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Research Article

Efficiency of Replacement Therapy by Genetically Engineered Growth Hormone Jintropin in Patients with Pituitary Adenomas after Transsphenoidal Adenomectomy

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Annotation

Purpose of the study: The aim of the study was to study the clinical efficacy (normalization of quality of life and GH level) and the tolerance of genetically engineered growth hormone Gentropine (Europharm) in case of somatotropic insufficiency after selective pituitary adenomectomy in patients with pituitary adenomas.

Material and methods: Patients - men (n = 10) and women (n = 3) - aged 2 to 55 years) who were on a stationary and outpatient examination in the RSMPS Endocrinology of the Ministry of Health of the Republic of Uzbekistan named by Acad. JH Turakulova MZ RUz, were selected in a group of patients with diagnosed somatotropic insufficiency (n = 13) and received treatment with the study drug Jintropin for 6 months.

Results of the study: Against the backdrop of GY "JINTROPIN" substitution therapy, there was a significant increase in baseline low IGF-1 and GH levels in the blood ($p < 0.05$) after 3 months of treatment, and an increase in STH ($p < 0.05$) at 6 months. Evaluation of the change in anthropometric indicators against the background of ongoing therapy GR "JINTROPIN" showed the normalization of QoL AGHD: 10.2 ± 2.5 points (over a 6-month period).A significant increase in the level of calcium ($p < 0.05$), phosphorus ($p < 0.001$) and an increase in the activity of alkaline phosphatase ($p < 0.01$) were noted, indicating an acceleration of the processes of bone metabolism against the background of the therapy.

Conclusions: 1) An assessment of changes in anthropometric indicators against the background of the therapy with the GH "JINTROPIN" showed a normalization of quality-of-life indicators according to the QoL AGHD questionnaire: 10.2 ± 2.5 points (over a period of 6 months). 2) Against the background of replacement therapy with GH "JINTROPIN", a reliable increase in the initially low values of IGF-1 and GH levels in the blood ($p < 0.05$) was recorded after 3 months of treatment, as well as an increase in STH ($p < 0.05$) after 6 months. 3) A significant reliable increase in the level of calcium ($p<0.05$), phosphorus ($p<0.001$), as well as an increase in the activity of alkaline phosphatase ($p<0.01$) was noted, indicating an acceleration of bone metabolism processes against the background of the therapy. 4) A decrease in the levels of total cholesterol and VLDL was recorded, which indicates a beneficial effect of GH "JINTROPIN" on lipid metabolism.

Keywords: Growth hormone deficiency (GHD) in adults; post-surgery hypopituitarism; therapy by growth hormone

Background

Growth hormone deficiency syndrome (GHD) is a well-defined clinical condition in adults that causes abnormalities in metabolism, body structure, physical and psychosocial functions that improve after replacement therapy with genetically engineered GH. [1-4]. In 2007, the International Consensus on GHD in Adults was published [5]. According to prof. Grossman AB (2005), the incidence of hypopituitarism reaches 12 to 42 new cases per 1,000,000 population each year and there is an increase in prevalence (300-455 cases per 1,000,000 [6]. According to the researchers, STH deficiency after hypophysectomy in patients with pituitary adenomas develops in 85.0% of cases, ACTH deficiency – in 58.33%. The combination of STH+ACTH+TSH+LH+FSH deficiency in 40.00%, and STH+ACTH+TSH+LH+FSH+ AVP and STH deficiency subsequently in 23.33 and 16.67%, respectively. According to data from another multicentre study conducted from 2008 to 2011, devoted to the study of cardiovascular risk markers in GHD in 80 patients (aged 18 to 25 years) with nonsecreting pituitary tumours after transsphenoidal hypophysectomy (TSE) - Assessment of Cardiovascular Risk in Patients with Growth Hormone Deficiency Following Transsphenoidal Surgery for Non-functional Pituitary Adenomas. (USA) - in the early postoperative period, these patients, in contrast to those who were not subjected to TSE, had markers of cardiovascular risk: dyslipidemia, increased CRP, IL6, homocysteine [7]. Numerous trial studies have shown that GHD in adults significantly aggravates the course of the disease and affects both the quality and duration of life in patients with pituitary adenomas after surgical or radiation therapy. [8-13].

As early as 1999 [6], Indian authors referred to literature data in which one of the indications for GH replacement therapy is patients after hypophysectomy, after radiation therapy, or idiopathic GHD, and these authors emphasized the tendency to increase such recommendations. According to neuroendocrinologists from the UK [14], who studied the effectiveness of GH therapy in the postoperative period for 5 years in patients with GHD due to NFPA (42 b-x), Cushing's disease and prolactinoma. The patients' glucose levels, lipid profile, HbA(1c), anthropometry and BMI were assessed every 6 months. It was found that the patients had similar sensitivity to GH therapy. This trial confirmed the need for GHD treatment in this category of patients. The KIMS (Pfizer International Metabolic Database) publications extend previous clinical trial data confirming that adults with GHD have an unfavourable cardiovascular risk profile. KIMS allowed us to follow a very large cohort of patients on GH replacement therapy for an extended period of time, and despite the lack of a randomized control group [13].

Studies from the Danish National Registry for the Treatment of GHD in Adults have recently presented results of 30-day treatment with engineered GH in patients with Cushing's disease, non-functional pituitary adenoma – NFPA (783) and even acromegaly (65) – after tumour removal or radiation therapy to study fracture prevention [15]. Many authors confirm the improvement of quality-of-life indicators (SF-36) in patients with GHD against the background of growth hormone therapy. There are publications on positive outcomes of growth hormone therapy even in patients with acromegaly after radiation therapy or TAE. All of the above emphasizes the relevance of this study.

Purpose of the study

The aim of the study -to study the clinical efficacy (normalization of quality-of-life indicators and GH levels) and tolerability of the genetically engineered growth hormone Jintropin (Europharm) in somatotropic insufficiency after selective pituitary adenomectomy (TAE) in patients with pituitary adenomas.

Material and Research Methods

Patients - men (n=10) and women (n=3) - aged from 2 to 55 years), who were undergoing inpatient and outpatient examination at the Republican Scientific and Practical Medical Center of Endocrinology of the Ministry of Health of the Republic of Uzbekistan named after academician Ya. Kh. Turakulov, were selected into the group of patients with diagnosed somatotropic insufficiency (n=13) and received treatment with the study by medicine Jintropin for 6 months.

The patients underwent the following range of studies: 1) anthropometric indicators: standing height, sitting height, proportionality index, weight, height and weight SDS, BMI: before, during the dynamics and at the end of the study; growth rate, SDS of growth rate at the end of the study, 2) general clinical studies: complete blood count, complete urine analysis at the beginning and at the end of the study, 3) biochemical analyses: test data (lipid spectrum, calcium, phosphorus, total protein in the blood, ALT, AST, bilirubin, creatinine, alkaline phosphatase, cancer embryonic AG): at the beginning and at the end of the study, 4) instrumental studies: MRI or CT of the pituitary gland, at the beginning of the study, in dynamics and at the end, 5) hormonal studies: blood STH, IGF-1, in dynamics and at the end of the study, TSH, LH, FSH, ACTH, cortisol - at the beginning of the study, 6) ophthalmologist consultation: examination of the fundus and visual fields in all colours at the beginning, in dynamics and at the end of the study, 7) questioning using the questionnaire for assessing the quality of life of adults with GHD QoL-AGHD - before, in dynamics and at the end of the study [16-20].

Scheme of Drug Administration

Patients in the study group received the drug Jintropin for 6 months under the control of objective examination data. The dose of the drug was prescribed at the rate of 0.033 mg/kg/day, daily subcutaneously, before bedtime (9-10 p.m.) multivariate analysis.

Research results and their discussion

Table 1 shows the distribution of patients by gender and age (Table 1).

Table 1: Distribution of patients by gender and age (according to WHO).

Age, Years	Number Women	Number Men	Total
2-4	-	2	2
16-29	1	5	6
30-44	1	1	2
45-59	1	2	3
60-74	-	-	-
75 and >	-	-	-
Total: n = 13	3	10	13

Table 1 shows that the majority of patients were over 16 years old – 11 observations (84.6%). According to etiology, patients were distributed as follows: NFPA - 7, BIC - 1, craniopharyngioma (CP) - 5. All patients were subjected to TAG, 2 of them + radiation therapy (1 with CP and 1 with NFPA). The diagnosis of GHD was established based on the levels of STH, IGF-1, and the determination of the deficiency of basal values of 2-3 more tropic hormones. All patients were found to have multiple deficiency of adenohypophysis hormones (MDHA).

Table 2 shows the clinical and hormonal status of patients with GHD after TAE at inclusion in the study. The initial stage of the study of the efficacy and tolerability of the drug JINTROPIN was the assessment of changes in anthropometric indicators during therapy with Jintropin (Tables 2&3).

Table 2: Clinical and hormonal status of patients with GHD at inclusion in the study.

Indicator	M±SD (min-max)
Number of patients	13
Gender (male/female)	10/3
Multiple pituitary hormone deficiency	13
Chronological age, years	31.2±4.7 (18.6 -45)
Peak STH in samples, ng/ml	1.4 (0.05-9.5)

Table 3: Anthropometric parameters (average data) of patients with GHD during GH treatment.

Indicators	0 months	3 months	6 months
Height, cm	168.8±6.3	168.8±6.3	168.8±6.3
SDS growth	4.6±0.3	4.6±0.3	4.6±0.3
Sitting height, cm	101.0±2.1	101.0±2.1	101.0±2.1
IP	1.6±0.1	1.6±0.1	1.6±0.1
Weight, kg	81.6±2.8	78.6±2.7	65.6±2.8*
OT, cm	87.2±1.3	81.3±1.5	76.1±1.8*
OB, cm	89, 2± 1.9	88, 7 ± 1.4	85, 9± 1.6*
OT/OB	0.97± 0.03	0.91± 0.04	0.88± 0.03*
BMI, kg/mI	31.38±0.9	30.2±0.7	25.6±0.3*

Note: * P<0.05 - values are significant compared to values before treatment

The analysis of the initial anthropometric parameters revealed harmonious development: the ratio of the upper and lower segments, the average BMI value are within normal values. Normal body proportions are maintained against the background of the therapy. The growth rate after 6 months of treatment did not change, while the BMI decreased from 31.38±0.9 to 25.6±0.3 kg/m^2. In addition, weight, as well as the WC, HR, WC/HR indicators, decreased significantly after 6 months of GH therapy. Next, we studied the dynamics of the indicators of this questionnaire when assessing the quality of life of 16 operated patients 3 months and 6 months after the TGE operation and hormonal data. These data are presented in Tables 4 and 5 (Table 4, Table 5).

Table 4: Dynamics of the QoL AGHD questionnaire indicators for assessing the quality of life of 13 operated patients and hormonal data 3 months after TAE surgery.

Number of patients	Average Score before TAE	Average Score after TAE	STH Before TAE	STH After TAE	IGF-1 To TAE	IGF-1 After TE
(n= 16)	23.0± 3.2	14.4 ± 3.4	0.11 ±0.03	1.13 ±0.04	84.10 ±11.6	154.3 ±22.6
Control	7.3± 0.4	7.3± 0.4				
Norm	< 11 b	< 11 b	2-5 ng/ml		134-836 ng/ml	
R	> 0.05	< 0.05	< 0.05		< 0.05	

Note: P – significance of differences with control, before and after surgery

Table 5: Dynamics of the QoL AGHD questionnaire indicators for assessing the quality of life of 13 operated patients and hormonal data 6 months after TGE surgery.

Number of Patients	Average Score 3 months after TAE	Average Score 6 months after TAE	STH 3 months after TAE	STH 6 months after TAE	IGF-1 3 months later TAE	IGF-1 6 months after TAE
(n= 16)	14.4 ± 3.4	10.2 ± 2.5	1.13 ±0.04	2.03 ±0.05	154.3 ±22.6	208.9 ±21.3
Control	7.3± 0.4	7.3± 0.4				
Norm	< 11 b	< 11 b	2-5 ng/ml		134-836 ng/ml	
R	> 0.05	< 0.05	< 0.05		< 0.05	

Note: P – significance of differences with control, before and after surgery

As can be seen from the data presented in Tables 4 and 5, 13 patients showed a decrease in the average score on the DHRV questionnaire 3 months and 6 months after TAE against the background of a significant increase in the average values of STH and IGF-1.

The second stage of the study was the study of growth factor levels (IGF-1) in patients with GHD before and during GH treatment. It is known that the IGF-1 level is an integrated indicator and correlates with the STH content, indirectly reflecting its endogenous function. The IGF-1 content reflects not only the absolute STH level in the blood, but also its biological activity. The IGF-1 values in the blood serum are a more stable indicator than STH and are subject to smaller fluctuations during the day. During the treatment, a study of GH in the blood and IGF-1 in dynamics was conducted. In the first 3 months, most patients showed a 2-fold increase in the initially low GH and IGF-1 values in the blood, but we did not observe such effectiveness in the following 3 months, although there was a proportional increase. This may be due to low doses of the drug per body surface area (m^2) subsequently. Against the background of replacement therapy with GH "JINTROPIN", a reliable increase in values of IGF-1 and GH levels in the blood ($P<0.05$) after 3 months of treatment and, accordingly, an increase in the values of IGF-1 and GH levels in the blood ($p<0.05$), as well as GH in the blood ($p<0.05$) after 6 months.

The next stage of the study was the study of biochemical parameters against the background of the therapy at the beginning and end of the study. GH is one of the most important factors influencing lipid metabolism and bone metabolism in the child's body. A decrease in the levels of total cholesterol and VLDL indicates a favourable (antiatherogenic) effect of GH therapy on lipid metabolism (Table 6), although statistical reliability of the parameters was not revealed. A significant reliable increase in the level of calcium ($p<0.05$), phosphorus ($p<0.001$), as well as an increase in the activity of alkaline phosphatase ($p<0.01$) were noted, indicating an acceleration of bone metabolism processes (Table 7) (Table 6, Table 7).

All the above results indicate the effectiveness of the drug "JINTROPIN" (Table 8).

Table 6: Lipid metabolism parameters during treatment.

Index, mmol/l	0 months	6 months
Cholesterol	5.1±0.3	4.8±0.2
HDL	1.6±0.2	1.4±0.2
LDL	2.9±0.2	3.0±0.2
VLDL	1.5±0.9	0.5±0.1*
Triglycerides	1.3±0.4	1.1±0.1

Note: *P<0.05; ** P<0.01; *** P<0.001 - the values are significant compared to the values before treatment.

Table 7: Mineral metabolism indicators during treatment

Indicator	0 months	6 months
Total calcium, mmol/l	2.2±0.1	2.4±0.1%
Phosphorus, mmol/l	1.6±0.1	2.1±0.1%
Alkaline phosphatase, U/L	359.3±38.1	520.0±35.3%

Note: *P<0.05; ** P<0.01; *** P<0.001 - values are significant compared to values before treatment

Table 8: Evaluation of the effectiveness of the drug "JINTROPIN".

3 points	High efficiency	2-3-fold increase in baseline IGF-1 levels. The level of STH in the blood is closer to normal values (more than 2 ng/ml) A decrease in scores on the QoL questionnaire AGHD < 11 points

Conclusions

1. An assessment of changes in anthropometric indicators against the background of the therapy with the GH "JINTROPIN" showed a normalization of quality-of-life indicators according to the QoL AGHD questionnaire: 10.2 ± 2.5 points (over a period of 6 months).
2. Against the background of replacement therapy with GH "JINTROPIN", a reliable increase in the initially low values of IGF-1 and GH levels in the blood ($p < 0.05$) was recorded after 3 months of treatment, as well as an increase in STH ($p < 0.05$) after 6 months.
3. A significant reliable increase in the level of calcium ($p<0.05$), phosphorus ($p<0.001$), as well as an increase in the activity of alkaline phosphatase ($p<0.01$) was noted, indicating an acceleration of bone metabolism processes against the background of the therapy.
4. A decrease in the levels of total cholesterol and VLDL was recorded, which indicates a beneficial effect of GH "JINTROPIN" on lipid metabolism.

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Conflict of interest

No conflict of interest.

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