

# Clinical Efficacy of Ertong Qingyan Oral Solution in the Treatment of Herpes in Children

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Wang *et al.*: Efficacy and Safety of Ertong Qingyan Oral Liquid

To observe the efficacy and safety of Ertong Qingyan oral liquid in the treatment of herpes pharyngitis is the objective of this study. 151 children having herpes pharyngitis who were admitted to the department of pediatrics of Henan Provincial Children's Hospital from January 2021 to September 2022 were selected and were randomly divided into control group (n=75) and observation group (n=76). The control group was supplemented with interferon alpha 1b spray on the basis of conventional treatment, while the observation group was supplemented with interferon alpha 1b spray combined with Ertong Qingyan heat and toxin relieving oral liquid. The efficacy of the two groups was evaluated and comparing evaluating parameters after 5 d of the treatment. The total effective rate of the observation group was higher than that of the control group (94.7 % vs. 89.3 %) ( $p<0.05$ ). The parameters such as time for body temperature to return to normal, the time for herpes to decrease, the time for salivary secretion to return to normal and the time for normal diet to start were better than that of the control group ( $p<0.05$ ). Similarly, the levels of interleukin-7, interleukin-10 and tumor necrosis factor alpha were significantly lower than that of the pre-treatment group and the control group ( $p<0.05$ ). The levels of immunoglobins A, G and M in the observation group were significantly higher than those in the control group after treatment ( $p<0.05$ ). No adverse reactions occurred during the treatment period. Finally it can be concluded that Ertong Qingyan oral solution is effective and safe in the treatment of herpes pharyngitis in children.

**Key words:** Ertong Qingyan Jiere oral liquid, interferon-alpha 1b spray, herpangina, tumor necrosis factor-alpha, *Scutellaria baicalensis*

Herpangina is an acute infectious disease among preschool children caused by *Enteroviruses*, which can be transmitted by the fecal-oral route, respiratory droplets, etc. Children with herpes pharyngitis may suffer from mouth pain, fever, salivation and other reasons that may affect their normal eating. Since humans are generally susceptible to *Enteroviruses* and children with latent infections, illness is an important source of infection. This disease can be seen in children of different ages, with a higher prevalence in preschool children. Currently, there is a lack of effective enteric antiviral drugs; Western medicine treatment of the disease is based on interferon topical drugs and oral drugs like ribavirin, etc., but antiviral drugs have certain limitations, poorly tolerated by children and are not recommended. Traditional Chinese Medicine (TCM) treatment of this disease is characterized by precise efficacy,

safety and rapid reduction<sup>[1-3]</sup>, in which Ertong Qingyan Jiere oral liquid is a kind of heat-clearing and detoxifying proprietary TCM, which has better efficacy in treating sore throat caused by pathogenic microorganisms, but the efficacy and safety of it in the treatment of children with herpangina has not yet been reported. In view of this, the purpose of this paper is to observe the clinical efficacy and safety of Ertong Qingyan Jiere oral liquid in the treatment of children's herpetic pharyngitis, with a view to provide a basis for the clinical treatment of this disease. 158 children with herpangina, admitted to the pediatric department of Henan Children's Hospital from January 2021 to September 2022 were selected for this study. The children were divided into control and observation groups using the random number table method, with 79 individuals in each group. The control group had 39 male and 40 female

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individuals with a mean age of  $(4.3 \pm 2.5)$  y, which including 62 individuals with fever, 79 individuals with herpes, 79 individuals with salivation, 79 individuals with decreased appetite and 32 individuals with increased count of white blood cells. The observation group enrolled 40 males and 39 females with a mean age of  $(4.6 \pm 2.6)$  y. 65, 79, 79, 79 and 33 children were reported with fever, herpes, salivation, decreased appetite and increased counts of white blood cells, respectively. In addition, 3 children in the observation group and 4 children in the control group who were categorized to have hand-foot-mouth diseases were excluded from the efficacy analysis. Children in different groups showed no great differences in terms of age, male-to-female ratio, symptoms or any other data before treatment ( $p > 0.05$ ). The study was approved by the hospital research ethics committee and all the enrolled children signed the informed consents. The children were enrolled according to the inclusion and exclusion criteria. Inclusion criteria included the children who met the diagnostic criteria of the expert consensus on diagnosis and treatment of herpangina (version 2019), developed by the Infection Group of the Pediatrics branch of the Chinese Medical Association<sup>[4]</sup>; children with the TCM syndrome who had lung-stomach excess-heat syndrome and patients of age range between (0.6-7) y old without specific requirements of gender. Similarly, exclusion criteria included children having combined organic diseases such as kidney, heart and liver; patients who were allergic to drugs used in the study such as Ertong Qingyan Jiere oral liquid and interferon spray; patients with lower respiratory tract infections (such as combined bronchitis, bronchitis, or pneumonia) and patients with a history of malignancy and patients who used hormones within the last 1 w. Treatment methods involved conventional treatments<sup>[4]</sup>. Primarily the children were isolated at homes for 2 w with more rest and ventilated living environment. Their families were informed to prepare light diets with appropriate temperature for children and were instructed to avoid irritable food like chili and garlic. All the children were recommended to feed with a liquid or semi-liquid diet. Meanwhile, it was suggested to rinse or wipe the children's mouths with 9 % sodium chloride after meals. In addition, children with fever were advised to drink more water and were monitored for their

temperature. Ibuprofen suspension for symptomatic hypothermia treatment was given when the temperature of the body was  $\geq 38.5^\circ$ . Children in the control group were supplemented with 2 MIU/d (20 ml/bottle) of interferon Alpha ( $\alpha$ ) 1b spray, 1-2 sprays/time 3 times/d at the site of oral herpes on the basis of clinical conventional treatments. Further, children with (1-3) y, (4-7) y and  $>7$  y old in the observation group were treated with 5 ml, 10 ml and 15 ml of Ertong Qingyan Jiere oral liquid respectively 3 times/d for 5 d. Observation indicators such as efficacy evaluation, serum inflammatory factors and humoral immunity factors were studied. The overall effective rate was calculated by dividing the total number of apparent and effective cases by the total number of cases in each group according to the determination criteria<sup>[5]</sup>. Efficacy was evaluated using different grades like markedly effective, effective and ineffective. If the body temperature returned to normal within 3 d, appetite improved significantly, no ulcers in the pharynx were observed and oral herpes reduced or disappeared, then it was considered to be remarkably effective (apparent effect). If the body temperature returns to normal, appetite improves significantly within 3-5 d after treatment with no ulcers in the pharynx and oral herpes decreases, then it was considered to be effective. If the axillary temperature is  $>37.2^\circ$  after 5<sup>th</sup> d of the treatment, accompanied by obvious ulcers and if the oral herpes has not been reduced then it was considered as ineffective. The time for the body temperature to return to normal is defined as axillary temperature which is  $\leq 37.2^\circ$  for  $>1$  d, i.e., 24 h<sup>[6]</sup>. Serum inflammatory factors such as Interleukin (IL)-10, Tumor Necrosis Factor (TNF)  $\alpha$ , IL-7 were tested after surgery between both the groups for comparative analysis<sup>[7,8]</sup>. Further, serological tests for specific immunoglobulins such as Immunoglobulin A (IgA), IgG and IgM which are considered as humoral immunity factors, were detected by Enzyme-Linked Immunosorbent Assay (ELISA) and immunoturbidimetric assay, respectively. Children were monitored closely during the study period to find out any adverse events or adverse reactions. Statistical analysis of the data was conducted using Statistical Package for Social Sciences (SPSS) version 26.0. The number of cases (n) and Percentage (%) was used to describe the counting data statistically, and the Chi-square ( $\chi^2$ ) test was

for the statistical hypothesis test. Mean±Standard Error of the Mean (SEM) ( $\bar{x}\pm s$ ) was selected to express the measurement of the data statistically, with student's t-test for the statistical hypothesis test, where  $p<0.05$  indicated that hypothesis testing exhibited a statistically significant difference. Comparison of the total effective rates of children in different groups was carried out. As shown in Table 1, the total effective rate in the observation group was higher than that in the control group after 5 d of the treatment (94.7 % vs. 89.3 %) with a great difference ( $p<0.05$ ). Symptom relief indices between the two groups were compared. The symptom relief indices of patients after they were treated with different modes were compared (Table 2). These results suggested that the time for temperature returning to normal, time for herpes and salivation returning to normal and the time for starting normal diet in the observation group were significantly short than those in the control group after 5<sup>th</sup> d of the treatment ( $p<0.05$ ). Serum inflammatory factors (IL-7, IL-10 and TNF- $\alpha$ ) between the two groups were compared (Table 3). The results denoted that they were significantly low in all children before treatment than the observation group ( $p<0.05$ ). Humoral immunity indices between the two groups were compared. As shown in Table 4, immunoglobulin markers such as serotype specific IgA, IgG and IgM were significantly higher in all the children after treatment, with more significant increase compared with the observation group ( $p<0.05$ ). Comparative analysis of safety of different intervention methods was carried out between the two groups. Conventional safety indicators such as routine blood test, liver and kidney functioning were examined in laboratory and were found to be normal for children in both groups after treatment. In addition, no adverse events or adverse reactions were observed during the study period. Herpangina which is a common acute infectious disease often occurs in preschool children mostly in the age group of (0-6) y. The main causative pathogens are *Enterovirus* like Coxsackie A virus (CV-A) and *Enterovirus-A71* (EV-A71). Clinically, herpangina is manifested as elevated body temperature with oral herpes, mouth pain and sore throat due to herpes in the isthmus, or loss of appetite due to salivation caused by mouth pain. A few children with herpangina may have high fever and fever-induced convulsions

and sometimes even develop into critical illnesses such as encephalitis due to the virus passing the blood-brain barrier. It is most common in childcare institutions, especial in spring and summer. Western medicine for treating herpangina refers to the isolation and symptomatic treatment because of its contagious nature, with antiviral drugs such as interferon spray on herpes to improve the local immunity and reduce the inflammatory response, thus relieving the herpes-induced stomatalgia. Therefore the effective etiological treatment methods by using the Western medicines is still lacking<sup>[9]</sup>. Ertong Qingyan Jiere oral liquid, a kind of Chinese patent medicine for clearing away heat and toxic materials and is mainly used for the treatment of upper respiratory tract infections with red, swollen, and hot symptoms in the throat. It has been proved to play the role of analgesic, anti-inflammatory, antipyretic, antibacterial, antiviral and immunomodulatory agents<sup>[10]</sup>. As a key factor in immune regulation of mucocutaneous inflammations, interferon- $\alpha$ 1b can be sprayed onto the broken surface of oral herpes for regulating immunity and antiviral activity<sup>[4]</sup>. From the analysis of product characteristics and solving practical clinical problems, it was hoped to verify the efficacy of Ertong Qingyan Jiere oral liquid combined with interferon- $\alpha$ 1b in herpangina treatment through observing the clinical effect of small samples. Therefore, this study was carried out. The results showed that at 5<sup>th</sup> d after treatment, the total effective rate in the observation group was much higher than that in the control group (94.7 % vs. 89.3 %) ( $p<0.05$ ). Meanwhile, the time for the temperature, time for herpes and salivation to return to normal and time for starting normal diet in the observation group were significantly shorter than those in the control group ( $p<0.05$ ). It indicated that the Ertong Qingyan Jiere oral liquid combined with the topical therapy with interferon spray can significantly relieve the clinical symptoms of children with herpangina, which was superior to the interferon alone. In addition, it was also found that the inflammatory factor indices such as IL-7, IL-10 and TNF- $\alpha$  were significantly lower in all children after treatment, with more significant decrease in the observation group ( $p<0.05$ ). Besides, the immunoglobulin indices serotype specific IgA, IgG and IgM were found to be significantly upregulated in all children after treatment, with more significant increase in the

observation group ( $p < 0.05$ ). Such findings suggested that the oral treatment with Ertong Qingyan Jiere oral liquid combined with the topical therapy with interferon spray can downregulate the IL-7, IL-10 and TNF- $\alpha$  levels. The possible mechanism of action may be that the synthesis and release of inflammatory factors such as IL-10 and IL-7 were reduced by Sachs virus-stimulated body mononuclear macrophages<sup>[11-13]</sup>. Such results are consistent with those reported by Hang *et al.*<sup>[14]</sup>. This study results also suggested that the Ertong Qingyan Jiere oral liquid combined with interferon- $\alpha$ 1b spray can elevate the levels of humoral immune indicators such as serotype specific IgA, IgG and IgM, which is consistent with the relevant reports<sup>[15]</sup>. The change in the levels of inflammation and humoral immunity suggested that systemic treatment with Ertong Qingyan Jiere oral liquid and interferon- $\alpha$ 1b spray may play the role of a local antiviral and may further improve the humoral immunity as the viral levels decrease. From the perspective of TCM, herpes is caused by a combination of internal and external factors. It is caused by internal heat accumulation in the spleen and stomach, external wind-heat and toxic invasion, internal and external heat and toxicity condensed in the throat<sup>[16,17]</sup>. Ertong Qinghe oral liquid is composed of 8 medicinal components, including Chaihu (*Radix Bupleuri*) and *Scutellaria baicalensis*. Modern pharmacological studies have found that the monarch drug Chaihu can antagonize multiple aspects of the inflammatory process, reduce capillary permeability to inhibit inflammatory exudation, inhibit cytokines and mediators and have anti-inflammatory and antiviral effects<sup>[18]</sup>. Meanwhile, Chaihu also mobilizes the immunoregulatory mechanism and enhances the immune response, thus regulating immunity and improving the immune status of children.

*Scutellaria baicalensis*, artificial *Oxalis* and other medicines have the effects of clearing heat, removing toxins and killing viruses. The combination of Chaihu as the principal medicine can clear the heat, while the use of *Astragalus* can reduce qi stagnation and the combination of the two can treat by clearing and nourish qi strengthening the immune system, effectively alleviate the symptoms and improve the therapeutic effect. Some studies have shown that baicalin can inhibit the expression of EV-71 three-dimensional polymerase and inhibit RD cell apoptosis induced by EV-71 viral infection by inhibiting the Fas Cell Surface Death Receptor (Fas)/Fas Ligand (FasL) signaling pathway<sup>[19]</sup>. Cornflower, balsam, *Houttuynia cordata* and other conductive medicines have the efficacy of clearing heat and detoxifying toxins, draining pus and resisting pathogenic microorganisms<sup>[20,21]</sup>. As auxiliary medicines, *Rehmannia* root can produce fluid, quench thirst and azuki bean can diuretically reduce swelling. The clinical evaluation of this formula which was provided by Wu *et al.* showed that it can be applied to effectively treat acute pharyngitis. In conclusion, Ertong Qingyan Jiere oral liquid possessed a good safety in herpangina treatment. Its application with interferon- $\alpha$ 1b spray on joint can significantly relieve the symptoms of herpangina, downregulate the level of inflammatory factors to accelerate the healing of skin-mucous membrane and elevate the level of humoral immunity, thereby improving the anti-microbial and anti-viral ability<sup>[22,23]</sup>. Thus, the study proved that it shortened the course of disease and improved the total effective rate, deserving the clinical expansion. However, this paper was subjected to several limitations. It is necessary to further investigate and prove how the Ertong Qingyan Jiere oral liquid combined with interferon spray can elevate the inflammatory factor levels in children and through which channels they can enhance the immune functions of children.

**TABLE 1: COMPARISON OF THE TOTAL EFFECTIVE RATES OF CHILDREN, n (%)**

Group	n	Remarkably effective	Effective	Ineffective	Total effective rate
Observation	76	56 (73.7)	16 (21.1)	4 (5.2)	94.7 %*
Control	75	52 (69.3)	15 (20.0)	8 (10.6)	89.3 %

Note: \* $p < 0.05$  compared with the control group

**TABLE 2: COMPARISON OF SYMPTOM RELIEF INDICES OF CHILDREN (d,  $\bar{x}\pm s$ )**

Group	n	Time for temperature returning to normal	Time for herpes to subside	Time of salivation returning to normal	Time for starting normal diet
Observation	76	2.8±1.5*	3.6±1.3*	2.3±0.9*	2.1±0.9*
Control	75	3.7±1.4	4.6±2.2	3.7±1.4	3.1±1.2

Note: \*p<0.05 compared with the control group

**TABLE 3: COMPARISON OF INFLAMMATORY FACTORS ( $\bar{x}\pm s$ )**

Group	n	Time point	IL-7 (ng/l)	IL-10 (ng/l)	TNF- $\alpha$ (ng/l)
Observation	76	Before treatment	24.35±3.11 <sup>#</sup>	34.69±2.21 <sup>#</sup>	105.51±8.21 <sup>#</sup>
		After treatment	15.89±2.13	26.51±1.98	83.56±5.82
Control	75	Before treatment	24.28±4.18 <sup>#</sup>	34.34±3.18 <sup>#</sup>	105.48±9.31 <sup>#</sup>
		After treatment	16.19±3.56	27.64±1.97	85.25±5.78

Note: \*p<0.05 and <sup>#</sup>p<0.05 compared with the control group after treatment

**TABLE 4: COMPARISON OF HUMORAL IMMUNE INDICES OF CHILDREN BEFORE AND AFTER TREATMENT (g/l,  $\bar{x}\pm s$ )**

Group	n	Time points	IgA	IgM	IgG
Observation	76	Before treatment	1.11±0.11 <sup>#</sup>	0.84±0.21 <sup>#</sup>	7.16±2.21 <sup>#</sup>
		After treatment	1.61±0.14	1.82±0.35	10.51±2.82
Control	75	Before treatment	1.12±0.12 <sup>#</sup>	0.86±0.18 <sup>#</sup>	7.29±2.31 <sup>#</sup>
		After treatment	1.59±0.11	1.05±0.11	10.43±2.78

Note: \*p<0.05 and <sup>#</sup>p<0.05 compared with the control group after treatment

### Conflict of interests:

The authors declared no conflict of interests.

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