked to do a questionnaire by their doctor, and they had to recall their adherence, which occurred during four weeks. Therefore, if possible, more than one measurement should be done to measure medical adherence, such as the BAASIS questionnaire, %CV, pill count, or other electrical monitoring. To prevent information bias, non-medical personnel should give and collect the questionnaire.

Despite the improvement in overall medical adherence after one year of eligibility, there was no difference in medical adherence improvement between the intervention and control groups. Accordingly, our intervention failed to meet our primary outcome of improving adherence. A plausible explanation might be the complexity of adherence, which the World Health Organization (WHO) has identified as five interrelated risk and protective categories that impact adherence.⁽¹⁴⁾ To improve the patient’s adherence, we should look at their problems individually and solve them directly, which might require a multidisciplinary

team approach.⁽¹⁵⁾ Our intervention provides them with education, regular assessment of adherence, reminders, and accessibility between the healthcare systems, but in some patients, this is not enough to solve their nonadherence. Therefore, medical nonadherence is still challenging and needs more attention. In the future, electronic monitoring and other artificial intelligence might help improve adherence. Another explanation might be due to the research environment that improves adherence in patients in both the intervention and control groups. However, the first explanation is more convincing.

Although we could not meet the primary outcome, the overall satisfaction from the intervention group was high. Many patients and their parents were willing to join the telemedicine visit and thought that it was helpful for them to connect with the doctor, re-check the drug regimens, and re-check themselves. Telemedicine can assist healthcare personnel in doing the regular adherence assessment.

About the associated factors of medical nonadherence, we found that only a % of CV was associated with medical nonadherence by univariate analysis. %CV of tacrolimus has been proposed to monitor patients at risk for allograft

rejection and donor-specific antibodies secondary to medical nonadherence.⁽¹¹⁾ Our study result emphasizes the correlation between the BAASIS questionnaire and %CV to assess adherence. Accordingly, we can use both of them to assess adherence. However, after we performed multivariate analysis, none of the baseline characteristics were significantly associated with medical nonadherence. Since our study could not include enough patients, there was insufficient power to represent the statistical significance. However, some factors had a significant trend, such as the number of drug types, which is one of the hindrances patients and their parents reported and described in the previous study.⁽¹⁶⁾ Therefore, the pill burden should be considered.

We tried to prove the association between medical adherence and the schedule of immunosuppressive agents (frequency of medication) to once-daily tacrolimus, which has been demonstrated to have similar pharmacokinetic profiles as twice-daily tacrolimus formulations.⁽¹⁶⁾ The result was also negative. Expanding the result might be difficult because other immunosuppressive agents, such as mycophenolic acid analogs, were taken twice daily.

This study had some limitations. First, the sample size was small. Second, our study used the BAASIS questionnaire, which is not the Thai version and a recall bias could occur.

Conclusion

The prevalence of medical nonadherence in pediatric kidney transplant recipients is higher than in adults. Medical nonadherence is a complex issue, and interventions to improve medical adherence need to be individualized and done with a multidisciplinary team. Telemedicine can assist healthcare personnel in assessing adherence regularly; further intelligence techniques should be helpful as an add-on intervention.

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