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Original Article

Effectiveness of a smartphone application on medication adherence in children with short stature receiving GH therapy: A multicenter prospective cohort study (GTL-App)

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Abstract. This multicenter prospective cohort study followed up Japanese children who had just started GH therapy using a drug delivery device (GROWJECTOR® L) linked to a newly developed smartphone application and analyzed precise medication adherence data stored in GROWJECTOR® L to evaluate the usefulness of the application in improving GH therapy adherence over a 24-wk observation period. Moreover, a questionnaire survey on GH therapy and the smartphone application was conducted, and factors affecting adherence to GH therapy were assessed. This study enrolled 60 children with short stature who had GH deficiency or Turner syndrome or were small for gestational age from 28 Japanese medical institutions and analyzed 57 of them. The median and mean adherence rates after 24 wk of observation were 96% and 93%, respectively. Although adherence rates were significantly lower from wk 16 to wk 20 than from wk 1 to wk 4, cumulative adherence rates remained high throughout the observation period. The questionnaire analysis revealed that most patients actively used the application. Overall, our results suggest that active discussion regarding the development of healthcare systems that contribute toward improving the patient quality of life is warranted.

Key words: adherence, GH therapy, short stature, smartphone application

Introduction

Approximately 2.3% of children have short stature, which is defined as a height of at least two standard deviations below the average (1). Short stature is often caused by various pathological conditions such as endocrine disorders (e.g., GH deficiency [GHD]), chromosome abnormalities (e.g., Turner syndrome [TS]), and neonatal complications (e.g., small for gestational age [SGA]) (2). The treatment of choice for children with short stature and the aforementioned conditions is GH therapy, which requires long-term daily self-injection of recombinant human GH at home. GH therapy is expected to improve the future quality of life (QoL) of children (3–5) by ultimately helping them achieve a normal adult height. However, suboptimal medication adherence can impair the long-term clinical effectiveness of GH therapy, thereby resulting in a shorter final adult height (6). Therefore, good treatment adherence by children and their parents or guardians is an essential requirement for achieving established therapeutic goals. Moreover, poor medication adherence should be addressed, considering the high costs of GH treatment and its consequent effects on health care economics (7). However, often poor adherence to GH therapy has been observed, with many children failing to achieve their target adult heights (8). Studies have reported that GH therapy may cause fear and evoke strong feelings among children and place a burden on those administering the medication (9). Therefore, concerns regarding poor medication adherence, which adversely affect the QoL of children, have been reported. Furthermore, various factors have been reported to be associated with poor adherence to GH treatment, such as poor understanding of the condition or treatment, adolescence stage, injection devices, and shorter or prolonged duration of GH prescriptions (10). Poor adherence observed immediately after initiating GH therapy is likely indicative of early dropout, and precise treatment monitoring by physicians might be required for adolescents vulnerable to poor adherence. Hence, physicians are required to detect subtle signs of nonadherence among children as early as possible to promote optimal adherence with professional instructions and advice at the appropriate time (11). However, no gold standard for assessing medication adherence of patients is available. This has hindered

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physicians from optimizing medication adherence in patients receiving GH therapy, although various indirect methods based on issued prescriptions, vial counting, patient diaries, questionnaires, biochemical measurements, or their combinations were used (10).

The GROWJECTOR® L (GTL) is a dedicated electronic drug delivery device manufactured and sold by the PHC Corporation (PHC, Tokyo, Japan) launched in January 2017 for the Japanese market only. The GTL was used for subcutaneous administration of GROWJECT® (6 and 12 mg), the recombinant human GH manufactured and sold by JCR Pharmaceuticals Co., Ltd. (JCR, Ashiya, Hyogo, Japan). The GTL enables a series of automatic injects and stores injection logs. Compared with its predecessors, the GTL is more user-friendly with a customizable interface and more compact, which may reduce the burden on children and parents or guardians during the daily injection procedure. Moreover, the GTL can be linked to smartphone applications, making it more convenient for both patients and physicians. In October 2020, JCR and PHC released a jointly developed smartphone application for the GTL that allows the assessment of dosing history stored in the GTL using a smartphone. Additionally, the application can create and display growth curves for height and weight and allow children to enjoy "fun" functions during treatment; thus, reducing the tension that children may experience during injections. Moreover, this reduces the burden of those responsible for administering injections and promotes medication adherence.

This multicenter prospective cohort study, GTL-App, followed up Japanese children who had just started GH therapy using the newly developed smartphone application and analyzed precise medication adherence data derived from the GTL to evaluate the usefulness of the application for improving adherence to GH therapy. Moreover, a questionnaire survey on GH therapy and smartphone application was conducted to explore factors affecting GH therapy adherence. To the best of our knowledge, this is the first study in Japan to use automatically collected data on GH treatment adherence and a smartphone-based application that supports children receiving GH therapy and their parents.

Materials and Methods

Subjects

This multicenter prospective cohort study was conducted between January 2019 and May 2020 at 28 Japanese medical institutions. Patients with short stature associated with GHD, TS, or SGA and open epiphyseal plates were screened for eligibility by the investigators at each institution. Eligible patients were registered at the contracted central data center (Kondo P.P. Inc.) after anonymization at each center. Inclusion criteria were as follows: never received GH therapy, age ≥ 3 yr, intention to use the GTL with type A needles 7-days-a-week, and written informed consent from parents or guardians of the patients, along with informed assent if applicable. Exclusion criteria were as follows: contraindications to GH therapy (e.g., diabetes, malignancy, and (possible) pregnancy), inability to properly answer the questionnaire (e.g., inability to read), and physician discretion. Considering the explorative nature of the study, the target sample size was determined based on the recruitment during a 10-mo period in the 28 study centers rather than statistics. Hence, approximately 50 patients were included in the study.

Study schedule

A smartphone preinstalled with the study application was provided to all participants during the initial visit for GH therapy. Investigators explained how to use the application using the instruction manual and videos. After a 1-wk preobservation period immediately post-GH therapy initiation, patients were followed up for 24 wk and adherence data were collected. During the clinical visit after the 24-wk observation period (end of the study), adherence data were obtained from the GTL using the smartphone application and the smartphone was returned. A questionnaire survey on GH therapy and study application was conducted during the initial visit and at the end of the study. No intervention was provided during the study. GH therapy was administered to patients as a part of routine daily clinical practice.

Questionnaires

Parents or guardians filled out the questionnaires during the initial visit and at the end of the study. The questionnaire included questions on GH therapy and the study application. The following questions on GH therapy were answered by parents or guardians using a 10-point facial scale:

1. How much does he/she seem to be scared of the GH injection?
2. How much burden do you feel when administering the GH injection?
3. How much do you worry about continuation of GH therapy?

Questions on the study application, such as general impression, impression regarding its function (at the end of the study), and impression regarding its use (at the end of the study), were answered by the parents or guardians using a 5-point Likert scale.

Smartphone application

The functions of the study application were classified into two categories: treatment-supporting functions for those administering the medication and "fun" functions for children receiving treatment. Supporting functions for GH therapy were as follows: records of injection sites, alert for scheduled injections, growth curve generation for height and weight, digital notepad for schedules or memorandums, and links for information on GH therapy.

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Meanwhile, the "fun" functions were as follows: avatar creation for individual patients, messages from in-application characters, messages from family members of the patient, patients' community, and reward points for continued therapy that can be exchanged for avatar data.

Endpoints

The primary endpoint was medication adherence rate, which was defined as the total number of injections received divided by the total number of injections planned over the 24-wk (168-d) observation period multiplied by 100. The period of time when GH therapy was suspended at the physician's discretion or when the GTL or smartphone was not available due to inevitable reasons such as mechanical problems was excluded from analysis based on the decision of the principal investigator. The secondary endpoints were as follows: change in adherence rate, which was calculated every 4 wk, relative to that at the start of the observation period; factors associated with nonadherence, defined as failure to administer the medication three times in a week; and questionnaire analysis.

Statistical analysis

Continuous variables are expressed as mean (standard deviation [SD]) and median (first and third quartile), whereas categorical variables are expressed as numbers (percentages). Adherence rates over the 24-wk observation period were compared between patient groups stratified by age (median), sex (male or female), and diagnosis (GHD, TS, or SGA) using the Kruskal–Wallis test and Mann–Whitney U test. Post-hoc exploratory analyses were conducted based on clinical interests such as the average daily injection time during the observation period. Adherence rates at each subsequent 4-wk evaluation point were compared with those in the initial 4-wk observation period using the Wilcoxon signed-rank test. Factors associated with nonadherence were explored using the Cox proportional hazards model. Moreover, the 10-point facial scale scores at the end of the study were compared with those at the initial visit using the Wilcoxon signed-rank test. The results for other questions are expressed as number (percentage). The association between application use and adherence rates was assessed using the Spearman's rank correlation coefficient. No adjustments were made for the multiplicity of statistical tests, considering the exploratory nature of the study. Statistical significance was set at $P < 0.05$. All statistical tests were performed using SPSS 25 (IBM Corporation, Armonk, NY, USA) and R ver. 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

Ethics approval

This study was conducted in accordance with the Declaration of Helsinki (Fortaleza revision, 2013) and ethical guidelines for medical and health research involving human subjects provided by the Japanese Ministry of Health, Labor and Welfare (revised 2017). The study protocol was approved by the Ethics Committee of Nihon University Hospital and the ethics review board of each study site. All participants provided written informed consent. This study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000035997).

Results

Disposition and baseline patient characteristics

This study enrolled 60 patients with short stature from 28 Japanese medical institutions. The patient flow diagram is presented in **Fig. 1**. Three patients discontinued shortly after GH therapy initiation due to medication change, unbearable pain, and failure to return to the hospital and were subsequently excluded from the statistical analysis. The baseline characteristics of the remaining 57 patients are summarized in **Table 1**.

The mean age (SD) of the patients was 7.2 (3.84) yr, and the proportions of male and female patients was almost similar. A total of 54.4%, 7.0%, and 38.6% of the included patients were diagnosed with GHD, TS, and SGA, respectively. A relatively high proportion of patients were diagnosed with SGA. Among all patients, patients with SGA started GH therapy at the lowest age ($P = 0.002$). The baseline mean (SD) height SD score was −2.71 (0.57).

Adherence rates during the 24-wk observation period

The median and mean adherence rates at the end of the 24-wk observation period were 96% and 93%, respectively. The histogram of the distribution of adherence rates is presented in **Fig. 2**. Although most patients had a high adherence rate, six patients had quite a low adherence rate (< 80%). The details of the six patients are presented in Supplementary Table 1. Analysis of the adherence rate after stratification by age revealed no difference; however, the adherence rate was significantly higher in female patients than in male patients ($P = 0.044$; Supplementary Figs. 1A and B).

The adherence rate was higher in patients with TS

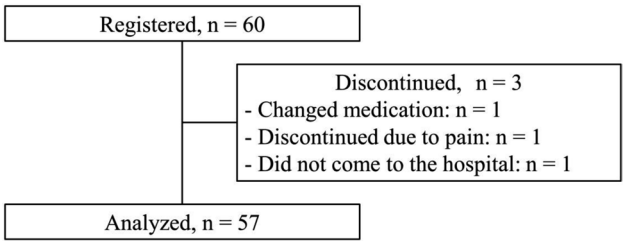

Fig. 1. Flow diagram of participants.

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Table 1. Baseline characteristics of the patients analyzed

Age, years	Mean (SD)	7.2 (3.84)
	Median (25th, 75th percentile)	7.0 (4.0, 9.0)
Sex		
Male	n (%)	28 (49.1)
Female		29 (50.9)
Diagnosis		
GHD	n (%)	31 (54.4)
TS		4 (7.0)
SGA		22 (38.6)
HtSDS	Mean (SD)	−2.71 (0.57)
	Median (25th, 75th percentile)	−2.63 (−2.99, −2.33)

GHD, GH deficiency; HtSDS, height SD scores; SGA, small for gestational age; TS, Turner syndrome.

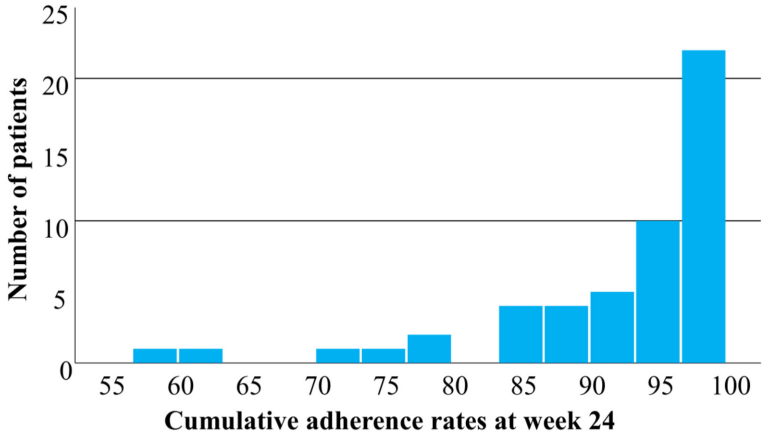

Fig. 2. Distribution of the adherence rates at the end of the 24-wk observation period.

and SGA than in those with GHD without significant difference (Supplementary Fig. 1C). No significant difference in the adherence rate was observed between patients who self-injected GH and those who were administered GH injection by their parents; however, subgroup analysis of patients with GHD revealed that the adherence rate tended to be lower among patients who self-injected GH than among those who were administered GH injection by their parents but without significance ($P = 0.071$). A post-hoc analysis of patients stratified by the quartile of average injection timing revealed significant differences in the adherence rate among the four groups ($P = 0.018$). Patients who received the injection between the second and third quartiles (approximately between 09:30 pm and 10:00 pm) had the highest adherence rate, whereas those who received the injection after the third quartile had the lowest adherence rate (Supplementary Fig. 1D). In addition, a significant association was observed between patient age and average injection time ($P = 037$), and the patient age with injection time after the third quartile was the highest.

Time course change in the adherence rate

Cumulative adherence rates during the observation period and adherence rates calculated every 4 wk are plotted in **Figs. 3A and B**. Although adherence rates were significantly lower from wk 16 to wk 20 than from wk 1 to wk 4, cumulative adherence rates remained high throughout the observation period.

Factors associated with nonadherence

Supplementary Table 2 shows the results of the univariate Cox proportional hazard analysis for nonadherence-free survival. No factor was significantly associated with nonadherence events (i.e., failure to take medication three times a week).

Questionnaire results on GH therapy

Psychological perceptions regarding GH therapy at the initial visit and at the end of the study are presented in **Fig. 4**. Significant improvements in the 10-point facial scale scores for the fear of injection among children, psychological burden among parents or guardians during injections, and anxiety regarding treatment continuation were observed at the end of the study ($P < 0.001$ each, **Figs. 4A–C**).

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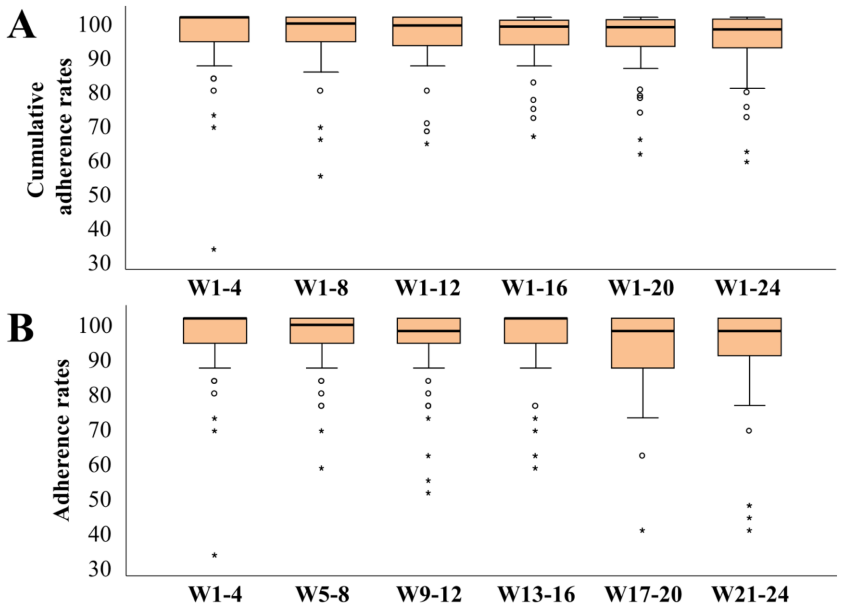

Fig. 3. Time course change in the adherence rate: A. cumulative adherence rates during the observation period and B. adherence rates calculated every 4 wk.

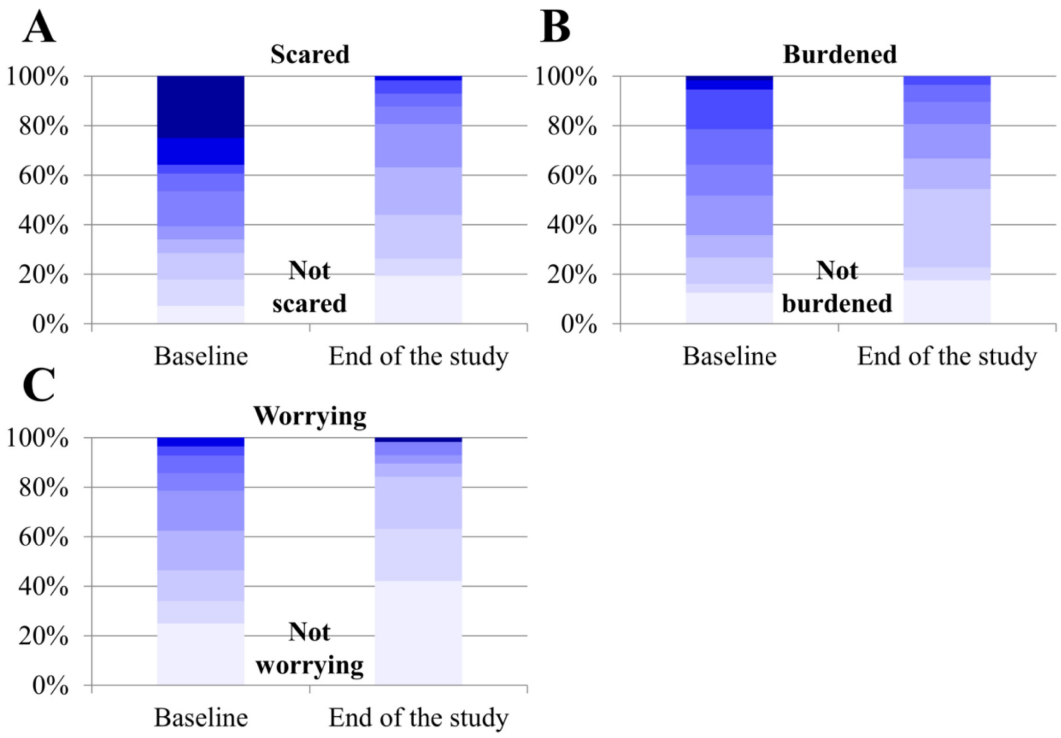

Fig. 4. Psychological perceptions regarding GH therapy during the initial visit and at the end of the study: A. fear of injection among children; B. psychological burden among parents or guardians during injections; and C. anxiety among parents or guardians regarding treatment continuation.

Questionnaire results on the smartphone application

General impressions regarding the smartphone application were favorable at the initial visit as well as at the end of the study. In addition, impressions regarding the functions and use of the study application were favorable at the end of the study, with almost all scores ranging from 3 (acceptable) to 5 (very favorable). The most frequently used functions are listed in **Table 2**.

Many of the supporting and fun functions were well utilized. The most commonly used function was the record of injection. Other functions used by ≥ 50% of the patients were avatar creation, reward points, and

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Table 2. The most frequently used functions of the study application

	n	%
Record of injection	46	80.7%
Avatar creation	41	71.9%
Point acquisition for continued injection	29	50.9%
Growth curve	29	50.9%
Messages from characters	21	36.8%
Patient community	16	28.1%
Alert for scheduled injection	11	19.3%
Digital notepad for schedules/memos	8	14.0%
Massages from family members	3	5.3%
Information links	2	3.5%
Not applicable	1	1.8%
Others	1	1.8%

Multiple answers were provided. Yellow highlights indicate supporting functions for GH therapy and blue highlights indicate fun functions.

growth curve. Almost all patients used the smartphone application, except for one who answered "not applicable" to this question.

Association between application use and the adherence rate

Significant positive associations were observed between the use of both treatment-supporting functions (assessed according to the frequency of injection; $P = 0.017$) and fun functions (assessed according to total continuation points acquired; $P < 0.001$) and the adherence rate of patients.

Discussion

The present study followed up children with short stature who had just started GH therapy using a smartphone application developed to support GH therapy and analyzed medication adherence data automatically recorded in the GTL throughout the 24-wk observation period. The current study is the first to investigate precise medication adherence data published in Japan using the GTL, the only electronic injection device for GH therapy commonly used in Japan, and a supporting smartphone application, the first supporting application developed for GH therapy.

The electronic injection device easypod® (Merck Serono, Darmstadt, Germany), which can collect precise adherence data through real-time recording of the timing, date, and dose of GH delivered, is widely used in more than 40 countries, and several clinical studies such as a series of multinational prospective cohort studies (the Easypod Connect Observational Study [ECOS]), have been conducted (12). This suggests the availability of overseas research on the automatic collection of precise medication adherence data. Notably, the findings of the ECOS are comparable to those of present study (i.e., the GTL-App study) considering a similar study design, except for the study sites (the ECOS was conducted across 24 countries, whereas this study was conducted in Japan) and the use of a treatment support application. Among the 1,203 patients enrolled in the ECOS, 610 were treatment-naïve. The median (mean) adherence rates at 12 and 24 wk of treatment among treatment-naïve patients in the ECOS were 95.6% (85.4%) and 94.9% (84.6%), respectively (12). In this study, the adherence rates at 12 and 24 wk of observation were 97.6% (93.9%) and 96.4% (93.0%), respectively.

The aforementioned data indicated that adherence rates in this study were relatively higher than those in the ECOS. Particularly, the larger differences in mean values, rather than in median values, revealed that although more than half of the patients in both the studies favorably adhered to the treatment, a large proportion of patients showed extremely poor adherence in the ECOS compared with that in the current study shortly after GH therapy initiation. Considering the similar study design in both the studies, the use of the supporting application might have somewhat facilitated patients in the current study to avoid the initial risks of decreased adherence, which could potentially lead to treatment dropouts. This finding is clinically meaningful in determining treatment strategies for managing the initial risk of low medication adherence in combination with the precise monitoring of adherence data. A 4-yr-old female patient in this study initially refused treatment because the initial instruction or training did not work well. Although her adherence rate was exceptionally poor immediately after treatment initiation, it increased rapidly and remained at an optimal level after sufficient and appropriate re-instruction during the subsequent hospital visit. This is a good example suggesting that initial low adherence can be recovered completely by relevant professional interventions suitable for individual patients.

Among the six patients with poor adherence (< 80%) in this study, one was a 3-yr-old male patient with SGA whose GTL broke down during the observation period and his adherence rate decreased for some time thereafter; one was the abovementioned 4-yr-old female patient with GHD; and the others were patients with

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GHD who had no particular reason for poor adherence. All four patients with GHD were aged ≥ 10 yr, and three of the four patients self-injected GH. The use of the smartphone application by six patients with poor adherence was less than the average. Overall, physicians should pay close attention to patients with GHD and school age who self-inject GH for treatment adherence.

Stratified analysis by age revealed that the older age group patients had relatively lower adherence rates but without statistical significance. Several studies have reported that older age and self-injection are associated with poor medication adherence (13, 14). Moreover, given that various psychological or adolescent-related factors may affect treatment adherence in older patients, simple initial instructions or the use of supporting applications by patients might not be sufficient when managing these patients (8, 15). Another stratified analysis revealed that the average timing of GH injections was significantly associated with the adherence rate. Particularly, patients with an average injection time after 10:00 pm had significantly lower adherence rates and were significantly older (mean age: 9.6 yr) than those with an earlier average injection time, indicating that further attention should be paid to the care of patients who tend to stay up until late at night.

Recent advancements in perinatal care systems have increased the survival rates of premature infants with fetal growth restrictions and have tended to increase the number of children with SGA receiving GH therapy (16). Indeed, among the patients included in the present study, the proportion of patients with SGA was high (38.6%). However, these patients had relatively higher adherence rates than patients with GHD and could maintain a sufficient adherence rate with the support application. Unfortunately, the current study failed to identify factors associated with poor adherence, presumably owing to the small sample size and short observation period. Further studies with larger cohorts and longer follow-up periods are warranted.

The questionnaire analysis revealed remarkable improvements in the perceptions of the patients and their parents regarding GH therapy. During the initial visit, 20 patients feared injections (scores ranged from 9 to 10). However, at the end of the study, almost none of the patients exhibited fear, except for one who had a score of 9. Several parents provided similar remarks. They reported that their child was initially scared of injections but gradually started to enjoy the application and was willing to receive the medication, indicating the effectiveness of the supporting application. Moreover, a reduction in the psychological burden of the parents was observed at the end of the study, and most of the parents became confident with continuing GH therapy.

Almost all patients actively used the treatment-supporting and fun functions of the application. Children enjoyed fun functions during the treatment, which might have contributed to continued daily injections after providing the initial instructions for GH therapy. Moreover, a deep understanding of the data and related information provided by the treatment-supporting functions facilitated parents to promote treatment adherence. Considerable positive feedback was received regarding application improvement, which may indicate the usefulness of the supporting application for both children and parents.

The present study had several limitations. First, sufficient statistical power might not have been obtained given the small sample size. Second, the lack of control groups prevented the verification of the usefulness of the supporting application. Third, a potential selection bias may have existed during recruitment. Finally, given that the present study was conducted under usual clinical settings, differences in initial instructions for GH therapy between institutions could not be addressed or adjusted.

Conclusions

Good adherence rates to GH therapy were observed with the use of the treatment-supporting application. Analyses of questionnaire answers revealed that most patients actively used the application. With the rapid progress of the Internet of Things in healthcare, active discussions on the development of health care systems that would contribute to the improvement of patient QoL are required.

Conflicts of Interest: The author received research funding from JCR Pharmaceuticals Co., Ltd. (Hyogo, Japan).

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