Introduction

Recombinant growth hormone (rGH) had been used since 1980s [1] and had been widely used to treat various growth disorders, both growth hormone deficient (GHD) and non-GHD. However, due to its high cost, there is a stringent criterion for the usage of rGH. The Malaysian Ministry of Health Clinical Practice Guideline 2010 [2] recommends the use of GH for only three main indications; proven growth hormone deficiency (GHD), Turner Syndrome (TS), and small for gestational age (SGA) with poor catch-up growth. We are a public-funded major paediatric endocrine referral centre in Malaysia, and our pharmacy’s drug expenditure report in the year 2020 showed that the expenses
on rGH were more than RM550,000 per year and likely to further increase over time.

Many factors influence the outcome of rGH in children. These include the underlying diagnosis, age of treatment, and appropriate dosing. Adherence to rGH treatment in children is crucial to ensure an optimal final height outcome [3-6]. There are not many studies involving Asian children and none in our local setting. Given the high expenses of GH therapy, studies are warranted to evaluate the compliance of patients to rGH and ascertain the factors affecting adherence and suboptimal outcome [7]. In 2011, HL Ooi et al [8] evaluated the response and factors affecting the final height of 17 Malaysian children with GHD treated with rGH. The majority of them achieved final height at the lower target height range with -0.7 SDS from the mid parental height, however compliance factors were not explored.

Based on the systematic review by Fisher et al. [9], estimates of non-compliance to GH treatment in children and adolescents varied from 5 to 82%, depending on the studied population, methods and definitions used for non-compliance. We decided to adopt the approach from Cutfield et al. study [10] in New Zealand, which measure compliance by counting the returned empty vials of medication; and compliance was defined as ≥85% adherence (equivalent to missing injection <1 per week).

The objectives of our study are to evaluate the compliance of children and adolescents to rGH, the effect of poor compliance on height velocity (HV), and factors affecting adherence.

Methods

This is a prospective cohort study over a period of 1 year from the year 2019 to 2020, aiming at all patients on rGH less than 18 years old in our centre. The study had been approved by the Medical Research and Ethics Committee (MREC), Ministry of Health, Malaysia (NMRR ID: NMRR-18-2969-44525), and informed consent had been obtained from all the participants.

All recruited patients and caretakers were reviewed and interviewed thrice by the pharmacists (co-authors) using a listed questionnaire (Appendix 1) to assess factors contributing to poor compliance, injection techniques, transport, and storage of medications. This was done at recruitment and subsequent two clinic follow-ups with a 3-4-months interval between visits. Corrective measures were taken if patients were noted to have wrong injection techniques or inappropriate transport and storage of medications. During every clinic visit, height was measured using a Harpenden Stadiometer and the average height of three measurements was used. The methodology is summarized in Figure 1.

\[
\text{First Clinic / Pharmacy Visit} \\
- Recruitment \\
- Return all empty pen or vials from home \\
- Measure height \\
- Interview & counselling \\
- Collect new prescription \\
\]

\[
\text{Second Visit} \\
- Measure height \\
- Interview & counselling \\
- Return used medication and calculation of compliance \\
- Collect new prescription \\
\]

\[
\text{Third Visit} \\
- Measure height \\
- Interview & counselling \\
- Return used medication and calculation of compliance \\
- Collect new prescription \\
\]

\[
\text{* Compliance (%) = } \frac{\text{Doses utilised}}{\text{Doses prescribed}} \times 100 \\
\text{(*Calculated during each visit to the hospital pharmacy upon returning used medication and collection of new ones).} \\
\text{Final compliance (%) } = \frac{\text{Compliance %}}{\text{Number of visit to the pharmacy}} \\
\text{Poor Compliance = utilised doses <86% of the prescribed doses @ equivalent to missed ≥1 injection a week} \\
\]

Figure 1. Summary of the Methodology
The percentage of compliance for each patient was calculated based on the doses utilized over the doses prescribed (Figure 1). Doses utilized were checked and calculated by the pharmacists during each visit to the pharmacy for the new collection of medications. Participants were required to bring the used medications and their GH devices during each visit. There were two types of GH device used, i.e., a single used disposable pen which is the self-inject device; and an auto-injector device equipped with an electronic device (Easypod) which auto-records the daily administration of medication and its dose. For the disposable pen, manual calculation of the utilized doses was based on the remaining doses in the returned used pen. Visits to the hospital pharmacy would coincide with the clinical review in the Paediatric Endocrine Clinic. However, there are additional visits required for the collection of medications between 1-3 monthly when there is a lack of supply in the hospital.

Poor compliance was defined as utilized doses < 86% of the prescribed doses which is equivalent to missing less than 1 injection a week (one injection per week = 14%) (Figure 1). This was similar to the definition used by Cutfield et al. study [10] in New Zealand, who defined compliance as ≥ 85% adherence (equivalent to no more than one missed dose a week on average to prescribed treatment).

Statistical analysis
Sample size calculation was done using Sample Size Calculator for Estimations v 1.0.03 (Naing L, Winn T and Rusli BN). The estimated prevalence of non-compliance to GH therapy was 66%, from Cutfield et al. [11]. The calculated sample size for a 95% level of confidence and precision of 0.05 was 345 samples. However, as our patient pool is only around 35 patients, finite population correction was applied and the corrected sample size was 33 patients. Given the very small patient population, the decision was made to include all patients to maximize data collection.

Statistics analysis was done using SPSS version 22. Descriptive data were expressed as mean ± standard deviation (SD) unless otherwise stated. Paired T-test was used to analyze outcomes before and after the intervention. For univariate analyses, the independent samples test was used for the analysis of normally distributed variables, while Mann Whitney Test was used for non-normally distributed data. Categorical data were analyzed using Chi-square or Fisher’s exact test. For multivariate analysis, binary logistic regression was used. A value of P < 0.05 is considered statistically significant. Height velocity standard deviation score (HV SDS) was calculated using the software Auxology version 1.0 b17 Copyright® 2003 Pfizer.

Results

Patients and baseline anthropometry
Thirty-four patients consented and were recruited for the study. Twenty participants (59%) had underlying GHD (sixteen patients had multiple pituitary deficiencies and four isolated GHD). The remainder 14 (41%) participants were girls with TS. The mean age of patients recruited in the study was 10.75 ± 3.58 years for GHD patients and 11.32 ± 3.33 years for TS patients. The age of initiating rGH was 7.26 ± 3.20 years for GHD patients and 8.39 ± 3.14 years for TS. For GHD patients, the baseline height standard deviation score (SDS) was -4.25 ± 1.32 and TS -3.45 ± 1.03. The duration of rGH treatment for GHD patients was 4.05 ± 2.81 years, with two patients within first year of treatment. Mean duration of rGH for TS patients was 3.48 ± 2.90 years. Two patients were still within the first year of rGH treatment. There were no significant differences in the baseline anthropometry between the two groups (Table 1).
Table 1. Baseline characteristics of patients

| Clinical characteristics                        | Total (n = 34 patients) | GH Deficiency (n= 20) | Turner Syndrome (n= 14) | p-value |
|------------------------------------------------|-------------------------|-----------------------|-------------------------|---------|
| Mean age +/- SD at recruitment (years)         | 10.75 ± 3.58 (4.21 - 16.95) | 11.32 ± 3.33 (4.71 - 15.24) | 0.637 |
| Mean age +/- SD on presentation (years)        | 5.11 ± 3.50 (0.25 - 11.00) | 7.11 ± 3.22 (2.10 - 12.10) | 0.096 |
| Mean age +/- SD at starting GH (years old)     | 7.26 ± 3.20 (0.48 - 12.10) | 8.39 ± 3.14 (3.27 - 13.75) | 0.315 |
| Height SDS when initiate GH                    | -4.25 ± 1.32            | -3.45 ± 1.03           | 0.072 |
| Duration of treatment (years)                  | 4.05 ± 2.81 (0.75 - 10.48) | 3.48 ± 2.90 (0.80 – 9.1) | 0.371 |

n=number, SD=standard deviation

Compliance rates and associated factors

The majority of the participants, 22 (65%) were adherent to treatment but 12 (35%) had poor compliance. There was poorer compliance among GHD participants as compared to TS (45% vs 21%). However, this was not statistically significant, p=0.275 (Table 2).

Paired T-test did not demonstrate an improvement in compliance for both GHD and TS groups from the first to final assessment during the study.

Table 2. Compliance in patients on GH treatment

| Overall (n=34) | GHD (n=20) | TS (n=14) | P value |
|---------------|-----------|-----------|---------|
| Good compliance | 65% (n=22) | 55% (n=11) | 79% (n=11) | 0.275 |
| Poor compliance | 35% (n=12) | 45% (n=9) | 21% (n=3) |

n=number, GHD=growth hormone deficient, TS=Turner Syndrome

Among the GHD participants, poor compliance was more common in the older age group or the adolescents (mean age 12.55 ± 3.33 years) as compared to the younger patients (9.28 ± 3.20 years) with a mean age difference of 3.27 years (p=0.038). There was a significant association found between compliance and duration of treatment in GHD patients. Good compliant patients had been on a shorter duration of treatment (mean 2.93 ± 2.18 years) while those with poor compliance had been on treatment for a longer duration (5.41 ± 3.0 years, difference 2.48 years, p=0.046.). There were no significant associations found in participants with Turner syndrome. These findings are summarized in Table 3.
The predominant ethnic group was Malay with 22 participants (64.7%) followed by Chinese, 8 (23.5%), Indian and others, 4 (11.8%), in keeping with the racial distribution in Malaysia. Six (17.7%) of the parents or caregivers had primary education, 15 (44.1%) secondary education and 13 (38.2%) tertiary education. Nineteen (55.9%) of the patients self-administer GH injection, while 15 (44.1%) were administered by the caregivers, of which the majority were the mother (63%) followed by the father (26%), grandparents (9%), and other caregivers (2%). From the questionnaire, 19 (55.9%) of the caregivers said they supervise the injections all the time, 15 (44.1%) only sometimes supervise. The majority (number, n=28, 82.4%) of the participants were using the self-inject pen device and the rest auto-injector easypod. All participants said they were satisfied with the GH treatment and the devices and were aware of the importance of GH therapy and compliance to medication. Eight (23.5%) of the participants had an unsatisfactory techniques of GH administration during the initial assessment, which improved by the end of the study. Most understood the mode of transport and storage of medication though 2 (5.9%) had to be corrected and counseled, despite already being on rGH for more than 2 years.

The older group of patients (>10 years old) were more likely to self-inject (p=0.068) and had less supervision on GH administration (p=0.052) though these were not statistically significant. Multivariate analysis did not demonstrate any statistically significant association between compliance with race, gender, diagnosis, education level, the person who administer medication, supervision or device used.

Demographics and other factors explored in the questionnaire are summarized in Table 4.

**Reasons cited by participants and families for missing injections**

Various reasons were cited by participants and their parents or caretakers for missing injections (refer to Figure 2). Common reasons cited were forgetfulness (n=20, 58.9%), insufficient medication supply (n=8, 5%), away from home (n=6, 17.6%), device malfunction (n=2, 5.9%) and being unwell (n=2, 5.9%) participants. None reported needle phobia or any adverse effects.
Table 4. Factors associated with compliance based on multivariate analysis

| Characteristic          | Compliant | No          | Total | P-value |
|-------------------------|-----------|-------------|-------|---------|
|                         | Yes       | Yes         |       |         |
|                         | n (%)     | n (%)       |       |         |
|                         |           |             |       |         |
| Gender                  |           |             |       |         |
| Male                    | 8 (36.4)  | 6 (50.0)    | 14 (41.2) | 0.114   |
| Female                  | 14 (63.6) | 6 (50.0)    | 20 (58.8) |         |
| Ethnicity               |           |             |       |         |
| Malay                   | 11 (50.0) | 11 (75.0)   | 22 (64.7) | 0.163   |
| Chinese                 | 7 (31.8)  | 1 (16.7)    | 8 (23.5) |         |
| Indian/others           | 4 (18.2)  | 0 (8.3)     | 4 (11.8) |         |
| Level of education      |           |             |       |         |
| Primary                 | 4 (17.4)  | 2 (18.2)    | 6 (17.7) | 0.106   |
| Secondary               | 10 (43.5) | 5 (45.5)    | 15 (44.1) |         |
| Tertiary                | 9 (39.1)  | 4 (36.4)    | 13 (38.2) |         |
| Diagnosis               |           |             |       |         |
| GH deficiency           | 11 (50)   | 9 (75)      | 20 (58.8) | 0.102   |
| Turner Syndrome         | 11 (50)   | 3 (25)      | 14 (41.2) |         |
| Device used             |           |             |       |         |
| Pen                     | 20 (90.9) | 8 (66.7)    | 28 (82.4) | 0.063   |
| Easypod                 | 2 (9.1)   | 4 (33.3)    | 6 (17.6) |         |
| Administration of injection by |   |             |       | 0.301   |
| Patient                 | 11 (50)   | 8 (66.7)    | 19 (55.9) |         |
| Parent/Caretaker        | 11 (50)   | 4 (33.3)    | 15 (44.1) |         |
| Supervision during administration | |             |       | 0.727   |
| Yes                     | 11 (50)   | 8 (66.7)    | 19 (55.9) |         |
| Sometimes/No            | 11 (50)   | 4 (33.3)    | 15 (44.1) |         |

Figure 2. Reasons Cited for Poor Compliance
**Effect of compliance on height velocity**

There were significant differences noted between height velocity (HV) and height velocity standard deviation score (HV SDS) with compliance in GH deficient patients. Patients who were compliant had mean height velocity 9.69 ± 1.75 cm/year versus 7.11 ± 2.71 cm/year in the group with poor compliance (Mean difference 2.58 ±1.00 cm, p-value 0.019). For height velocity SDS, the group with good compliance had a mean SDS of 4.19 ± 2.35 versus 1.76 ± 2.11 in the poor compliant group (mean difference 2.43 ± 1.01, p-value 0.027) (Figure 3) (Table 5).

The association of HV and HV SDS with compliance remained significant after excluding patients on the first year of rGH (Supplementary Table 1).

However, no significant difference was found in patients with TS (Table 5).

![Height Velocity and Height Velocity SDS in Compliance Group in GHD](image)

**Figure 3.** Comparison of HV and HV SDS with compliance in GHD Patients

**Table 5. HV and HV SDS According to Compliance for GHD and TS Patient**

| Compliance | Good | Poor |
|------------|------|------|
| Mean ± SD  | Mean Difference | P-value |
| GHD, n     |      |      |
| HV (cm/year)| 11  | 9    | 2.58 ± 1.00 | 0.019 |
| HV SDS     | 9.69 ± 1.75 | 7.11 ± 2.71 |             |
| TS, n      |      |      |
| HV (cm/year)| 11  | 3    | 1.11 ± 1.30 | 0.410 |
| HV SDS     | 5.97 ± 2.03 | 4.86 ± 1.85 |             |

n=number, SD=standard deviation, GHD=growth hormone deficient, TS=Turner Syndrome, HV=height velocity, HV SDS=height velocity standard deviation score
Supplementary Table 1. HV and HV SDS According to Compliance for GHD Patients (excluding those in the first year of rGH)

| GHD patients | Compliance | Mean Difference | P-value |
|--------------|------------|----------------|---------|
|               | Good       | Poor           |         |
| **Mean SD**   |            |                |         |
| Mean HV SDS   | 3.97±2.30(9)| 1.76±2.11(9)  | 2.21±1.04| 0.049   |
| Mean HV       | 9.57±1.77(9)| 7.11±2.71(9)  | 2.46±1.08| 0.036   |

HV=height velocity, HV SDS= height velocity standard deviation score

Discussion

rGH had been widely used for the treatment of growth disorders in children and adolescents [12], and compliance is important to ensure efficacy and the best outcome of treatment [9,13]. A recent systematic review by Graham Selina et al. looking at studies from 1985 to 2018 measuring treatment adherence in paediatric GHD population [6] reported various methods in assessing compliance to treatment and definitions of compliance. Methods measuring medications adherence included redeemed rhGH prescriptions/vials [4,10,14], self-report questionnaires to the patient and/or parents [15,16], and electronic monitoring device in conjunction with a clinical kit software [17-21].

Majority of the studies [7,10,14,17] had adopted similar cut-offs proposed by Cutfield et al [10]. The cut-offs were divided into good/high adherence (≥85% adherence equivalent to missed ≤1 dose per week); medium adherence (missed >1 but <3 doses per week) and poor/low adherence (missed ≥3 doses per week). Another study [16] had used the adherence criteria established by Smith et al. [22] based on the percentage of doses omitted during each evaluation period, with a classification of: 0%, excellent; 5%, good; 5–10%, fair; and >10%, poor.

We had chosen to adopt the approach of Cutfield et al [10]. However, given the relatively small sample size, we had divided to only two categories i.e., good and poor compliance. The poor compliance rate was defined as <86% of the prescribed doses which is equivalent to missing more than 1 injection a week (1 injection per week =14%). Good compliance was defined as ≥86% of prescribed doses which is equivalent to missing less than 1 injection a week. Using this threshold, Cutfield et al. had reported a reduced HV in their participants. Hence, we felt it was a reasonable threshold to adopt. However, we acknowledge there are variable definitions for compliance rate with different studies and this is a limitation of our study.

Poor compliance was noted in 35% of participants in our study. The compliance rate was better compared to Cutfield et al. who reported non-compliance to GH treatment in 66% of their subjects [8]. Kapoor et al. (2007) (n=75) reported 39% had missed more than 1 injection per week and 23% missed 2 injections per week [4]. Our compliance rate could have been higher as the participants were aware that they were being monitored and hence likely to be more compliant [12].

Differences in adherence rate reported could also be due to variations in the way it was defined, assessed and the methodology of the studies. The definition of compliance in this study was consistent with a few other studies which defined poor compliance as missing at least 1 injection in a week [4,10]. However, these studies were cross-sectional whereas ours was a prospective study. Unfortunately, as there were limited suitable prospective studies which we could adopt, we decided to modify the model from Cutfield et al. after consultation with our statistician. In our study, poor compliance was higher among GHD patients as compared to TS; however, this was not statistically significant possibly because the number of TS participants was small.
Our study showed poorer HV and HV SDS in participants with GHD with poor compliance \((p<0.05)\). This was consistent with the results published by Cutfield et. al \([10]\) showing significantly greater linear growth in patients who had good compliance \((\geq85\%\) compliance or missed less than 1 dose a week of injection). Similarly, Kapoor et. al \([4]\) reported poor compliance \((\text{missing } >1 \text{ dose per week})\) was associated with reduced height velocity \((p<0.005)\).

The height velocity for children naïve to rGH is usually highest during the first year of treatment. Thus, we had done a separate statistical analysis excluding patients on the first year of rGH. The association of HV and HV SDS with compliance in GHD patients remained significant after this exclusion (Supplementary Table 1). However, no significant difference was found in TS patients, likely due to the small sample.

Two main factors were found to be significantly associated with poor compliance in this study, i.e., the duration of treatment and the age of the patients. There was a negative correlation between compliance and the duration of GH therapy. Participants with GHD who had poor compliance had a longer duration of treatment. There was also a significantly higher rate of poor compliance in the older age group of patients. These were consistent with the findings in other studies which reported poor adherence with longer duration of GH therapy \([4,6]\) and among adolescents \([3,14,23,24]\). This further highlights the challenges in maintaining good compliance to treatment in chronic illnesses. Compliance in drug therapy is often poor in chronic non-life-threatening conditions such as GHD \([25]\). Motivation may be low as the benefits are not immediately apparent and daily subcutaneous injections may present a significant burden \([4,26]\).

Thus, regular checks on adherence and repeated motivation to patients are important throughout the course of GH treatment. This is especially important among adolescents given the unique developmental, psychosocial and lifestyle issues implicit in their transition to adulthood \([27]\). Defiance, rebellious, attention-seeking, and denial can be manifested by not taking required medications \([24]\). The process of transition from parental dependency to autonomy at this age also leads to confusion as to who is responsible for the administration of medication \([14]\). There were a few adolescents in our study who were studying at boarding schools away from home who cited lack of motivation and supervision as the reasons for poor compliance. Thus, extra attention and supportive treatment such as motivational and behavioral therapy may be needed to improve treatment adherence in adolescents. This is especially so for those who had been on therapy for a long duration of time.

There were no significant associations found between compliance with other variables which included demographic characteristics, gender, race, education level; personnel who administer the medication, supervision from caregivers, or types of devices. This was consistent with other studies which did not find a major influence of demographic factors on patient's adherence to medications \([24]\). However, one would expect involvement of parents and caregivers in drug administration to influence compliance \([17,28]\).

Drug adherence in children is unique because of the involvement of a third party who is involved in supervision or administration of the medication, i.e., the parent/guardian \([7]\). Self-administration of medication had been reported to be associated with lower treatment adherence compared to administration by parents \([14]\). Our study did not find a significant association between supervision with compliance, possibly because of the small sample size. Our study showed there was only occasional supervision by \(44\%\) of parents/caretakers especially in the older age group \((>10 \text{ years old})\). Parents or caregivers should be reminded to monitor administration regularly, even if the child or adolescent have been self-injecting for a long period.

We also found no significant differences in compliance between the GH devices. This was similar to other studies \([29]\) though some suggested improved compliance if patients were given the option to choose the device \([4,22]\). A few observational studies by Saizen ® using Easypod devices claimed high compliance rates can be achieved with precise and objective measurements of adherence \([17,19,30]\). However, caregivers or patients may have different preferences on the devices. The majority of our patients on GH treatment were using self-inject pen devices thus it would be difficult to compare the compliance rate between the two devices. Level of understanding is usually one of the main factors for poor compliance \([31]\), and few studies
suggested the association of the education level of caregivers with compliance [7]. This was not reflected in our study.

Reasons for missing medications reported in other studies include a short prescription of duration less than 4 weeks, scheduling issues (away from home), forgetfulness, inter-current illness and pain [4,23]. The majority of the participants in this study cited forgetfulness as the main reason for missing doses followed by insufficient medications, travelling away from home and being unwell. None of the participants had complaints of pain or needle phobia, which is a common belief of poor compliance [15,28]. All the participants were satisfied with their GH therapy and device used, though few of them were found to have technical issues in administration, which were promptly rectified. None complained of adverse effects. Recognition of reasons and factors contributing to poor compliance is necessary to enable remedial measures to be taken. Measures to address the common shortcoming of being forgetful include the suggestion of a reminder mechanism for example a calendar chart or reminder alarm, and commitment from parents to consistently supervise the injection. Provision of a longer supply of medication may also help with adherence, as inadequate supply of medications was a commonly cited reason for missing doses. In our current setting, most patients were required to collect new medications every 1-2 months at the hospital pharmacy thus logistics can be a major hinder.

Regular monitoring of adherence is important not just at initiation but throughout treatment as compliance tends to reduce with increased years of treatment. In our study, despite the frequent counseling given to the participants; missing injections still happen. We did not demonstrate a significant change in compliance rate over time in our study, likely because counseling was already provided at recruitment and the short duration of the study. However, we demonstrated that 8 (23.5%) participants with unsatisfactory GH administration techniques during the initial assessment improved at the end of the study.

Accurate methods for assessing medication compliance are also necessary. Ideally, patients should be instructed to bring their devices each visit to show proof of compliance and exchange used medication for every new collection of prescriptions. Doctors, pharmacists or specialized nurses can play an important influence on medication-taking behavior [24]. Regular counseling and review sessions may help reinforce drug compliance and identify cases at risk of poor treatment adherence. Patient knowledge including injection technique, transportation and storage of medication should be evaluated from time to time, as a longer duration of treatment is not necessarily associated with better techniques or understanding, as noted in our study.

The findings of this study had reaffirmed the importance of compliance to daily rGH injection to ensure a good treatment outcome. Education and creating awareness should be emphasized early from the time of initiating rGH, as patients and families may have a different perception of what constitutes poor compliance [7]. They may not realize missing an injection once a week could lead to a significant reduction in long-term growth velocity. More attention should be focus on poor compliance in adolescents and those with a longer duration of treatment, as they are at higher risk of poor drug adherence. Long-acting GH (LAGH) preparations are currently being developed [32,33]; however, these will not necessarily promise good drug adherence if the basic principles of education and constant monitoring were not practiced.

The strength of this study was the prospective nature enabling accuracy in clinical data, measurements of growth velocity and assessment of compliance. In addition to the calculation of returned vials and checking of devices, interviews based on a questionnaire to assess compliance were done to enable better assessment of adherence rates. At the same setting, reasons for poor compliance and confounding factors contributing to impaired growth velocity were also explored, such as issues with devices, the technique of drug administration, transport, and storage of the medication.

The limitation of this study was the small sample size, which could have resulted in the lack of significant associations for some of the variables analyzed, especially among patients with TS. Since this was not a blinded randomised study, the compliance and height velocity rate could have been artificially raised during the study. The interview sessions may hinder the participants from giving truthful answers and may explain the
low incidence of needle phobia or dissatisfaction with the medication or devices demonstrated in this study.

**Conclusion**

Poor compliance resulted in a significantly reduced height velocity in patients with GHD and is more common in adolescents and those who had been on treatment for a longer duration. As forgetfulness is the commonest reason for missing an injection, parents and caregivers should play their role to regularly supervise the injections. Measures to improve compliance should address underlying reasons and monitoring adherence throughout therapy. This is important to ensure an optimal height outcome and prevent wastage of funds for public-funded treatment. Larger, multi-centre double-blinded randomized studies in the future is needed to provide more evidence on the cause and effect of poor drug compliances.

**Acknowledgements:**

We would like to thank the Director-General of the Ministry of Health, Malaysia for his permission to publish this study.

**References**

[1] Flodh H. Human growth hormone produced with recombinant DNA technology: Development and production. Acta Paediatr Scand. 1986;75(SUPPL. 325):1–9.

[2] Ministry of Health Malaysia. The use of growth hormone in children and adults- Clinical Practice Guidelines. 2010;1–84. Available from: http://www.moh.gov.my

[3] Haverkamp F, Johansson L, Dumas H, Langham S, Tauber M, Veimo D, et al. Observations of nonadherence to recombinant human growth hormone therapy in clinical practice. Clin Ther. 2008;30(2):307–16.

[4] Kapoor RR, Burke SA, Sparrow SE, Hughes IA, Dunger DB, Ong KK, et al. Monitoring of concordance in growth hormone therapy. Arch Dis Child. 2008;93(2):147–8.

[5] Lustig RH. Optimizing growth hormone efficacy: an evidence-based analysis. Horm Res. 2004;62 Suppl 3(suppl 3):93–7.

[6] Graham S, Weinman J, Auyeung V. Identifying potentially modifiable factors associated with treatment non-adherence in paediatric growth hormone deficiency: A systematic review. Horm Res Paediatr. 2019;90(4):221–7.

[7] Haverkamp F, Gasteyger C. A review of biopsychosocial strategies to prevent and overcome early-recognized poor adherence in growth hormone therapy of children. J Med Econ. 2011;14(4):448–57.

[8] Ooi HL, Wu LL. Final height in growth-hormone-treated children with idiopathic growth hormone deficiency: The Malaysian Experience. Med J Malaysia. 2011;66(5):479–83.

[9] Fisher BG, Acerini CL. Understanding the growth hormone therapy adherence paradigm: A systematic review. Horm Res Paediatr. 2013;79(4):189–96.

[10] Cutfield WS, Derraik JGB, Gunn AJ, Reid K, Delany T, Robinson E, et al. Non-compliance with growth hormone treatment in children is common and impairs linear growth. PLoS One. 2011;6(1):5–7.

[11] Hindmarsh PC, Brook CGD, Ministry of Health Malaysia, Matsui DM, Cutfield WS, Karagiannis G, et al. Optimizing growth hormone efficacy: an evidence-based analysis. PLoS One [Internet]. 2008;18(1):929–41. Available from: http://www.moh.gov.my http://www.academic.org.my http://www.endocrine.my/index.php

[12] Lanes R. Long-term outcome of growth hormone therapy in children and adolescents. Treat Endocrinol. 2004;3(1):53–66.

[13] Acerini C, Albanese A, Casey A, Denvir L, Jones J, Mathew V et al. Initiating growth hormone therapy for children and adolescents. Br J Nurs. 2012;Oct 11-24;21(18):1091-7.

[14] Lass N, Reinehr T. Low treatment adherence in pubertal children treated with thyroxin or growth hormone. Horm Res Paediatr. 2015;84(4):240–7.

[15] Rosenfeld RG, Bakker B. Compliance and persistence in pediatric and adult patients receiving growth hormone therapy. Endocr Pract. 2008;14(2):143–54.

[16] Aydin BK, Aycan Z, Şiklar Z BM, Öcal G, Çetinkaya S et al. Adherence to growth
hormone therapy: Results of a multicenter study. Endocr Pract. 2014;Jan;20(1):46–51.

[17] Hartmann K, Ittner J, Müller-Rossberg E, Schönau E, Stephan R, Ullrich KP, et al. Growth hormone treatment adherence in prepubertal and pubertal children with different growth disorders. Horm Res Paediatr. 2013;80(1):1–5.

[18] Van Dommelen P, Koledova E, Wit JM. Effect of adherence to growth hormone treatment on 0-2 year catch-up growth in children with growth hormone deficiency. PLoS One. 2018;13(10):1–12.

[19] Arnao MDR, Sánchez AR, López ID, Fernández JR, De La Vega JAB, Fernández DY, et al. Adherence and long-term outcomes of growth hormone therapy with easypod™ in pediatric subjects: Spanish eco study. Endocr Connect. 2019;8(9):1240–9.

[20] Koledova E, Tornincasa V, Van Dommelen P. Analysis of real-world data on growth hormone therapy adherence using a connected injection device. BMC Med Inform Decis Mak. 2020;20(1):1–7.

[21] Blanco-López A, Antillón-Ferreira C, Saavedra-Castillo E, Barrientos-Pérez M, Rivero-Escalante H, Flores-Caloca O, et al. Adherence to treatment in children with growth hormone deficiency, small for gestational age and Turner syndrome in Mexico: results of the Easypod™ connect observational study (ECOS). J Endocrinol Invest [Internet]. 2020;43(10):1447–52. Available from: https://doi.org/10.1007/s40618-020-01218-4

[22] Smith SL, Hindmarsh PC BC. Compliance with growth hormone treatment – are they getting it? Arch Dis Child. 1995;73:527.

[23] Bagnasco F, Iorgi N Di, Roveda A, Gallizia A, Haupt R, Maghnie M. Prevalence and correlates of adherence in children and adolescents treated with growth hormone: A multicenter Italian study. Endocr Pract. 2017;23(8):929–41.

[24] Matsui DM. Drug compliance in pediatrics: Clinical and research issues. Pediatr Clin North Am. 1997;44(1):1–14.

[25] Hunter I, DeVries C MA. Human growth hormone therapy: poor adherence equals poor growth. Arch Dis Child. 2000;82: A8.

[26] Mohseni S, Heydari Z, Qorbani M, Radfar M. Adherence to growth hormone therapy in children and its potential barriers. J Pediatr Endocrinol Metab. 2018;31(1):13–20.

[27] Friedman IM LI. Adolescents’ compliance with therapeutic regimens. Psychological and social aspects and intervention. J Adolesc Heal Care. 1987;8: 52–67.

[28] Oyarzabal M, Aliaga M, Chueca M E, G UA. Multicentre survey on compliance with growth hormone therapy: what can be improved? Acta Paediatr. 1998;87: 387–39.

[29] Wickramasuriya BPN, Case A, Akhtar S Z, R, Ehtisham S, Barrett TG et al. Factors determining patient choice of device for GH therapy. Horm Res. 2006;65: 18–22.

[30] Höybye C, Sävendahl L, Christesen HT, Lee P, Pedersen BT, Schlumpf M, et al. The NordiNet® International Outcome Study and NovoNet® ANSWER Program®: Rationale, design, and methodology of two international pharmacoepidemiological registry-based studies monitoring long-term clinical and safety outcomes of growth hormone therapy. Nor. Clin Epidemiol. 2013;5(1):119–27.

[31] Stanhope R, Moyle L MM. Patient knowledge and compliance with growth hormone treatment. J. Arch Dis Child. 1993;68:525.

[32] Miller BS, Velazquez E YK. Long-acting growth hormone preparations – current status and future considerations. J Clin Endocrinol Metab. 2020;105(6):e21:1–31.

[33] Luo X, Hou L, Liang L, Dong G, Shen S, Zhao Z, et al. Long-acting PEGylated recombinant human growth hormone (Jintrolong) for children with growth hormone deficiency: Phase II and phase III multicenter, randomized studies. Eur J Endocrinol. 2017;177(2):195–205.
Statement

What is already known on this topic?

- Good compliance to recombinant growth hormone in children and adolescents is necessary to ensure optimal treatment outcomes.

- Reported non-compliance to growth hormone treatment in the paediatric population range from 5-82% with little data on any Asian cohort.

What does this study add?

- Poor compliance is common especially in adolescents and those who had been on a longer duration of treatment.

- Poor compliance resulted in a significantly reduced height velocity in participants with growth hormone deficiency.

- The most common reason cited for non-compliant was forgetfulness.

- Almost half of the patients' injections were not regularly supervised by their parents or caregivers.

- Addressing underlying reasons for poor compliance and monitoring of adherence is important throughout the course of treatment.