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Original Research Article

Effect of levothyroxine sodium on preterm infants with hypothyroidism

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Abstract

Purpose: *To investigate the effect of levothyroxine sodium on preterm infants with hypothyroidism.*
Methods: *The study involved a total of 96 preterm infants with hypothyroidism who were admitted to the Shengli Oilfield Central Hospital, Dongying, from January 2020 to October 2021. These patients were divided randomly into a study group and control group with 48 patients in each group. The control group was given routine treatment, while study group received levothyroxine sodium tablets orally. Growth and development (height, and weight), mental development index (MDI score), psychomotor development index (PDI score), and thyroxine levels (thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4)) between both groups were recorded.*
Results: *After treatment, thyroxine indices in both groups were significantly improved, but the indices in study group were better than in control group ($p < 0.05$). Growth, mental and psychomotor development indices in the improved groups were improved, but the improvements in the study group were significantly better than in control group ($p < 0.05$). The overall response rate (ORR) in the study group (93.75 %) was significantly higher than in the control group (77.08 %; $p < 0.05$).*
Conclusion: *Levothyroxine sodium improves growth, mental and psychomotor development, and thyroxine level in preterm infants with hypothyroidism. This protocol will benefit from further large-scale investigation prior to application in clinical practice.*

Keywords: *Levothyroxine sodium, Preterm infants, Hypothyroidism, Mental development, Psychomotor development, Thyroxine*

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INTRODUCTION

In recent years, various epidemiological studies have shown that the incidence of congenital hypothyroidism (CH) is rising, especially in preterm infants which is much higher than the general population [1,2]. Congenital hypothyroidism is more likely to cause serious and irreversible damage to the development of nervous systems in preterm infants. It not only reduces the quality of life of children but also has serious adverse effects on their growth and development. Therefore, studies aimed at clinical treatment of preterm infants with hypothyroidism are critically important [3,4].

At present, there are many treatments for preterm infants with hypothyroidism, but no unified standard has been developed and approved. Furthermore, serious caution is required for the clinical treatment of preterm infants with CH because of the impact of the disease and its treatment on their growth and development. Therefore, this study aimed to investigate the effect of levothyroxine sodium on the growth, mental and motor development, and thyroxine levels of preterm infants with hypothyroidism.

METHODS

Clinical data

A total of 96 hypothyroid preterm infants admitted to the Shengli Oilfield Central Hospital, Dongying, from January 2020 to October 2021 were screened as subjects for this clinical treatment. They were divided into a study group and control group via random number table, with 48 patients in each group. All procedures were performed in accordance with the standards laid down by the Ethics Committee of Shengli Oilfield Central Hospital (approval no. LCYJ2019132) and complied with the guidelines of 1964 Helsinki Declaration and its later amendments for ethical research involving human subjects [5]. Written informed consent was obtained from legally authorized representative(s) for anonymized patient information to be published in this article.

Inclusion criteria

Infants who meet the relevant clinical diagnostic criteria for hypothyroidism described in the literature were included [6]. These infants had gestational age less than 37 weeks, and thyroid-stimulating hormone (TSH) level > 10 mIU/L.

Exclusion criteria

Infants with any one of the following diseases; intracranial hemorrhage, asphyxia, severe infection, congenital diseases, or allergic to the drugs used were excluded from this study.

Treatments

Control group

Infants in this group were subjected to conventional treatment. They received early micro-feeding, with supplemented nutrition via intravenous infusion. Depending on the individual situation of each child, measures like active respiratory support, warming and heat preservation were administered. The relevant thyroxine parameters of the infants were determined regularly until the parameters returned to normal, and then treatment was stopped.

Study group

Infants in this group were given levothyroxine sodium tablets (manufacturer: China Associate Pharmaceutical Co., Ltd. National Medicine Permission number H20010008; strength: 25 μg) for treatment with 5 μg/kg daily in addition to the conventional treatment. Relevant thyroxine indicators of the children were periodically determined, and doses were adjusted according to the recovery conditions of each child, and then treatment was ceased until the relevant indicators returned to normal.

Evaluation of indices

Growth and development

The growth and development (height, and weight), mental development index (MDI score), psychomotor development index (PDI score) and thyroxine levels (thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4)) were compared between groups.

Determination of thyroxine levels

Levels of TSH, FT3 and FT4 were determined using the chemiluminescence method. The equipment was an automatic electrochemiluminescence immunoassay system (Roche Cobas e601).

MDI score and PDI score

The MDI scores and PDI scores were derived from Bayley Scales of Infant Development (BSID), with higher scores indicating better development. Scores less than 70 indicate developmental delay; scores equal to, or more than 90 indicate normal development.

Efficacy determination

Marked response

Therapeutic responses are considered marked if clinical symptoms of infants disappeared, and thyroxine levels returned to normal.

Moderate response

This occurs if clinical symptoms of infants were significantly improved, and thyroxine levels were significantly improved or returned to normal.

No response

In this case, infants did not show any improvement in clinical symptoms and thyroxine levels.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) 22.0 was used for statistical analysis. Measurement data and enumeration data are presented as mean ± standard deviation (SD) and cases (%), respectively. Student's *t*-test and χ^2 test were applied for data analysis, respectively. $P < 0.05$ indicated significant differences.

RESULTS

Baseline data

In the study group, there were 26 male and 22 female infants, with gestational age of 29 - 35 weeks, and mean gestational age of 31.25 ± 1.21 weeks. The age range was 7 - 10 days, and mean age (8.46 ± 0.62) days. The weight was 1850.35 ± 89.93 g, height range from 38 - 47 cm, and mean height was 43.15 ± 2.00 cm. The head circumference was 27 - 34 cm, and mean head circumference was 30.25 ± 1.93 cm. Twenty (20) infants were delivered transvaginally while 28 by cesarean section. On the other hand, control group consisted of 27 male and 21 female infants, with a gestational age ranging from 29 - 34 weeks, and mean of 31.33 ± 1.19 weeks.

The age range was 8 - 9 days, and mean age was 8.50 ± 0.61 days. The mean weight was 1851.04 ± 89.88 g. The height ranged from 39 - 48 cm, and the mean height was 43.17 ± 1.96 cm. The head circumference was 25 - 33 cm, and the mean head circumference was 30.33 ± 1.88 cm. The mode of delivery comprised 21 cases of vaginal delivery and 27 cases of cesarean section. The clinical data demonstrated no significant differences between both groups ($p < 0.05$).

Thyroxine index

Before the treatment, there were no significant differences in thyroxine indicators between both groups. After the treatment, all thyroxine indicators in both groups were significantly improved, but the indicators in the study group were better than in control group, and the differences were significant ($p < 0.05$). The results were shown in Table 1.

Growth

Before the treatment, there were no noticeable differences in height and weight between both groups. After treatment, the height and weight of both groups improved, but the study group indicators were superior to control group, and the differences were significant ($p < 0.05$). The outcomes are shown in Table 2.

Mental development index (MDI) and psychomotor development index (PDI)

Before treatment, there were no significant differences in mental and psychomotor development index between the two groups. After treatment, growth, mental and psychomotor development indicators of the two groups improved, but the indicators in the study group were significantly better than in control group ($p < 0.05$; Table 3).

Clinical efficacy

Overall response rate in the study group was 93.75 %, which was significantly higher than 77.08 % in the control group ($p < 0.05$; Table 4).

DISCUSSION

Congenital hypothyroidism remains a highly prevalent disease in preterm infants, and is triggered by maternal factors, perinatal and delivery complications, genetic abnormalities, thyroid malformations, as well as side effects of drugs and regimens. Typically, clinical symptoms of hypothyroidism in preterm infants manifest as hypometabolism, and typical features are hypothermia, low stool output, and feeding difficulties [6,7]. Given that hypothyroidism is a type of self-limiting disease, the duration of related symptoms in children cannot be effectively controlled if clinical treatment is not appropriate [8,9]. Lack of thyroxine not only affects the later growth and development of infants, but may even lead to serious complications such as cerebral palsy [10,11]. Therefore, it will be of great significance to investigate possible interventions in preterm infants with hypothyroidism in clinical practice.

Clinical studies have revealed that levothyroxine sodium is one of the commonly used synthetic drugs for the treatment of hypothyroidism [12]. The pharmacological action of this drug nearly resembles the physiological hormonal action. Levothyroxine sodium is metabolized and broken down to triiodothyronine (T3), which in turn supplements the thyroxine that is lacking in infants [13].

Table 1: Comparison of thyroxine index between the two groups (mean ± SD, n = 48)

Group	TSH (mIU/L)		*t*-value	*P*-value	FT3 (pmol/L)		*t*-value	*P*-value	FT4 (pmol/L)		*t*-value	*P*-value
	Before treatment	***After treatment***			***Before treatment***	***After treatment***			***Before treatment***	***After treatment***		
Study	12.69±1.11	2.68±0.31	60.176	0.0000	2.34±0.22	4.88±0.36	41.7104	0.0000	7.46±0.65	12.95±1.24	27.1678	0.0000
Control	12.72±1.06	6.23±0.65	36.1615	0.0000	2.36±0.19	3.00±0.28	13.1038	0.0000	7.44±0.59	9.07±0.84	11.0014	0.0000
t-value	0.1354	34.1533	-	-	0.4767	28.5593	-	-	0.1578	17.9481	-	-
P-value	0.8926	0.0000	-	-	0.6347	0.0000	-	-	0.8749	0.0000	-	-

Table 2: Comparison of growth between the two groups (mean ± SD, n = 48)

Group	Height (cm)		t-value	*P*-value	Weight (kg)		*t*-value	*P*-value
	Before treatment	**After treatment**			**Before treatment**	**After treatment**		
Study	43.15±2.00	68.94±2.73	70.0351	0.0000	1.85±0.09	8.85±0.80	60.2418	0.0000
Control	43.17±1.96	66.15±2.60	48.8973	0.0000	1.85±0.09	7.81±0.76	53.9547	0.0000
t value	0.0495	5.1272	-	-	0	6.5298	-	-
P-value	0.9606	0.0000	-	-	1.0000	0.0000	-	-

Table 3: Comparison of mental development index (MDI) and psychomotor development index (PDI) between the two groups (mean ± SD, n = 48)

Group	MDI score (points)	PDI score (points)
Study group	95.35±3.15	97.35±2.15
Control group	90.54±3.01	92.15±2.05
t-value	7.6487	12.1274
P-value	0.0000	0.0000

Table 4: Comparison of clinical efficacy between the two groups (n = 48)

Group	Markedly effective	Effective	Ineffective	Overall response rate
Study	28 (58.33)	17 (35.42)	3 (6.25)	45 (93.75)
Control	23 (47.92)	14 (29.17)	11 (22.92)	37 (77.08)
χ^2		-		5.3519
P-value		-		0.0207

Simultaneously, levothyroxine sodium is absorbed by the human body and stored in large quantities, and then slowly metabolized and released. The absorption rate of oral medication in children reaches as high as 50 % [14]. Moreover, levothyroxine sodium continuously activates the activity of sympathetic adrenal system and accelerates metabolic processes in humans. Hence, levothyroxine sodium promote development while improving clinical symptoms of patients [15,16].

During the practice of levothyroxine sodium in treating preterm infants with hypothyroidism, there are some differences in dosages of thyroxine sodium used, and the approximate dosage is in the range of 2 - 8 μg/kg daily [17,18]. However, given that the duration of this study was relatively long, the dose of thyroxine sodium used was 5 μg/kg daily. After treatment, the indicators of growth, mental and psychomotor development of both groups were significantly improved, but the indicators of study group were superior to that of control group, and the differences were significant. As for clinical efficacy, overall response rate in study group was significantly higher than in control group. This result further validated the comparative advantage of levothyroxine sodium in the treatment of preterm infants with hypothyroidism, and is consistent with similar reports [19-21].

Following further investigations, it was observed that studies in this field mainly focused on pregnant women with hypothyroidism, and there are many studies on pregnancy outcomes of these women as well as the development of preterm infants. However, there are limited studies on the treatment of preterm infants with hypothyroidism. Statistics of clinical cases imply that for most preterm infants with hypothyroidism, thyroid function parameters also return to normal at 6 weeks after birth usually without treatment. In this case, there are distinct perspectives on whether or not to treat preterm infants with hypothyroidism in clinical practice. Some clinicians deemed that a treatment regimen that improved the thyroid hormone levels of preterm infants, improve the symptoms in children, especially in improving clinical prognosis, growth and development of children with obvious advantages. Some reports have shown that no evidence of combined treatment in the treatment of preterm infants with hypothyroidism has been found in clinical case reports in the past 5 years, but the effect of levothyroxine sodium alone has been recognized [22-24].

Limitations of this study

Subjects in this study were patients admitted to the Department of Pediatric Clinic, Shengli Oilfield Central Hospital, Dongying, within a specified period, hence, the limited number. In the future, levothyroxine sodium will need to be used to treat preterm infants with hypothyroidism on a large scale to make a more comprehensive and scientific evaluation on the clinical efficacy of this method.

CONCLUSION

Levothyroxine sodium effectively improves the level of thyroxine, promotes the growth, mental and psychomotor development of preterm infants with hypothyroidism. The outcome of this study provides a basis for future clinical practice after large-scale validation.

DECLARATIONS

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None provided.

Ethical approval

Approval for this work was obtained from the Ethics Committee of Shengli Oilfield Central Hospital, Dongying (approval no. LCYJ2019132).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Haimei Jiao, Peng Yu, Jia Feng, Bingjin Zhang, Jingjing Li and Xuexiang Li supervised the data collection, analyzed and interpreted the data. Haimei Jiao and Peng Yu prepared the manuscript for publication and reviewed the draft of the manuscript. All authors read and approved the manuscript.

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