Abstract

Idiopathic short stature (ISS) is a kind of low height among children in which children’s height is more than 2 standard deviation (SD) scores below the mean score of the height of other children with the same age and gender. It is one of the disorders that physicians use growth hormone for its treatment. Therefore, the purpose of the current study was to investigate the effect of growth hormone treatment on the adulthood height of children with ISS through meta-analysis method. In total 20 studies with a sample size of 1,517 were included in the meta-analysis through searching in external databases, including Web of science, Pubmed, Cochran, Medline, Embase, Springer, Scopus, and Science Direct using mesh keywords as growth hormone, final height, adult height, and idiopathic short stature. Mean score and SD were utilized for measuring any increase in height growth and random effect model was used for combining studies. Further, I² index was used for determining the heterogeneity of studies. Results indicated that before treatment, according to standard mean difference percentile of children’s height was -1.64 (95% confidence interval (CI): -2.01 to -1.28) which is equal to 5%. After treatment, according to standard mean difference percentile of children’s height came out to be 0.11 (95% CI: 0.07 - 0.14) which is equal to 54.38%. This indicates that percentile of children’s height has increased as a result of treatment with growth hormone. Through combining the results of all studies, the mean score for participants’ height before treatment was 5% and after treatment it reached 54%. Therefore, obtained mean difference for adult height after treatment with growth hormone was reported to be more than 1.4 SD score (about 7.6 cm). Growth hormone can be influential in increasing the adult height of children with ISS.

Keywords: Idiopathic short stature; Adult height; Final height; Growth hormone; Meta-analysis

Introduction

Growth hormone which is secreted from hypophysis due to proteins metabolism would increase their biosynthesis in cells which, in turn, increases the number and the dimensions of cells. Furthermore, growth hormone would stimulate growth plate of long bones before maturity. After maturation, these growth plates will become bony, thus the linear growth of bones stops and their diagonal growth will continue. Any kind of disorder in growth hormone secretion would decrease the growth rate and cause growth disorder in children. As a result, height of these children would be lower than the average height of other children of the same age and gender [1-3]. According to the reports of UNISEF regarding nourishment in 2013, approximately one child of every four children less than 5 years of age suffer from short stature in the world, 3.4% of which are living in Africa and South Asia. Further, in this report, Iran was among no data countries [4]. Short stature is classified into three main groups: initial growth disorder (regarding growth plate), secondary growth disorder (changes in the growth plate physiology), and the third group for which there is no specified reason, i.e. idiopathic short stature (ISS) [5]. ISS is predicated upon the assumption that the child’s height is more than two standard deviation (SD) scores below the average height of children of the same age and gender that he/she has no systematic, trophic, or chromosomal disorder [6, 7]. It is estimated that approximately 80% of children were diagnosed with ISS [8]. Although growth hormone treatment increases the height growth rate, there is disagreement over its use for the treatment of ISS and how much it can increase the height [9-12]. In this regard, many studies have been conducted throughout the world; accordingly, the purpose of this study was to conduct a meta-analysis in order to bring all documents together and arrive at a more accurate conclusion as to the effectiveness of growth hormone treatment among children with ISS.

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Methodology

Searching strategy

The present study was a systematic review and meta-analysis and has been conducted based on PRISMA guideline that reviewed articles and theses investigating the effect of growth hormone treatment on children diagnosed with ISS from 1995 to March 2016 [13]. Articles were collected through using mesh keywords from external databases including Web of science, Pubmed, Cochran, Medline, Embase, Springer, Scopus, and Science Direct. Also, Google scholars search engine was utilized. Moreover, searching was carried out using keywords such as “growth hormone”, “final height”, “adult height”, and “idiopathic short stature” and their Persian equivalents using “and” and “or” conjunctions. In addition, a list of related articles was also utilized for finding articles.

Exclusion and inclusion criteria

In the current study, main inclusion criteria for the studies were initial short stature, defined as height more than 2 SD scores below the mean; peak growth hormone responses greater than 10 μg/L; prepubertal stage; no previous growth hormone therapy; and no comorbid conditions that would impair growth, such as chromosomal abnormalities, bone diseases, chronic diseases interfering with growth, treatment with steroids or sex steroids, and dysmorphic syndromes. Adult height was considered achieved when growth rate was < 1.5 cm/year or bone age was 15 years in females and 16 years in males [14].

Exclusion criteria included: 1) exclusion of studies not involving children with ISS; 2) non-random sample size; 3) unrelated topics; 4) insufficient data; 5) lack of required information and unavailability of the full text of the studies; and 6) studies with low quality. In order to reduce tropism, searching and data extraction were carried out by two researchers independently.

Study selection

Study selection was carried out by two reviewers independently. At first, duplicate studies were removed and studies’ abstracts were investigated; then, if related, they were included. Finally, the full texts of the remained articles were read and if unrelated they were excluded. Following that, randomized controlled trials and cohort studies in which SD and 95% CI were reported were included in the meta-analysis.

Data extraction

In order for decreasing bias and error in data gathering, data extraction was done by two researchers independently using...
were analyzed using STATA software, Ver. 11. A P-value < 0.05 was considered as significance level. Data regarding the dose of growth hormone and duration of treatment. Subgroup analysis was done according to the dose of growth hormone and duration of treatment. Publication bias was checked with funnel plot and Egger test. A P-value < 0.05 was considered as significance level. Data were analyzed using STATA software, Ver. 11.

**Statistical analysis**

Mean, SD and z-score of height before and after treatment were defined as effects size. Z-score was computed using normal distribution. Standard mean difference (SMD) for each study was computed. To pool effects size (ES) or SMD among studies, random effects models were used. Heterogeneity of studies was checked using Q and I² statistics and meta-regression. We considered a mean difference in adult height of more than 0.9 SD scores (about 6 cm) as a satisfactory response to growth hormone therapy [13]. Subgroup analysis was done according to the dose of growth hormone and duration of treatment. Publication bias was checked with funnel plot and Egger test. A P-value < 0.05 was considered as significance level. Data were analyzed using STATA software, Ver. 11.

**Results**

The current study was a systematic review conducted from 1995 to March 2016. Twenty studies related to the effect of treatment with growth hormone on the adult height of children with ISS with a total sample size of 1,517 were included in the meta-analysis (Fig. 1 and Table 1 [10, 11, 15-32]).

**Mean score of participants’ treatment start age**

Generally, there were 20 related studies including four studies of cohort type with an SMD of 11.34 (95% CI: 10.48 - 12.20) for treatment start age, six clinical trial studies without a control group with an SMD of 9.73 (95% CI: 8.84 - 10.63) for treatment start age, seven non-random clinical trial studies with a control group and an SMD of 10.63 (95% CI: 9.83 - 11.48) for treatment start age, and three random clinical trial studies with a group and an SMD of 10.07 (95% CI: 5.90 - 14.25). After combining studies using random effects model, SMD at treatment start age was 10.42 years (95% CI: 9.90 - 11.24) (Fig. 2).

**Mean score of height before treatment start**

There were four cohort studies with an SMD of -1.24 (95% CI: -1.69 to -0.79) for treatment start height, six clinical trial studies without a control group with an SMD of -1.83 (95% CI: -2.70 to -0.97), seven non-random clinical trial studies with a control group and an SMD of -1.70 (95% CI: -2.01 to -1.40) for treatment start height, and three random clinical trial studies without a control group with an SMD of -1.62 (95% CI: -1.82 to -1.41) for treatment start height. When results of studies were combined using random effects model, SMD for treatment start height was -1.64 (95% CI: -2.01 to -1.28) which is equal to 5% (their height was higher than 5% of participants) (Fig. 3).

**Mean score of height after treatment**

It has been indicated that the standardized mean score of height in the three cohort studies was 0.11 (95% CI: 0.08 - 0.14), the standardized mean score of height in the six clinical trial studies without control group was 0.06 (95% CI: 0.05 - 0.07), standardized mean score of height in the seven non-random clinical trial studies with a control group was 0.19 (95% CI: 0.07 - 0.32), and the standardized mean score of height in the three random clinical trial studies with a control group was 0.17 (95% CI: 0.01 - 0.33). Generally, after combining studies through random effects model, the standardized mean score of height after treatment was estimated to be 0.11 (95% CI: 0.07 - 0.14) which is equivalent to 54.38% (mean score of their height came out to be than 54% of participants) (Fig. 4).

Before treatment, percentile of children’s height according to mean of SD (MSD) was obtained to be -1.64 (95% CI: -2.01 to -1.28) that was equal to 5%. In the same way, after treatment according to MSD, percentile of children’s height came out to be 0.11 (95% CI: 0.07 - 0.14) that was equal to 54.38%. This shows that increase in the percentile of children’s height is due to treatment with growth hormone.

Therefore, through combining the results of all studies, the mean score of participants’ height before treatment was higher than 5% of participants; however, after treatment, 54% of participants grew taller, so in the absence of treatment, it is expected to remain at the same 5%.

Differences in the mean score of adult height after treatment with growth hormone was reported to be more than 1.4 SD score (about 7.6 cm).

In addition, heterogeneity of studies was, totally, 60.2% which is considered as moderate heterogeneity which is significant with a P-value of 0.000.

**The effect of treatment duration on the final height increase**

Treatment duration has been classified into three groups. SMD among persons whose treatment duration was 4 years or less was reported to be 0.12 (95% CI: 0.10 - 0.14), it was 0.06 (95% CI: 0.05 - 0.07) in persons whose treatment duration was 4 - 6 years, and finally among those with a treatment duration of 6 years or more was 0.08 (95% CI: 0.00 - 0.15). Generally, according to the combination of studies through random effect model, SMD for height was calculated to be...
## Table 1. Characteristics of Studies Qualified for Meta-Analysis Review

<table>
<thead>
<tr>
<th>Author, publication year, reference</th>
<th>Type design</th>
<th>Country</th>
<th>Continent</th>
<th>No. of patient</th>
<th>Mean age start</th>
<th>SD of age</th>
<th>Mean height start</th>
<th>SD of height</th>
<th>Growth hormone dose</th>
<th>Mean duration</th>
<th>Adult height MSD</th>
<th>Adult height SD</th>
<th>Estimate height gain</th>
<th>P-value</th>
</tr>
</thead>
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<tr>
<td>Bernasconi et al, 1997 [15]</td>
<td>Cohort</td>
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<td>0.1</td>
<td>0.035</td>
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<td>0.07</td>
<td>0.91</td>
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<td>0.5</td>
<td>0.7</td>
<td>-</td>
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<td>-2.9</td>
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<td>7</td>
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<td>0.7</td>
<td>1.6</td>
<td>-</td>
</tr>
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<td>0.08</td>
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<td>-2.6</td>
<td>0.9</td>
<td>1.1</td>
<td>0.0001</td>
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<td>North America</td>
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<td>-1.64</td>
<td>0.84</td>
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<td>Europe</td>
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<td>-1.14</td>
<td>1.06</td>
<td>1.38</td>
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<td>0.8</td>
<td>0.93</td>
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<tr>
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<td>Europe</td>
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<td>2.8</td>
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<td>0.04</td>
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<td>0.034</td>
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<td>0.9</td>
<td>1.4</td>
<td>0.04</td>
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</table>
Figure 2. Mean score of participants’ treatment start age.

Figure 3. Mean score of height before treatment start.
0.11 (95% CI: 0.07 - 0.15) which is equivalent to 54.38% (Fig. 5).

The effect of received dose on the final height

Received doses are divided into two classes. SMD in persons receiving doses less than 0.04 mg/kg/day was 0.12 (95% CI: 0.10 - 0.14) and among person receiving doses more than 0.04 mg/kg/day was 0.06 (95% CI: 0.05 - 0.07) (Fig. 6).

Relationship between treatment duration and final height increase

The longer the treatment duration, the more the mean score of height, but this increase is not statistically significant (P > 0.05) (Fig. 7).
Figure 6. The effect of received dose on the final height increase.

Figure 7. Relationship between treatment duration and final height increase.
Relationship between the consumed dose and final height increase

Treatment with growth hormone has had an incremental effect on the final height; however, the relationship between height increase and increasing the consumed dose was statistically insignificant (P > 0.05) (Fig. 8).

Begg’s funnel plot

This plot was used to check publication bias and showed that the effect of publication bias was not significant with a P-value more than 0.05 (Fig. 9).

Discussion

In this meta-analysis study, there were 20 clinical trial studies investigating the effect of growth hormone on the adult height of children with ISS. It was attempted to select only studies with high quality. Results of the current study indicated that before treatment, SMD for height was -1.64 (95% CI: -2.01 to -1.28) which was equal to 5% and after treatment SMD for height increased to 0.11 (95% CI: 0.07 - 0.14) which is equal to 54.38%. The obtained mean difference for adult height after treatment with growth hormone was estimated to be approximately equal to SD score (about 6.7 cm) while according to a meta-analysis conducted by Deodati et al [14], mean difference for adult height after treatment with
growth hormone was equal to SD score (0.57 - 0.70 (3.4 - 4.2 cm)); therefore, the differences between the results of the current study and Deodati’s study indicate that SMD for adult height has increased due to growth hormone as compared to before treatment.

**Strengths of the study**

Most of studies were clinical trial studies and results of these studies are more reliable. In the current study, analysis was carried out according to cohort and clinical trial classification of studies and SMD for height has been calculated for each group. Then, random effect model was utilized to combine the studies and overall results were also estimated. Just studies of high quality and weight were included in the meta-analysis. Throughout all process of meta-analysis heterogeneity was estimated.

**Weaknesses of the study**

The most important limitation of this study was the heterogeneity of the population understudy. Some studies were excluded because the reason of low height was not specified. Further, there were some studies that had a small sample size; in such studies, the existence of bias is more probable. It was impossible to accomplish searching process through combined use of keywords in external and internal data bases. Many studies were excluded due to insufficient epidemiologic information.

**Conclusion**

The present meta-analysis contained cohort, randomized controlled trials and non-randomized controlled trials studies of growth hormone therapy. Growth hormone can be influential in increasing the adult height of children with ISS up to the achievement of adult height in children with ISS.

**Acknowledgments**

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**Conflicts of Interest**

There are no conflicts of interest.

**Funding Source**

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