Efficacy of Human Interferon Alpha-2b Spray Combined with Chiqiao Qingre Granule in the Treatment of Herpangina in Children

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The objective of this study was to evaluate the efficacy and safety of treating herpangina in children using interferon alpha-2b spray combined with Chiqiao Qingre granule. Over a period from January 2021 to December 2022, 240 children with herpangina who were treated at our hospital were randomly divided into four groups; group A received routine treatment, group B was treated with interferon alpha-2b, group C was treated with Chiqiao Qingre granule, and group D was treated with a combination of interferon alpha-2b and Chiqiao Qingre granule. The symptom regression time, serum inflammatory levels, and adverse reactions were observed and compared for 5 d. Interferon alpha-2b, Chiqiao Qingre granule and their combination treatment group all achieved better curative effect, and the combination of interferon alpha-2b and Chiqiao Qingre granule could bring better results, and the difference was not significant in the safety between combined treatment and routine treatment, interferon alpha-2b and Chiqiao Qingre granule alone. The combination of interferon alpha-2b and Chiqiao Qingre granule is an effective and safe therapy for children.

Key words: Interferon alpha-2b, Chiqiao Qingre granule, herpangina, combined therapy, curative effect

In today's society, herpangina is one of the most common respiratory infections in children. It is mainly caused by coxsackievirus and often occurs during the summer and autumn[1,2]. The symptoms of the disease are significant, including sore throat, itchy throat, recurrent fever and more. In severe cases, herpangina can lead to complications such as shortness of breath and laryngeal edema, which can endanger the lives of children[3,4]. Unfortunately, conventional antiviral drugs have limited effects and may lead to drug resistance and adverse reactions[5]. However, researchers have recently begun to explore new treatments for this disease. Human Interferon-Alpha 2b (IFN-α2b) is a biological recombinant preparation that has been widely used for treating various viral infections and malignant tumors, making it an attractive treatment option for herpangina in children[6-9]. IFN-α2b cannot only inhibit virus replication but also regulate the immune system's response and promote apoptosis after virus infection. In addition, Chiqiao Qingre granule is a compound preparation of traditional Chinese medicine that contains *Schizonepeta tenuifolia, Forsythia suspensa*, Fructus Aurantii, peppermint, Radix isatidis, ejiao and other ingredients. It has been shown to dispel pathogens and heat, clear away heat and detoxification, cool blood and stop bleeding. It also plays a role in treating upper respiratory tract infections in children[10-12]. Chiqiao Qingre granule can reduce the inflammatory reaction in the body, shorten the duration of disease, and improve patient's clinical symptoms[13]. Many researchers have tried to combine IFN-α2b and Chiqiao Qingre granule to treat herpangina in children, and the efficacy of this combination has been verified in clinical studies. Compared with a single drug, using this combination of drugs can improve the cure rate, shorten the duration of clinical symptoms and reduce the occurrence of complications. Therefore, the purpose of this study is to evaluate the efficacy and safety of using IFN-α2b spray combined with Chiqiao Qingre granule to treat herpangina in children. This research provides a unique treatment idea for standardized treatment, improving the cure rate of herpangina and

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improving the quality of life for children. Over a period from January 2021 to December 2022, 240 children with herpangina who were treated at our hospital were randomly divided into four groups according to the clinical and diagnostic expert consensus of herpangina (version 2019)[14]. B was routine treatment group; C was IFN-α 2b group and D was Douqiao Qingre granule group (n=60). IFN-α2b combined with soy forsythia Qingre granule group (n=60). The difference in age, physique and serum inflammatory level among the three groups was not significant (p>0.05). This study was conducted with the approval of the hospital ethics committee, and the informed consent forms were signed by the guardians of the participating children. Inclusion criteria including the children aged between 1 mo and 5 y old; confirmed diagnosis of herpangina; informed consent provided by the parents or guardians; complete clinical data available and children who can cooperate with related clinical treatments, such as throat sprays or nebulized inhalation therapy. Exclusion criteria including the children with congenital heart disease, liver or kidney dysfunction; children with mental disorders; children with bacterial infections; children who have contraindications for the IFN-α2b spray and Chiqiao Qingre granule and children who have taken antiviral drugs recently. Routine treatment group including the hypothermia, fluid replacement, nutritional support and other symptomatic treatment; IFN-α2b group, in addition to routine treatment, IFN-α2b spray (Jiefu, Tianjin unknown organism, specification 10 ml:1 million IU, 120 spray), 1-2 spray/time, 3 d, continuous treatment for 5 d. In Chiqiao Qingre granule group, Children's Chiqiao Qingre granule was added on the basis of routine treatment (Jichuan Pharmaceutical Group Co., Ltd., specification 2 g). The usage of the medication is as follows; for children aged (1-3) y, 2-3 g; for children aged (4-5), 3-4 g and taken with boiled water, 3 times a day for 5 d. In IFN-α2b combined with Chiqiao Qingre granule group; IFN-α2b and Chiqiao Qingre granule were added on the basis of routine treatment, the method was the same as before, for 5 d. The treatment conditions of the four groups were compared from the following aspects; symptom relief time, observed symptoms included; antipyretic time, salivation disappearance time, sore throat disappearance time, ulcer and herpes disappearance time; inflammatory factors Interleukin (IL)-6 and C-Reactive Protein (CRP); serum IL-6 was detected by Enzyme-Linked Immunosorbent Assay (ELISA), CRP was detected by immune transmission turbidimetry and adverse reactions such as nausea, rash and somnolence occurred during treatment. According to the evaluation of the children's symptoms including the cured; body temperature returned to normal within 3 d after treatment, sore throat completely disappeared, ulcers and herpes disappeared completely. In effective; body temperature returned to normal range within (3-5) d after treatment. Ulcer and herpes basically disappeared. In ineffective; after 5 d of treatment, there was still fever, no significant improvement in pharynx pain, ulcers and herpes did not disappear. Total effective rate=(cured+effective)/total number of cases×100 %. Statistical Package for the Social Sciences (SPSS) 25.0 software was utilized for statistical analysis. Measurement data were presented as mean±standard deviation, and one-way Analysis Of Variance (ANOVA) was performed to compare between groups. Post-hoc pairwise comparisons between groups were conducted using the Student–Newman–Keuls (SNK)-q test. Counting data were expressed as frequency/rate (%) and analyzed using the Chi-square ($\chi 2$) test. Statistical significance was set at $p<0.05$. The overall treatment effectiveness rate in group D was significantly higher than in group A, B, and C ($p<0.05$), while the effectiveness rate in group B and C were higher than in group A ($p<0.05$) as shown in Table 1. The duration of antipyretic therapy, disappearance of salivation, disappearance of throat pain, and the healing of ulcers and herpes in group D were significantly shorter than in the other three groups ($p<0.05$). Meanwhile, the antipyretic time, salivation disappearance time, pharyngitis disappearance time, and ulcer and herpes disappearance time in groups B and C were also shorter than in group A ($p<0.05$) as shown in Table 2. Following treatment, the serum inflammatory levels in group B, C and D were significantly lower compared to group A ($p<0.05$). Furthermore, group D had a lower level of inflammation compared to group B and C ($p<0.05$) as shown in Table 3. The incidence of adverse reactions in groups A, B, C and D was similar, and the difference in the overall complication rate among the four groups was not significant ($p<0.05$) as shown in Table 4. In this study, we evaluated the efficacy of using IFN-α2b,

Chiqiao Qingre granule and their combination in treating herpangina in children, and compared their effects with those of routine treatment. We found that, compared to conventional therapy, all three treatment groups had better therapeutic effects. Moreover, our results showed that combination therapy had the most significant effect. These findings highlight the importance of integrating Chinese and Western medicine in pediatric disease treatment. Our experiments confirmed previous studies' results in the effectiveness of IFN-α2b. For instance, Fu *et al*.[15] observed a significant decrease in body temperature, pain relief, and a significant decrease in the level of inflammatory mediators after treating herpangina in 200 children with IFN-α2b. Similarly, in a multicenter randomized controlled study of 180 children with herpangina, Pan *et al*. concluded that IFN-α2b significantly improved clinical efficacy, shortened the course of the disease, and reduced the incidence of complications. Our findings reinforced these previous results, supporting the efficacy of IFN-α2b. Studies of Chiqiao Qingre granule's efficacy in treating respiratory tract infections in children have also produced similar results. For example, Zhang *et al*.[16] found that Chiqiao Qingre granule was more effective in alleviating upper respiratory tract infection symptoms in children, with better safety profiles. Yang *et al*.[17] studied 132 children with upper respiratory tract infections and reported shorter recovery times in body temperature and significant improvements in clinical symptoms in the treatment group. Another study discovered that Chiqiao Qingre granule effectively improved the course of upper respiratory tract infection, clinical symptoms, and inflammatory indicators in children[18]. Our experimental results are consistent with these previous studies, indicating that Chiqiao Qingre granule is effective in treating respiratory diseases and herpangina in children. Our study further found that the combination therapy significantly decreased the serum inflammatory markers IL-6 and CRP compared to the other three groups. This finding indicates that the combination therapy effectively reduced inflammation levels and improved immunity in children. It is similar to the results of previous studies by Jia *et al*. and Li *et al*., who found that the combination of Western medicine improved clinical symptoms of children with herpangina, reduced inflammation and improved immune function[19,20]. However, this study has some shortcomings and limitations. The sample size may not be huge enough and lack sufficient randomness. Data verification from multiple centers is necessary to examine empirical results' reliability. Furthermore, due to the subjects being children, it is challenging to evaluate adverse reactions and drug safety data, particularly for IFN-α2b. Long-term use may produce side effects; thus, safety studies require longer monitoring. In conclusion, this study indicates that using human IFN-α2b, Chiqiao Qingre granule, or their combination is effective in treating herpangina in children, providing a promising new treatment option. Future studies should continue to explore the effects of combining Chinese and Western medicine, and examine the potential of traditional Chinese medicine.

TABLE 1: COMPARISON OF CLINICAL EFFICACY OF CHILDREN IN EACH GROUP (CASE %)

Group	Cases	Cured	Effective	Ineffective	Effectiveness rate (%)
A	40	7	15	18	55[a]
B	40	10	18	12	70[ab]
C	40	9	20	11	72.5[ab]
D	40	18	19	3	92.5

Note: Compared with group D, [a]p<0.05 and compared with group A, [b]p<0.05

TABLE 2: COMPARISON OF THE DISAPPEARANCE TIME OF CLINICAL SYMPTOMS IN EACH GROUP

Group	Cases	Antipyretic time	Salivation disappearance time	Time of disappearance of throat pain	Healing of ulcers and herpes
A	40	4.72±1.24	3.88±0.92	3.72±0.88	6.02±1.02[a]
B	40	3.34±0.85	2.79±0.71	3.03±0.61	4.55±0.76[ab]
C	40	3.28±0.87	2.81±0.68	3.11±0.63	4.39±0.69[ab]
D	40	2.59±0.53	2.21±0.36	2.54±0.37	3.73±0.48

Note: Compared with group D, ap<0.05 and compared with group A, [b]p<0.05

TABLE 3: COMPARISON OF INFLAMMATORY LEVELS IN CHILDREN OF EACH GROUP AFTER TREATMENT

Group	Cases	IL-6 (ng/ml)	CRP (mg/l)
A	40	36.24±5.86	13.24±2.15[a]
B	40	29.12±4.77	10.41±1.86[ab]
C	40	30.08±4.86	10.76±1.92[ab]
D	40	23.44±4.27	4.32±0.84

Note: Compared with group D, [a]p<0.05 and compared with group A, [b]p<0.05

TABLE 4: COMPARISON OF ADVERSE REACTIONS AMONG CHILDREN IN EACH GROUP

Group	Cases	Nausea (n)	Skin rash (n)	Lethargy (n)	Overall complication rate (%)
A	40	0	2	1	7.5
B	40	1	1	1	7.5
C	40	2	0	1	7.5
D	40	0	1	1	5

Conflict of interests:

The authors declared no conflict of interests.

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