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META-ANALYSIS

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Efficacy and safety of long-acting growth hormone in children with short stature: a systematic review and meta-analysis

Yingying Yang[1] · Xi Bai[1] · Xianxian Yuan[1] · Yuelun Zhang[1] · Shi Chen[1] · Hongbo Yang[1] · Hanze Du[1] · Huijuan Zhu[1] · Hui Pan[1]

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Abstract

Purpose Long-acting growth hormone (GH) has been developed to address the noncompliance and decreased efficacy associated with daily GH injections. We aimed to evaluate the efficacy and safety of long-acting GH replacement therapy in children with short stature.

Methods Randomized controlled trials (RCTs) that investigated the efficacy and safety of long-acting GH therapy in children with short stature in comparison with daily GH injections were searched in Medline, Embase, and the Cochrane Central Register of Controlled Trials. A random-effect model was used to pool data using mean difference and odds ratios (OR). (PROSPERO registration number: CRD42018111105).

Results Seven relevant studies were finally included. Meta-analysis found there was no significant difference between high-dose long-acting GH and daily GH in terms of height velocity (HV) (mean difference (MD) = −0.10, 95% CI, −0.79 to 0.60, $P = 0.79$). Moreover, no significant difference was observed in height standard deviation scores (Ht SDS) between high-dose long-acting GH and daily GH (MD = −0.07, 95% CI, −0.18 to 0.03, $P = 0.17$). Treatment with high-dose long-acting GH significantly increased IGF-1 SDS when compared with daily GH (MD = 0.31, 95% CI, 0.06–0.56, $P = 0.02$). In safety assessment, no significant difference was observed in the incidence of adverse events between high-dose long-acting GH and daily GH (OR 1.42, 95% CI, 0.65–3.11, $P = 0.38$).

Conclusions There is no evidence to support differences in the effects of long-acting GH compared with those of daily GH. More RCTs that focus on the safety of high-dose long-acting GH treatment, especially the detection of adverse events caused by elevated levels of serum IGF-1, are needed in the future.

Keywords Long-acting growth hormone · Meta-analysis · Randomized controlled trials · Short stature · Insulin-like growth factor-1

Introduction

In 1958, growth hormone (GH) was first reported to treat growth hormone deficiency (GHD) [1]. In 1985, GH was produced by recombinant DNA technology, which expanded its potential uses [2]. There have already been ten indications since 1985 for GH use that have been approved by the FDA, including GHD, chronic kidney disease, Turner syndrome, AIDS wasting, Prader-Willi syndrome, small for gestational age, idiopathic short stature (ISS), small bowel syndrome, SHOX deletion, and Noonan syndrome [3]. Randomized controlled trials (RCTs) have demonstrated that daily recombinant human GH (rhGH) can increase height velocity (HV) and effectively improve body composition in patients with the above conditions [4–6].

These authors contributed equally: Yingying Yang, Xi Bai

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✉ Hui Pan
panhui20111111@163.com

[1] Department of Endocrinology, Key Lab of Endocrinology, Ministry of Health, Peking Union Medical College Hospital (PUMCH), Chinese Academe of Medical Sciences & Peking Union Medical College (CAMS & PUMC), Beijing 100730, China

Early GH treatment was restricted to two or three intramuscular injections per week, which were quickly replaced by daily subcutaneous injections because of the added convenience and tolerance. Numerous studies have shown that daily subcutaneous injections are as effective as the early regimens of GH therapy in terms of producing IGF-1 and promoting linear growth [7, 8].

However, the necessity of daily injections leads to noncompliance, increased health care costs and decreased efficacy. Noncompliance exists in up to 75% of teenagers, and HV is reduced in patients with poor compliance [9–11]. For instance, a national survey of daily rhGH compliance carried out in New Zealand showed that significantly greater linear growth was observed in patients with good compliance than in patients with poor compliance over the study period [10]. Multiple inherent obstacles exist in the long-term administration of GH treatment that can reduce the final efficacy of such treatment. Some of the identified obstacles for long-term adherence include the frequency and route of injections, the injection complexity, pain caused by the injections, the need for restruction or cartridge insertion, the type of device used for the injections, parental perceived benefits and formulary changes, delays in filling drugs from insurance carriers or pharmacies, among many others [10, 11]. Ways to improve compliance include the invention of pens, needle-free devices and once infusion pumps, all of which are limited in applications because they are not always physiologic [12].

To address this problem, the expansion of GH therapy to new uses requires new administration formats. Currently, oral administration have not been proved to be equally effective as injections in clinical practice [12]. In this context, a variety of long-acting GH preparations that require one injection weekly, every 2 weeks, or monthly have been developed with the hope of offering a possible alternative to achieve comparable efficacy and safety while needing fewer total injections [13]. Compared to daily rhGH therapy, a long-acting GH regimen requiring one injection weekly could possibly save more than 1500 injections in a 5-year regimen, and could also provide greater convenience, tolerance, and compliance than daily injections [14].

To maximize the growth-promoting effects of GH therapy as well as its other physiological benefits, there have been many different innovative pharmaceutical technologies used to improve the GH formulations [15–17]. The six general types of long-acting GH preparations that have been studied include PEGylated molecules, depot formulations, GH molecules bound to albumin, prodrug compounds, GH molecules bound to Fab antibodies, and GH fusion proteins. Currently, there are several long-acting GH formulations available at various clinical trial status (Table 1) [18]. However, it is unclear whether long-acting GH is as effective as daily synthetic GH while maintaining a high safety profile in children with short stature. As a result, we aimed to conduct a systematic review and meta-analysis to evaluate the efficacy and safety of long-acting GH replacement therapy in children with short stature.

Materials and methods

Our study was registered with PROSPERO (PROSPERO registration number: CRD42018111105).

Search strategy

To identify eligible RCTs that investigated the efficacy and safety of long-acting GH therapy in children with short stature, a comprehensive electronic search of Medline, Embase, and the Cochrane Central Register of Controlled Trials was performed up to September 2018. The clinicaltrials.gov registry (http://www.clinicaltrials.gov) was also searched. Search strategies were developed to focus on long-acting GH, children, and RCTs. All relevant terms, including free-text terms and MeSH terms, were used in the literature search. All reference lists of the relevant reviews were hand-searched for additional relevant trials. The complete search strategy for Medline is provided in Supplementary Table 1.

Inclusion and exclusion criteria

Design

RCTs.

Participants

Patients aged below 18 years old who were diagnosed with short stature (defined as a height lower than the population mean by 2SDs).

Intervention and control

Long-acting GH compared with daily rhGH. There were no limitations on the dosages.

Outcome

The primary outcomes are as follows: HV and Ht SDS. The secondary outcomes are as follows: IGF-1 SDS, and safety indicators including glucose level, hemoglobin A1c, thyroid function and adverse events. Studies that lacked primary outcomes were excluded.

Table 1 Current technologies and long-acting GH preparations

Technology	Product	Manufacturer	Frequency of administration
Depot	LB03002	LG Life Sciences/ BioPartners	7 days
Depot	CP016	Critical Pharmaceuticals	14 days (planned)
Prodrug	TransCon ACP-001	Ascendis	7 days
GH fusion protein	ProFuse GH	Asterion	1 month (planned)
GH fusion protein	GX-H9	Genexine, Inc. And Handok, Inc.	7–14 days
GH fusion protein	LAPSrhGH/HM10560A	Hanmi Pharmaceutical Co.	7–14 days
GH fusion protein	MOD-4023	Pfizer, Inc.	7 days
GH molecule bound to albumin	Somapacitan NNC0195–0092	Novo Nordisk	7 days
GH molecule bound to Fab antibody	AG-B1512	Ahngook Pharmaceutical Co.	14–28 days (planned)
PEGylated	BBT-031	Bolder Biotechnology	7 days (planned)
PEGylated	Jintrolong	GeneScience Pharmaceuticals	7 days

Any inconsistencies between the reviewers were solved by consensus or by consulting a senior researcher (Prof. Pan, Hui).

Risk of bias assessment

Two reviewers (YYY and BX) independently used the risk of bias tool in the Cochrane Handbook to assess the risk of bias of the included studies, including the aspects of sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other items (baseline imbalance).

Data extraction

Two reviewers (YYY and BX) independently extracted all data using standard data collection forms. Data were collected on the participant characteristics (disease, country, age, pubertal stage, bone age, number), intervention (type of long-acting GH, dose, duration, comparison) and primary and secondary outcome data. If the primary outcome data were missing or incomplete, we contacted the corresponding authors to request further information. Any disparities were resolved by consensus or by consulting a senior researcher (Prof. Pan, Hui).

Statistical analysis

Statistical analysis was performed using RevMan5.3 software. For continuous and discontinuous variables, the differences were estimated using MD and OR, respectively. All results were estimated from each trial with a 95% confidence interval (CI). Heterogeneity was assessed using the chi-square test and the I^2 statistic. We adopted the random-effect model regardless of the I^2 value. When necessary, sensitivity analysis was performed to estimate how the overall results were influenced with and without the involvement of studies with a high risk of bias for incomplete outcomes. A two-sided $P < 0.05$ was regarded as statistically significant.

Results

Identification and selection

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram shows the results of the study selection (Fig. 1). From the original 952 potentially relevant studies screened through database searches, 921 were excluded based on the title and abstract. Thirty-one trials were retrieved for detailed assessment: eight were excluded for lack of daily rhGH as a control, and sixteen studies did not report efficacy outcomes. Therefore, we found seven studies [19–25] that were eligible for inclusion.

Study characteristics

Seven relevant studies were finally included, and the studies involved a total of 743 participants, of which, 430 were in the long-acting GH group, and 313 were in the daily GH group. Luo's study included a phase II study and a phase III study. The study was analyzed as two separate studies. All study results were published between 2012 and 2018. Table 2 displays the demographic characteristics of the patients and interventions in the included RCTs.

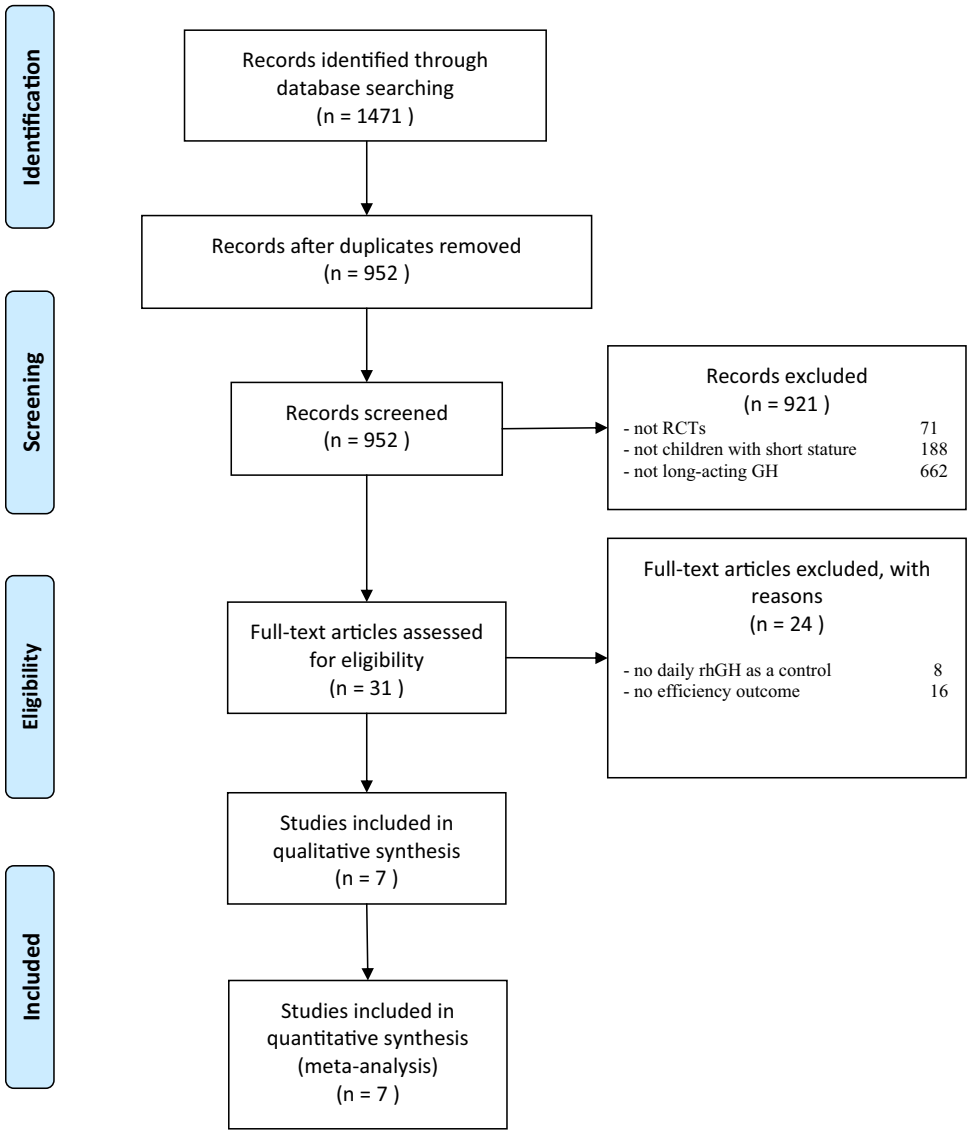


Fig. 1 PRISMA flow diagram of study selection

All studies were multicenter RCTs. The patients involved in these studies, which were all in prepubertal status, were diagnosed with GHD or ISS. The category of long-acting GH in these studies included LB03002 (four studies), MOD-4023 (one study), TransCon GH (one study), and Jintrolong (one study). All studies enrolled were daily rhGH parallel controlled trials. The duration of treatment in four trials was 12 months and 26 weeks in two other trials. Only one trial conducted a 25-week treatment study.

Risk of bias assessment

With the risk of bias tool in the Cochrane Handbook, we assessed the quality of the included studies according to the following six aspects: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other source of bias (Supplementary Table 2 displays the assessment results of the seven included studies). A total of 37.5% of the studies reported adequate random sequence generation, 25% reported allocation concealment, 75% used blinding for personnel, 50% avoided incomplete results, 12.5% avoided selective reporting, and 75% avoided baseline imbalance.

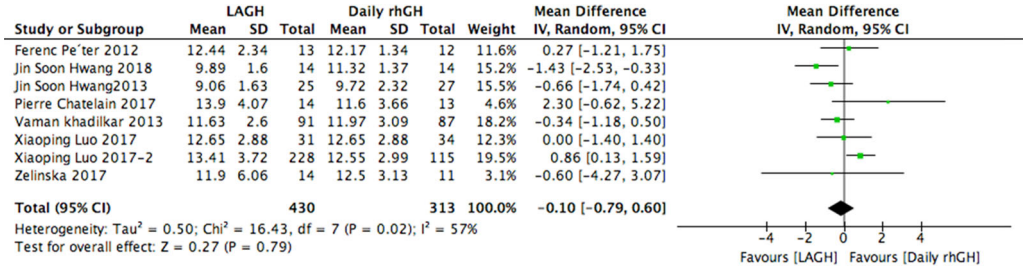
Efficacy of long-acting GH therapy on HV

Seven studies were included in the meta-analysis with HV as an efficacy parameter. The meta-analysis found that there was no significant difference between high-dose long-acting GH and daily GH in terms of HV ($N = 743$, MD $= -0.10$, 95% CI, -0.79 to 0.60, $P = 0.79$, $I^2 = 57\%$) (Fig. 2). The sensitivity analysis after excluding trials with a high risk of

Table 2 Demographic characteristics of the trials included

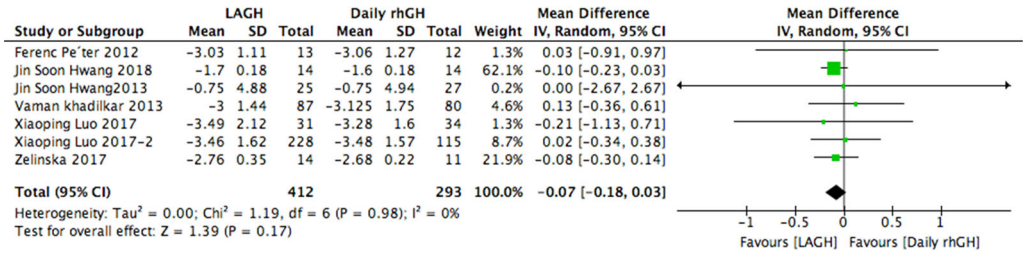
Trial	Patient	Country	Duration	Intervention	Intervention				Comparison (daily rhGH)			
					N	Dose (mg/kg/wk)	Age	BA	*N*	Dose (mg/kg/wk)	Age	BA
Hwang [19]	GHD	Korean	12 months	LB03002	25	0.5	9.05 (2.55)	7.21 (1.79)	27	0.21	9.25 (2.46)	6.92 (1.78)
Hwang [20]	ISS	Korean	26 weeks	LB03002	LD:14	LD:0.5	LD 5.36 (1.22)	LD 4.72 (0.82)	14	0.37	5.86 (1.29)	5.6 (1.53)
					HD:14	HD:0.7	HD 6.07 (1.54)	HD 5.49 (1.92)				
Zelinska [21]	GHD	Europe	12 months	MOD-4023	LD:13	LD:0.25	LD 6.2 (2.2)		11	0.24	5.7 (1.9)	
					MD:15	MD:0.48	MD 5.8 (2.3)					
					HD:14	HD:0.66	HD 6.1 (2.2)					
Chatelain [22]	GHD	Europe and Egypt	26 weeks	TransCon GH	LD:12	LD:0.14	LD 8.2 (2.9)	LD 5.2 (2.3)	13	0.21	7.7 (2.5)	4.9 (2.3)
					MD:14	MD:0.21	MD 8.4 (2.1)	MD 6.5 (2.1)				
					HD:14	HD:0.3	HD 7.5 (2.8)	HD 4.7 (2.6)				
Peter [23]	GHD	Europe	12 months	LB03002	LD:13	LD:0.2	LD 7.0 (2.0)		12	0.21	7.3 (2.3)	
					MD:13	MD:0.5	MD 7.1 (2.1)					
					HD:13	HD:0.7	HD 7.8 (2.1)					
Vaman Khadilkar [24]	GHD	USA, Europe, India, South America and Egypt	12 months	LB03002	91	0.5	7.8 (2.5)		87	0.21	7.8 (2.5)	
								Male				Male
Luo Xiaoping-1 [25]	GHD	China	25 weeks	Jintrolong	LD:32	LD:0.1	LD 10.91 (3.31)	LD 6.19 (2.2)	34	0.25	10.54 (4.05)	6.16 (2.51)
					HD:31	HD:0.2	HD 11.75 (3.95)	HD 7.65 (2.42)				
								Female				Female
								LD 5.51 (1.54)				4.81 (2.16)
								HD 5.6 (1.5)				
Luo Xiaoping-2 [25]	GHD	China	25 weeks	Jintrolong	228	0.2	11.30 (3.50)		115	0.25	11.77 (3.60)	

BA bone age (years), *GHD* growth hormone deficiency, *ISS* idiopathic short stature, *LD* low-dose group, *MD* medium-dose group, *HD* high-dose group



LAGH = long-acting growth hormone; rhGH = recombinant human growth hormone; SD = standard deviation; 95% CI = 95% confidence interval

Fig. 2 Forest plot comparing HV between high-dose long-acting GH and daily GH. Results of meta-analysis according to a random model



LAGH = long-acting growth hormone; rhGH = recombinant human growth hormone; SD = standard deviation; 95% CI = 95% confidence interval

Fig. 3 Forest plot comparing Ht SDS between high-dose long-acting GH and daily GH. Results of meta-analysis according to a random model

bias showed little to no change in the effect on HV. However, the results showed that low-dose long-acting GH had a worse effect on HV than daily GH ($N = 165$, MD = −1.69, 95% CI, −2.42 to −0.97, $P < 0.00001$, $I^2 = 12\%$). The result is detailed in Supplementary Fig. 1.

The post hoc subgroup analysis according to various mechanisms of long-acting GH revealed that there were no significant differences between any subgroups of high-dose long-acting GH and daily GH groups in terms of HV.

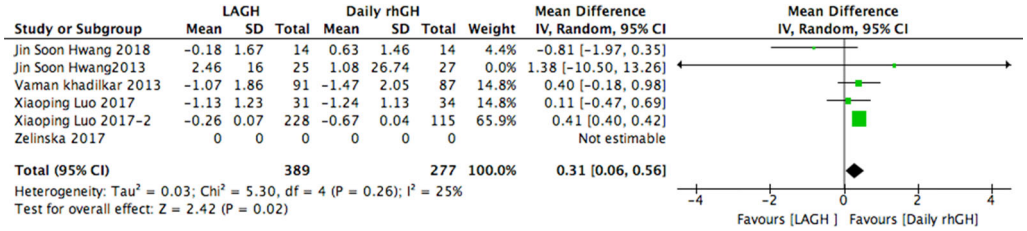
Efficacy of long-acting GH therapy on Ht SDS

Ht SDS was included as an outcome indicator in six studies. No statistically significant difference was observed in Ht SDS between high-dose long-acting GH and daily GH ($N = 705$, MD = −0.07, 95% CI, −0.18 to 0.03, $P = 0.17$, $I^2 = 0\%$) (Fig. 3). However, unlike the results for HV, the meta-analysis found that there was also no statistically significant difference between low-dose long-acting GH and daily GH in Ht SDS ($N = 143$, MD = −0.19, 95% CI, −0.52 to 0.15, $P = 0.28$, $I^2 = 78\%$) (Supplementary Fig. 2). The sensitivity analysis after excluding trials with a high risk of bias showed little to no change in the effect on Ht SDS.

A post hoc subgroup analysis according to various mechanisms of long-acting GH revealed that there were no significant differences between any subgroups of high-dose long-acting GH and daily GH groups in terms of Ht SDS.

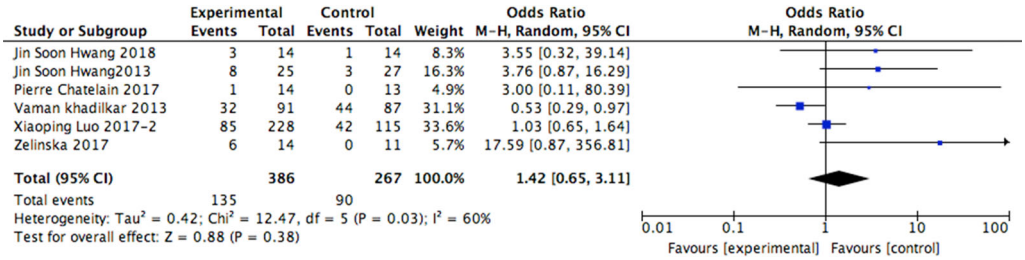
Efficacy of long-acting GH therapy on IGF-1 SDS

Five of the enrolled studies provided IGF-1 SDS in as an outcome. Figure 4 shows that treatment with high-dose long-acting GH significantly increased IGF-1 SDS when compared with treatment with daily GH ($N = 666$, MD = 0.31, 95% CI, 0.06–0.56, $P = 0.02$, $I^2 = 25\%$). The IGF-1 SDS levels reported in these trials were within the normal range, except for one study in which the IGF-1 SDS exceeded +2 [19]. Only two studies provided IGF-1 SDS data for low-dose long-acting GH groups. The results demonstrated that there was also a statistically significant difference between low-dose long-acting GH and daily GH in IGF-1 SDS ($N = 94$, MD = −0.51, 95% CI, −0.99 to −0.04, $P = 0.03$, $I^2 = 0\%$) (Supplementary Fig. 3).



LAGH = long-acting growth hormone; rhGH = recombinant human growth hormone; SD = standard deviation; 95% CI = 95% confidence interval

Fig. 4 Forest plot comparing IGF-1 SDS between high-dose long-acting GH and daily GH. Results of meta-analysis according to a random model



Experimental = long-acting growth hormone group; Control = daily recombinant human growth hormone group; 95% CI = 95% confidence interval

Fig. 5 Forest plot comparing incidence of adverse events between high-dose long-acting GH group and daily GH group. Results of meta-analysis according to a random model

Safety assessment

Adverse events were reported in six trials. No statistically significant difference was observed in the incidence of adverse events between high-dose long-acting GH and daily GH (OR 1.42, 95% CI, 0.65–3.11, $P = 0.38$, $I^2 = 60\%$) (Fig. 5). The sensitivity analysis after excluding trials with a high risk of bias showed little to no change in the effect on adverse events. Additionally, no statistically significant difference was observed between the low-dose long-acting GH group and the control group (OR 3.65, 95% CI, 0.70–19.02, $P = 0.12$, $I^2 = 0\%$) (Supplementary Fig. 4). There were no deaths in any trial. The adverse events most commonly reported to occur in patients receiving long-acting GH treatment included injection site pruritus, anemia, hypothyroidism, pyrexia, rash, headache and vomiting, but all of these events were mostly mild in intensity and resolved on their own. No severe adverse events related to long-acting GH occurred in the included trials except for the two reported by Khadilkar [24], but the adverse events did not lead to subject withdrawal.

No significant difference between high-dose long-acting GH and daily GH was observed in glucose metabolism (glucose level, hemoglobin A1c) (Supplementary Figs 5 and 6). A single case of impaired fasting glucose was reported by Zelinska et al. [21], but it was mild and clinically insignificant. The data of the low-dose long-acting GH group with respect to glucose metabolism were not available because only one study reported those results.

None of the included studies reported data on thyroid function, so the analysis of this variable was not available.

Discussion

Our meta-analysis evaluated the efficacy and safety of long-acting GH treatment compared to those of daily GH in children with short stature. The results of the meta-analysis suggested that long-acting GH significantly improved HV and Ht SDS in a dose-dependent manner.

However, the level of IGF-1 in the long-acting GH group of our meta-analysis was significantly higher than that in the daily GH group. The IGF-1 SDS levels reported in these trials were within the normal range, except for one study, in which the IGF-1 SDS exceeded +2 [19]. Previous studies have also reported the elevation of serum IGF-1 levels after long-acting GH therapy, but the mean IGF-1 SDS levels were all maintained within +2 SD values [26–31]. This finding might be related to the slow release of long-acting GH, which promotes liver-production of IGF-1. In general,

there was a significant increase in the free IGF-1 level, which is normally considered to represent its biological activity after GH therapy, without a significant increase in IGFBP-3 levels. As a result, the level of free IGF-1 is considered to be a good predictor of recombinant human GH treatment response [32]. Guidelines developed by the Pediatric Endocrine Society in 2016 recommend that measuring the serum IGF-1 levels can be a tool to monitor compliance and the production of IGF-1 when the GH dose changes. The GH dose should be decreased if the levels of serum IGF-1 are above the laboratory-defined upper limit of the normal range for the age or stage of puberty of the patient [33]. The Growth Hormone Research Society states that there is no evidence that after an injection of long-acting GH, the impact of potential supraphysiological and sustained IGF-1 levels is associated with an increased risk of adverse side effects [15]. However, as previously reported [34], men in the highest quartile of plasma IGF-1 levels showed an increased risk of prostate cancers compared with those in the lowest quartile (relative risk = 4.32, 95% CI, 1.76–10.6). Additionally, another two epidemiological studies demonstrated that IGF-1 levels in the highest tertile or quintile were associated with an increased risk of breast cancer or colorectal cancer, respectively [35, 36]. Additionally, elevated IGF-1 SDS during GH therapy is related to the risk of impaired insulin sensitivity [37]. Therefore, treatment with long-acting GH requires close monitoring of the IGF-1 levels. Long-acting GH formulations differ in the kinetics of induction of serum IGF-1. Trials need to consider the pharmacokinetics and pharmacodynamics of each preparation for the purpose of gauging the clinically optimal time point to measure IGF-1 levels [15]. In addition, the optimal dose and the administration frequency of long-acting GH with different mechanisms should be determined based on the IGF-1 levels.

In terms of safety, our analysis showed that neither the low-dose long-acting GH group nor the high-dose long-acting GH group experienced an increased number of adverse events when compared with the daily GH group. The adverse events related to long-acting GH treatment included injection site pruritus, arthralgia, hematoma, hematuria, adrenal insufficiency, erythema, anemia, abnormal liver function test results, peripheral edema, hypothyroidism, pyrexia, rash, headache, and vomiting. These events were mostly mild in intensity, and none of the adverse events resulted in subject withdrawal. The most frequently reported adverse events in patients receiving long-acting GH therapy included injection site pruritus, anemia, hypothyroidism, pyrexia, rash, headache, and vomiting [19–25]. These adverse events were very rare, and the sample size should be expanded for further study to monitor these events. Additionally, our results demonstrated that there was no significant difference between high-dose long-acting GH treatment and daily GH treatment in glucose metabolism (glucose, hemoglobin A1c).

Limitations of this meta-analysis need to be mentioned. First, the quality of the included studies needs to be considered. None of the seven RCTs that met our inclusion criteria were defined as a low risk of bias according to the risk of bias tool in the Cochrane Handbook. As a result, high-quality RCTs with large samples are needed in this area. Second, among the seven trials included, there were three non-inferiority trials [20, 24, 25], which may limit the power of the superiority conclusion. Although these trials were designed to achieve a non-inferiority conclusion, they still provided the necessary outcome data for our systematic review; hence, to include the maximum amount of information and achieve the largest statistical power, we combined the non-inferiority trials with the other trials in our analysis. Third, none of the included studies reported data on thyroid function, so the analysis of this secondary outcome was not available. Another limitation of our study is publication bias. However, the funnel plot was not available because of the low number of included studies.

In conclusion, our study illustrated the efficacy and safety of long-acting GH. We found that there was no significant difference between the high-dose long-acting GH group and the daily GH group in terms of efficacy, but the levels of serum IGF-1 in the high-dose long-acting GH group were higher than that in the daily GH group. There should be more RCTs with large samples and long-term follow-up that focus on the safety of high-dose long-acting GH treatment, especially in the detection of adverse events caused by elevated levels of serum IGF-1.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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