Curative effect and safety of propranolol combined with prednisone in the treatment of infantile hemangiomas

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Received November 13, 2017; Accepted January 9, 2018

DOI: 10.3892/etm.2018.6035

Abstract. The object of this study was to analyze the curative effect and safety of propranolol combined with prednisone in the treatment of infantile hemangiomas (IHs). Forty-four children with IHs on the head and face at the proliferative phase admitted to Jinan Center Hospital Affiliated to Shandong University were randomly divided into two groups. Children in group A took orally propranolol 2 mg/kg/day in three divided doses combined with prednisone 2 mg/kg/day in two divided doses in the first two weeks; children in group B took orally propranolol alone, and the dose was the same as that in group A. The treatment time of the two groups was up to 6 months, and the clinical curative effect and the incidence rate of adverse reactions were compared between the two groups. In the comparison of the curative effect between two groups of children with the tumor size decrease as the evaluation index, the total effective rate of group A was 100%, which was better than that of group B (81.82%), and the results were significantly different ($P<0.05$). In the same comparison with the surface of hemangiomas becoming flat and the color becoming light as evaluation indexes, the total effective rates of group A were 95.45 and 100%, which was not significantly different ($P>0.05$) compared with those of group B (86.36 and 77.27%) with a significant difference. The treatment in group A was superior to that in group B in terms of the curative effect on IH children younger than 6 months and was effective for different types of IHs. In group A, adverse reactions included loss of appetite (n=1) and bronchial and upper respiratory tract infections (n=1); in group B, adverse reactions included crying at night (n=1), lowered heart rate (n=1) and loss of appetite (n=2). The incidence rate of adverse reactions was compared between the two groups, and the difference was not significant ($P>0.05$), indicating that the combination therapy did not aggravate adverse reactions, and adverse reactions in the two groups were less and not severe. In the treatment of IHs, propranolol combined with prednisone can significantly reduce the tumor volume at the proliferative phase and significantly improve the tumor color with a low incidence rate of adverse reactions in a mild degree. Children have high tolerance to this treatment method, and the treatment method is highly safe and of great significance in clinical practice.

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Key words: infantile hemangioma, propranolol, prednisone, curative effect, safety

Introduction

An infantile hemangioma (IH), also known as hemangioma, is a common benign endothelial cell-derived tumor and often occurs in infancy with the incidence rate of approximately 5-10% (1). IHs can often be found on the head and face, limbs and other regions of the body. An IH has a unique clinical course, in which it rapidly proliferates in children at the age of 3-9 months, and then enters the self-extinction phase (2). Although most IHs can naturally fade away, approximately 20% of the severe IHs cannot fade away, which directly affects the vision and breathing of infants and young children, and even directly oppresses adjacent organs (3). At the same time, IHs grow rapidly at the proliferative phase, which may be accompanied by ulcers, bleeding and dysfunction of adjacent parts. Under severe conditions, these symptoms will affect the appearance, organ functions, growth and development of infants and young children, thus bringing great psychological pressures to patients' family members. Therefore, most children's parents expect the intervention can be conducted as early as possible to achieve early regression of IHs.

Although there are many clinical treatments of IHs, which are generally divided into surgical resection, physical therapy and drug therapy (4), each has its own limitations with varying degrees of adverse reactions. Besides, due to the lack of the standard treatment program for IHs currently, to explore a highly efficient and safe treatment is very urgent.

Glucocorticoid is a traditional first-line drug for treating IHs (5), but due to its large individual differences in the curative effect and relatively more adverse reactions, it has been gradually used as an auxiliary drug in the clinical treatment of IHs. In 2008, Izadpanah *et al* (6) accidentally found that propranolol has a relatively better curative effect in the treatment of IHs, and since then, many scholars from various countries

paid attention to and studied propranolol. Now, it has become the first-choice drug for clinical treatment of IHs. In order to improve the curative effect of propranolol while reducing the side effects of adverse reactions and complications, drug dose, route of administration, maintenance treatment time and other aspects are discussed in current studies (7), but there are relatively less studies on the combination of drugs. From November 2015 to August 2016, the authors adopted oral propranolol combined with oral prednisone for the treatment of IHs on the head and face at the proliferative phase, and conducted a preliminary study on the curative effect and safety of it. The results are reported as follows:

Materials and methods

General data. Forty-four children with IHs on the head and face treated in Jinan Center Hospital Affiliated to Shandong University (Jinan, China) from January 2015 to August 2016 were selected, including 10 males and 34 females aged 1-8 months with an average age of 4.5 months. All children were eligible for the diagnostic criteria of the World Health Organization (WHO) for IHs (8). Inclusion criteria: 1) Children aged less than 9 months with IHs on the head and face; 2) children whose IHs were growing rapidly and tumor bodies were increased by over 2 times within 1-2 weeks; 3) children receiving no other treatment methods before; 4) children with no congenital cardiovascular disease, pulmonary disease (bronchial asthma and bronchitis), diabetes and visceral hemangioma; 5) children whose parents or guardians signed the relevant informed consent before the treatment. This study was approved by the medical Ethics Committee of Jinan Center Hospital. Signed written informed consents were obtained from the patients' guardians. The children studied were divided into the treatment group (n=22) and the control group (n=22) using a random number table. Comparisons showed that the general data (including age, sex and complications) in this study were not significantly different (P>0.05) (Table I), and the data were comparable and met the needs of this study.

Examinations before treatment. Before treatment, all children received electrocardiogram, blood routine examination, liver and kidney function examination, fasting blood glucose examination, Doppler echocardiography, chest X-ray and examinations for other parts. In addition, the location, size, color and surface texture of IHs at admission were recorded for preparation as controls for those after administration.

Treatment methods. Treatment methods in group A: Children took orally prednisone in the first week at 2 mg/kg/day in two divided doses and propranolol at 2 mg/kg/day in three divided doses. Within the second week, the dose of prednisone was gradually reduced to zero, but the dose of propranolol was unchanged. Then, children orally took propranolol for 5 consecutive months, and finally the dose was gradually reduced to zero within two weeks. Treatment methods in group B: Children received monotherapy with the same dose of propranolol as that in group A for 6 months. The clinical curative effects and the incidence rates of adverse drug reactions of group A and B were recorded. Finally, relevant conclusions were obtained by statistical analysis.

Clinical observation and follow-ups. During hospitalization, the pulse, blood pressure, blood glucose, respiratory rate and other indexes were observed all day. Adverse reactions were closely monitored and the corresponding measures were taken. In particular, treatment plans were stopped when the heart rate was <70% of the normal value, systolic blood pressure was reduced by >25% of the normal value, bronchospasm appeared or the symptomatic blood glucose was reduced.

The two groups were followed up for a total of 9 months (including 6 months during the treatment and 3 months after the treatment). In the first month, children were followed up every 2 weeks, followed by once a calender month. The volume, texture and color of IHs were recorded at each follow-up in detail, and the dose of propranolol was adjusted according to the weight of the children.

Evaluation of curative effects. The size of IHs was recorded by hemispheric measurement (9), and the curative effect was evaluated using the 4-Grade standard proposed by Achauer *et al* (10). Grade I: Poor curative effects with the tumor volume shrinking <25%; grade II: moderate curative effects with the tumor volume shrinking 26-50%; grade III: good curative effects with the tumor volume shrinking 51-75%; grade IV: excellent curative effects with the tumor volume shrinking 76-100%. The total effective rate of treatment = (excellent + good + moderate)/total number of cases x100%.

Conditions of the color of IHs becoming light and the surface becoming flat were recorded by a digital photography, and the curative effect was analyzed using the fractional evaluation method adopted by Hogeling *et al* (11), that is, 2 points for significant changes; 1 point for moderate changes; 0 point for no change. The total effective rate of treatment = (2 points + 1 points)/total number of cases x100%.

Evaluation of the effective rate of treatment: 1) Recovery: the tumor completely disappeared, and the skin function returned to normal; 2) effective treatment: the tumor volume was significantly reduced, and most skin functions returned to normal; 3) ineffective treatment: there was no significant change in the tumor or the tumor recurs after the treatment.

Statistical analysis. The data were analyzed by SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA). Measurement data were expressed as mean ± SD. Intergroup comparisons were detected using the t-test. Enumeration data were expressed as %, and intergroup comparisons were detected using χ^2 test. P<0.05 represent that the difference was significant, and the results were statistically significant.

Results

Changes in the tumor volume. The following results were obtained from different treatments for two groups of IH patients with changes in the tumor volume as the observation indexes: The total effective rate of the clinical treatment in group A (combination therapy group with propranolol and prednisone) was as high as 100%, which was significantly higher than that in group B (monotherapy group with propranolol; 81.82%). The statistical analysis showed that differences between the two groups were significant and of

Table I. Comparisons of general data between two groups of children.

Groups	Case (n)	Age (m)	Sex (n)		Complications (n)		
			Male	Female	Deformed appearance	Hemorrhage	Anabrosis
A	22	4.5±3.0	6	16	3	2	3
B	22	3.5±3.5	4	18	4	3	2

Table II. Comparisons of the tumor volume shrinking status between two groups of children.

Group	Case (n)	Grade IV (excellent)	Grade III (good)	Grade II (moderate)	Grade I (poor)	Total effective rate
A	22	15	3	4	0	100%
B	22	8	5	5	4	81.82%

Table III. Comparisons of the tumor surface becoming flat between two groups of children.

Group	Case (n)	2 points	1 point	0 point	Total effective rate
A	22	14	7	1	95.45%
B	22	10	9	3	86.36%

Table IV. Comparison of the color shade of the tumor between two groups of children.

Group	Case (n)	2 points	1 point	0 point	Total effective rate
A	22	14	8	0	100%
B	22	11	6	5	77.27%

Table V. Comparisons of curative effects on children of different age.

	Younger than 6 months		Older than 6 months	
	A	B	A	B
Case (n)	14	14	8	8
Excellent	12	8	3	0
Good	2	2	1	3
Moderate	0	1	4	4
Poor	0	3	0	1

statistical significance (P<0.05) (Table II). The curative effect of group A is shown in Fig. 1.

Changes in the tumor surface. In addition, the following results were obtained with the surface of IHs becoming flat as the observation index after the treatment: The total effective rate of group A was 95.45%, and in the comparison with group B (86.36%), the results were not significantly different between the two groups (P>0.05), and of no statistical significance (Table III). The curative effect of group A is shown in Fig. 2.

Comparison of the color shade of the tumor. The following results were concluded with the tumor color becoming light as the observation index: The total effective rates of clinical treatment in group A and B were 100 and 77.27%, respectively, and the comparison showed that the difference was significant (P<0.05). It was found that the curative effect in group A was significantly better than that in group B (Table IV), and the curative effect of group A is shown in Fig. 3.

Comparisons of curative effects on children based on age. In children younger than 6 months, those with excellent and good curative effects accounted for 100% in group A and 78.6% in group B, indicating that the curative effect of group A was significantly better than that of group B (P<0.05). However, in children older than 6 months, those with excellent and good curative effects in the two groups accounted for 50% and 37.5%, respectively, and the comparison revealed that the difference was not significant (P>0.05) (Table V). At the same time, at the end of the treatment, all children were followed up for 3 months, and the recurrence of IHs was not found in any case.

Comparisons of effective rates of the treatment of different types of IHs. The effective rates of the combination therapy group (group A) was higher than those in monotherapy group with propranolol (group B) in the treatment of strawberry hemangiomas and cavernous hemangiomas, and the differences were statistically significant (P<0.05) (Table VI).

Adverse reactions. In the course of each follow-up, adverse reactions of two groups of IH children were observed closely.

Table VI. Comparisons of effective rates of the treatment of different types of IHs between the two groups n (%).

Type of IHs	Group	Case (n)	Recovery	Effective	Ineffective	Total effective	P-value
Strawberry hemangiomas	A	10	6 (60.0%)	4 (40.0%)	0 (0)	100%	0
	B	10	4 (40.0%)	4 (40.0%)	2 (20.0%)	80%	
Spider angiomas	A	5	5 (100.0%)	0 (0)	0 (0)	100%	1
	B	5	3 (60.0%)	2 (40.0%)	0 (0)	100%	
Cavernous hemangiomas	A	7	4 (57.1%)	2 (28.6%)	1 (14.3%)	83.70%	0.037
	B	7	1 (14.3%)	4 (57.1%)	2 (28.6%)	71.40%	

Table VII. Comparison of the total incidence rate of adverse reactions between two groups of children.

Group	Case (n)	Crying at night	Reduced heart rate	Loss of appetite	Bronchial and upper respiratory tract infections	Total incidence rate of adverse reactions
A	22	0	0	1	1	9.1%
B	22	1	1	2	0	18.2%

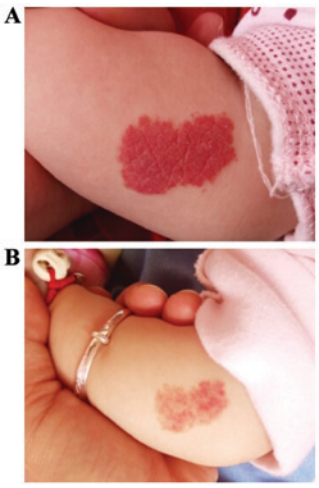

Figure 1. Changes in the tumor volume: (A) before treatment; (B) after treatment.

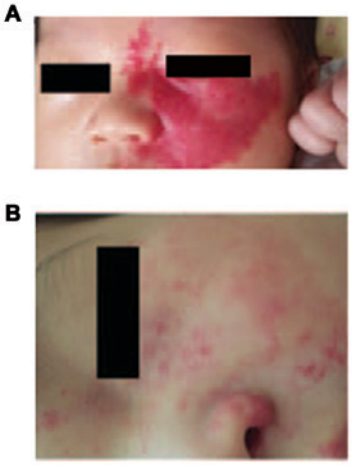

Figure 2. Changes in the tumor surface: (A) before treatment; (B) after treatment.

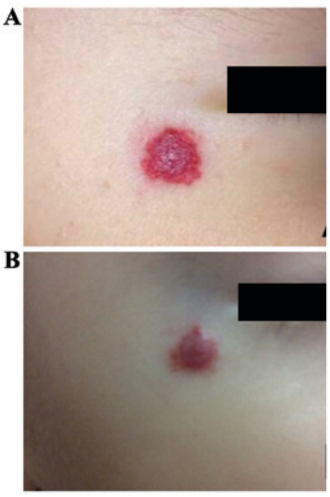

Figure 3. Comparison of the color shade of the tumor: (A) before treatment; (B) after treatment.

In group A, adverse reactions included loss of appetite (n=1) and bronchial and upper respiratory tract infections (n=1); in group B, adverse reactions included crying at night (n=1), reduced heart rate (n=1) and loss of appetite (n=2). These adverse reactions were not severe, and became naturally alleviated after the treatment. Adverse reactions such as hypotension, hypoglycemia and facial edema were not found. The incidence rate of adverse reactions was compared between the two groups, and the difference was not significant (P>0.05), indicating that the administration method in group A did not increase the incidence rate of adverse reactions (Table VII).

Discussion

An infantile hemangioma (IH) is a recognized type of hemangioma worldwide (12), and is the most common type in many

benign tumors occurring in infants and young children. Its pathogenesis and unique regression process have not been completely explained. IH often occur in females on the head and face and grows rapidly at the proliferative phase. Besides, the regression period is long, which not only seriously affects the appearance, but also oppresses the lesion, thus causing local dysfunction, so early intervention treatment is conducive to restricting the growth of tumor body, speeding up its regression process, reducing complications and improving the physical and mental health of children.

Propranolol (also known as inderal), is a traditional non-selective β-blocker that has been used for the treatment of arrhythmia and hypertension for nearly 50 years, and used for the treatment of IHs since 2008 when Storch and Hoeger accidentally found that propranolol can inhibit the growth of IHs. The mechanism of propranolol in the treatment of IHs is still not very clear, which may be to inhibit β receptor resulting in vasoconstriction at the lesion sites, thus inhibiting angiogenesis and inducing IH endothelial cell apoptosis (13); and the mechanism may also be to regulate the mitogen-activated protein kinase (MAPK) pathway, thus reducing the expression of basic fibroblast growth factors and vascular endothelial growth factor genes (14). In view of the cardiovascular side effects of propranolol, there are still many uncertainties about using propranolol as the best method to treat IH children, including dose, frequency of medication, time of treatment, optimal timing of treatment and reduction methods. Clinically, the 'stepped-care treatment program' proposed by Siegfried *et al* (15) is widely used. In the existing studies, the dose range of propranolol was 1-3 mg/kg/day in two divided doses; in this study, the dose of propranolol was 2 mg/kg/day in three divided doses, which is the most commonly used dose in the current literature. Twice a day of medication can simplify the number of medication times and reduce the risk of nocturnal hypoglycemia, but in this study, it was increased to three times a day in view of the relatively shorter half-life of propranolol (3-6 h) (16). The treatment time was set at 6 months because the time period covered most of the proliferative phase (17).

Prednisone is a corticosteroid hormone, which has been used as a first-line drug in the treatment of IHs, and its mechanism of action is not fully defined. Some studies suggest that the mechanism may be associated with the inhibition of the activity of IH stem cells, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), thus, reducing the expression levels of vascular endothelial growth factor A (VEGF-A) and other angiogenic cytokines, including monocyte chemotactic protein 1 (MCP-1), matrix metalloproteinase-1 (MMP-1), urokinase-type plasminogen activator and receptor (uPAR) and interleukin 6 (IL-6) (18). Some other studies indicated that the mechanism may be that the competitive binding of prednisone to IH estrogen receptors inhibits the growth of tumors by acting as antagonists. Although prednisone has certain curative effect in the treatment of IHs, it causes many adverse reactions, and the long-term use will lead to dysplasia or immune disorders of children (19), so it is currently used as an auxiliary drug in the clinical treatment of IHs. Previously, Koay *et al* (20) tried to use prednisone combined with propranolol in the treatment of a child with IHs on the orbital region aged 3 months, and the curative effect was good without any adverse reactions. Although it is an individual case, this treatment program is a new attempt for drug therapy of IHs. The dose of prednisone was 2 mg/kg/day in two divided doses in this study, and as it was within the usual dose range, the relevant adverse reactions were relatively lighter and became naturally alleviated at the end of the treatment.

In this study, the comparison of the clinical curative effect between group A and group B revealed that the clinical curative effect in group A was significantly better than that in group B, and that on children younger than 6 months was better, which further confirmed that the best timing for IH children was at the age of less than 6 months at the proliferative stage. The comparison of adverse reactions between the two groups showed that the difference was not significant, and the total incidence rate of adverse reactions in group A was lower.

In summary, the combination therapy with propranolol and prednisone in the treatment of IHs can significantly reduce the tumor volume at the proliferative phase and significantly improve the tumor color with a low incidence rate of adverse reactions in a mild degree. Children have high tolerance to this treatment method, and the treatment method is highly safe and of great significance in clinical practice.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

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

Authors' contributions

HL conceived and designed the study. RH and GX were responsible for the collection and analysis of the patient data. HL interpreted the data and drafted the manuscript. HL revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of Jinan Center Hospital (Jinan, China). Signed written informed consents were obtained from the patients' guardians.

Consent for publication

The patients' guardians have provided written informed consent for the publication of any associated data and accompanying images.

Competing interests

The authors declare that they have no competing interests.

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