

Adherence to Growth Hormone Therapy in Children with Primary Isolated Growth Hormone Deficiency

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Abstract

Original Research Article

Background: Poor or non-adherence to growth hormone (GH) therapy is the most vital factor that could affect the growth potential of the individual. **Aim:** To assess the adherence and growth outcomes in growth hormone-deficient children treated with recombinant human growth hormone (r-hGH) via easypod™. **Methods:** The medical records of children with primary isolated GH deficiency and treated with r-hGH via easypod™ were retrospectively analyzed. The primary endpoint was to assess the mean rate of treatment adherence. Secondary endpoints were to study the changes in height, height standard deviation (SD) score, height velocity, and height velocity SD score after one-year of r-hGH treatment and the impact of adherence on the growth outcomes. **Results:** The mean age of the children included in this study was 10 years (age range: 8 to 11 years). Adherence to the r-hGH varied from 74-98% (mean 87%). Annular height velocity, the height SD score, and Insulin growth factor-1 level were 2 - 4 cm, -6.2 SD to -2.1 SD, and 22 to 218 ng/ml, respectively before initiation of the therapy, and reaches to 5 - 8 cm, -5.4 SD to -1.25 SD, and 85 to 545 ng/ml after one-year of r-hGH therapy. A good correlation between adherence and height was observed ($r=0.85$, $p<0.01$). **Conclusion:** We found an acceptable adherence to r-hGH treatment among children with primary isolated GH deficiency. We also found a significant relationship between drug adherence and improved growth outcomes.

Keywords: Adherence; ECOS; Growth hormone; Saizen, Easypod.

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INTRODUCTION

In pediatric endocrinology clinics, patients with short stature are commonly encountered, and one of the important endocrine causes is growth hormone deficiency (GHD), accounting for 2.8% to 69% of cases of short stature in children [1]. It is also a common treatable cause of short stature and is commonly treated with recombinant human growth hormone (r-hGH) [2]. The response to growth hormone (GH) therapy is influenced by various factors like the patient's age, proper GH therapy, including correct doses and duration, as well as the responsiveness of the individual [3-5]. Among them, the most crucial factor is individual responsiveness resulting in the adherence to GH therapy, which has been shown to reach up to 70% in the past studies [6-8].

Non-adherence is an important problem in chronic diseases as it interferes with the effectiveness of

the treatment, leading to poor clinical outcomes, and increased healthcare costs [9]. According to a systematic review conducted by Fischer *et al.*, the prevalence of non-adherence ranged widely from 5 to 82% according to the definition and methods adopted in that study [10]. An association was observed between the adherence to the treatment, and duration of the treatment, a device used for injection, age, and the socioeconomic status of the patient [10]. Poor or non-adherence to GH therapy could affect the growth potential of the individual and has been linked with several factors, including lower socioeconomic status, difficulty or discomfort in administration with injection, lack of choice of the injection device, etc [10]. Hence, various strategies were proposed by the researchers to improve the patients' adherence and also to encourage self-administration. One of these strategies is the administration of the Easypod™ auto-injector.

The Easypod™ auto-injector connected digital device is a solution for the patients with poor adherence to GH therapy, as it makes the r-hGH administration easier and also allows the patients to measure their adherence objectively. Easypod™ device works by delivering a pre-fixed dose of r-hGH (Saizen®). Also, it stores these data electronically that can be easily shared with the patient's physician, who can thus monitor the adherence to the therapy [11-14]. The acceptance and adherence rate of this device was found to be good in several previous studies [12, 13].

Despite all these methods, adherence to GH therapy remains suboptimal; especially, in the pediatric population. Therefore, we planned this study to evaluate the adherence to the treatment with r-hGH using Easypod™ in children with primary isolated GH deficiency and correlate the adherence rate with clinical growth outcomes.

METHODS

A retrospective, observational, monocentric study was carried at the pediatric endocrinology clinics, King Faisal Specialist Hospital and Research Center, and Security Forces Hospital. The primary objective was to assess the adherence and growth outcomes, which were determined by the changes in the height velocity standard deviation score (Δ HVSDS), height standard deviation score (Δ HtSDS), and insulin growth factor-1 (IGF-1) levels over one year. The secondary objectives were to correlate the drug adherence rate with the growth outcomes as well as IGF-1 levels.

The children below 18 years and treated with r-hGH using the Easypod™ auto-injector from February 2019 until January 2020 were enrolled in this study. The medical records of 22 children with primary isolated GH deficiency and treated with r-hGH via easypod™ were retrospectively analyzed.

The diagnosis of GH deficiency was suspected in short children with height more than 2.5 SD below the mean and confirmed by a stimulated GH level of $<10\mu\text{g/L}$ by clonidine and glucagon stimulation tests. Other pituitary hormone levels were confirmed normal by random measurement of thyroid-stimulating hormone (TSH), free thyroxine (fT4), luteinizing hormone (LH), follicular stimulating hormone (FSH), adrenocorticotrophic hormone (ACTH), and morning cortisol levels. Bone age was measured using the Greulich and Pyle method. Other structural anomalies were ruled out in all the patients by Magnetic Resonance Imaging (MRI) brain and pituitary.

To provide a precise and objective measure of adherence, an electronic auto-injector device, easypod™ (Merck Serono International S.A.) was used.

At a dose ranging from 0.03-0.035 mg/kg/day, the growth hormone was given as a daily subcutaneous injection by patients or under parent's supervision.

The compliant population was defined as those with $\geq 85\%$ adherence to the prescribed treatment, and it was determined if the average doses missed by the patient were not more than one dose per week. Adherence was determined as the percentage of adherence over the period of time (calculated by dividing the number of days when the patient received injections by the number of days when the injection was planned). We also recorded the responses of the parents to know about the reasons for missing GH injections as they were also interviewed routinely for the same.

Correlations between adherence and growth outcomes were calculated using Spearman's product-moment correlation. Alpha errors (p values) reported are two-sided. Significance was measured at $p < 0.05$.

RESULTS

A total of 22 children aged 8-11 years (mean age 10 years) were included in the study. All children were prepubertal with a bone age ranging from 7 to 11 years with a mean age of 9 years. Among 22 children, 12 (54.5%) were males, and 10 (45.5%) were females.

Adherence to r-hGH varied from 74-98% (mean 87%). GH peak in response to the stimulation test ranged from 0.5-8.6 (mean 3.9ng/ml). Prior to r-hGH therapy, HtSDS ranged from -6.2 SD to -2.1 SD (mean -2.7 SD), annular HV ranged from 2-4 cm (mean 3.2 cm), and IGF-1 level ranged from 22 to 218 ng/ml (mean 118) (normal range: 87-399 ng/ml) (Table 1). One year post therapy, HtSDS ranged from -5.4 SD to -1.25 SD (mean -2.4 SD), annual HV ranged from 5 - 8 cm (mean 6.5 cm) with HVSDS change (Δ HVSDS) of 2.1 SD. IGF-1 level ranged from 85 to 545 ng/ml (mean 242 ng/ml). HtSDS change (Δ HtSDS) over one year ranged from 0 - 0.9 SD (mean 0.43 SD) (Table 1).

A good correlation was found between the rate of adherence and Δ HtSDS ($r=0.85$, $p<0.01$), while an inverse correlation was observed between the rate of adherence and age of the children ($r=-0.37$, $p=0.09$). However, we could not find any correlation of rate of adherence with IGF-1 levels ($r=0.38$, $p=0.08$) or Δ HVSDS ($r=0.01$, $p=0.95$).

The reasons behind missing injections as per children and parent's interviews as follows; 63% reported that they forgot the injection, 23% were tired of injections, and 15% ran out of needle/ cartridge. MRI showed a small pituitary gland in two children and unremarkable in the rest of the patients.

Table 1: Comparison between the parameters over the period of one year

	Baseline evaluation	Follow-up evaluation (after one year)
Height standard deviation score	-6.2 SD to -2.1 SD (mean -2.7 SD)	5.4 SD to -1.25 SD (mean -2.4 SD)
Annular height velocity	2-4cm (mean 3.2cm)	5-8cm (mean 6.5cm)
Insulin growth factor level	22 to 218ng/ml (mean 118)	85 to 545ng/ml (mean 242).
HtSDS change over one year	-	0-0.9SD (mean 0.43SD).
Adherence to recombinant human growth hormone	-	74-98% (mean 87%).

DISCUSSION

This retrospective, single-center observational study evaluated the adherence rate to r-hGH therapy using Easypod™ in a group of children with primary isolated GHD and to correlate the adherence rate with clinical growth outcomes. Since 1985, r-hGH is widely used to treat a number of disorders related to growth [15]. It was found that early initiation of the r-hGH treatment improves the height of the patient. Also, poor or non-adherence to the therapy could restrict the growth of the individual [12]. Thus, the most vital factor affecting the success of the treatment is the adherence of the patient towards its treatment [13].

We found that the overall mean adherence rate was 87%, which was higher as compared to the minimum percentage (85%) require to define good adherence to r-hGH therapy. Based on this rate, we decided to increase the frequency of visits to the clinic every three months instead of four months and to be supplemented by phone calls to ensure better adherence. We also decided to educate the treating team to utilize the Saizen®'s e-Health software and web platform to access patients' information and monitor adherence periodically. A high rate of adherence to r-hGH therapy was observed among children and adolescent (92.2%) in a retrospective study conducted by Maggio MC *et al.* They also found that the adherence was related inversely to the age of the patients ($R = -0.358$, $p = 0.023$) [16]. Bozzola *et al.* found an average adherence rate of 87.5% in 824 children [12].

Koledova E *et al.*, conducted a large-scale Easypod™ connect observational study (ECOS) among children diagnosed with growth disorders. Data was collected from 1190 children of 24 nations, and they found an overall rate of adherence of 93.7%. However, the adherence decreased with increasing treatment duration and remained at 70.2% after five years. Also, a statistically significant correlation was observed between the adherence rate and change in height SDS and height velocity SDS over a period of one year [11]. Charmandari E *et al.*, conducted a Greek ECOS study constituting 86 patients. The mean adherence to Saizen®, as recorded via easypod™, was 95.5% after one year of treatment, but no significant correlation was noted between adherence and growth outcomes [17].

In the present study, the change in HtSDS over one year ranged from 0 - 0.9 SD (0.43 SD), which is comparable to other ECOS studies [11, 18]. Centonze C *et al.*, included 73 GHD children in their study. They found a consistently higher adherence rate throughout the study period of three years (88.5%, 86.6%, and 85.7% after one, two, and three years, respectively). In their short-term study, they recorded a high level of adherence rate of over 92% in more than half of the study population (57%) [19]. Studies following the patients for a short-period found a higher adherence rate (from 87.5% to 99%) among pediatric patients receiving r-hGH via the Easypod device [13, 20].

Children with primary isolated GH deficiency were responsive to the recommended GH dose for this indication. A dose of 0.03 - 0.035 mg/kg/day significantly improved IGF-1 level and growth outcomes without side effects. However, in the present study, we were not able to find any correlation between the adherence rate and IGF-1 levels ($r=0.38$, $p=0.08$).

An inverse correlation was observed between the rate of adherence and the age of the patient ($r=-0.37$, $p=0.09$) in our study. Similar results were obtained by Maggio MC *et al.* in their retrospective study with respect to the patient's age and adherence rate ($R = -0.358$, $p = 0.023$), and the relation was higher in the children aged 10 and 13 years [16].

We found a good correlation between adherence and Δ HtSDS ($r=0.85$, $p<0.01$), which is almost similar to the other published studies [18, 21]. In a recently published study, conducted among 147 Easypod™-naïve Mexican children, the adherence rate was associated with the change in height SDS ($r = 0.239$, $p= 0.005$) and height velocity SDS ($r = 0.194$, $p= 0.027$) [17]. Centonze C *et al.* demonstrated an association of the treatment with the increase in height [19]. In contrast to our study, no significant correlation was found between the adherence rate and height of the patients ($R = -0.067$, $p = 0.683$) in a study conducted by Maggio MC *et al.*, [16].

We observed variability of response to GH therapy, which is a quite known phenomenon as the response to the therapy varies from person to person, depending upon the age of the patient, its individual

response towards the treatment, and the severity of the GHD [19].

The limitations of the present study are primarily defined by the limitations of all retrospective studies, as a retrospective study is dependent upon the medical records and written documentation of several doctors. So, the chances of error and missing data would be higher in these studies. Secondly, the sample size of our study is small, and lastly, this was a single institutional study, so the findings of the study cannot be generalized to other centers. Hence, a prospective study should be conducted where more information could be assessed. Our future plan is to continue these children on Saizen® to monitor their adherence and the early detection of any decline in compliance over the following years.

CONCLUSION

In conclusion, children with primary isolated GHD on r-hGH with the electronic device easypod™ showed and maintained a relatively high adherence to the treatment. A significant relationship exists between the adherence rate and the growth outcomes associated with r-hGH therapy. The easypod™ device allows the patient and physicians to monitor the adherence to the r-hGH therapy objectively and helps in achieving a higher compliance rate.

Author's contribution: The authors contributed equally to the manuscript

Conflict of Interest: None

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