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Effects of Huangqi and bear bile on recurrent parotitis in children: a new clinical approach*

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Abstract: Objective: To evaluate the pharmacological effects of traditional Chinese medicine, bear bile capsule and Huangqi granule, on recurrent parotitis in children. Methods: In this prospective, controlled, and randomized study, a total of 151 young children were divided into three groups: Group A included massaging the children's parotid region and melting vitamin C in their mouth daily; Group B included swallowing bear bile capsule and Huangqi granule daily; and Group C included massages and vitamin C as prescribed in Group A, and traditional Chinese medicine as prescribed in Group B. Children were treated individually for one month and then a follow-up study was conducted for 1 to 3.5 years. Analysis of variance (ANOVA) and Ridit analysis were employed for statistical analysis. Results: The recurrence rate decreased in every group, but was significantly more in Groups B and C when compared to Group A. The recurrences significantly decreased (P<0.01) in Group B and their recovery rate was as high as 63%, significantly better than those of the other groups (P<0.01). Conclusions: Huangqi and bear bile could be a novel clinical approach for treating recurrent parotitis in children.

Key words: Juvenile recurrent parotitis, Therapy, Pediatrics, Traditional Chinese medicine, Prospective study
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1 Introduction

Juvenile recurrent parotitis (JRP) is the second most common infectious salivary gland disease during childhood after mumps. It is characterized by recurrent episodes of swelling and pain in the unilateral or bilateral parotid region over a period of years. There are no ideal treatments for this disease except for the usage of antibiotics in the acute inflammation stage. The acute symptoms bring the patients and their parents serious discomfort and ultimately hamper their normal life. Therefore, it is very important to find an effective method to cure this illness.

Traditionally, sialography was normally used to aid in the diagnosis and treatment of recurrent parotitis (Mu *et al*., 2003; Miziara and Campelo, 2005). Reports showed that sialography could assist in acquiring an 87% cure rate (Mu *et al*., 2003) because of the long lipiodol retention in the periphery of the gland (Katz *et al*., 2009; Schortinghuis *et al*., 2009). Currently, sialendoscopy is being used in the examination and treatment of JRP (Kopeć and Szyfter, 2010; Martins-Carvalho *et al*., 2010; Zenk *et al*., 2010; Konstantinidis *et al*., 2011). By means of sialendoscopy under general anesthesia, Martins-Carvalho *et al*. (2010) revealed that diagnostic sialendoscopy was possible in all pediatric patients and 84% of these patients could be treated endoscopically. Of the 18

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patients with stenosis of the parotid duct who underwent sialendoscopic dilation with intraductal corticosteroid administration, 14 patients showed no recurrence during a follow-up of about 24 months and only 4 patients developed a recurrence of symptoms after a remission of about 6 months. Under general anesthesia, Nahlieli *et al*. (2004) diagnosed and treated 26 patients by means of sialendoscopy and only 8% suffered from the recurrence during a 4–36-month follow-up period. However, these approaches require much cooperation from the patient and an adept surgeon during the whole procedure (Konstantinidis *et al*., 2011). Moreover, all these studies on sialendoscopy as a treatment modality lacked control groups. Therefore, the aim of this study is to search for an easier and non-invasive method to treat this illness.

Traditional Chinese medicine (TCM) originated in China several thousand years ago. It is one of the most important alternative medicines, emphasizing the concept of viewing the body and its functions as a whole and basing any treatment on syndrome differentiation (Xie, 2011). According to its philosophy, JRP belongs to the disease category where a build-up of exudate in the region of the salivary gland cannot easily be expelled by the person. Thus, the primary principle is to remove these toxic substances and promote subsidence of the swelling. In this study two preparations of TCM, Huangqi granule and bear bile capsule, were used to test the hypothesis that these TCMs could cure the disease to some extent.

Huangqi granule is a preparation of an extract of Radix Astragali. Modern pharmacological research has shown that Huangqi preparation can enhance myocardial contractility, improve circulation, protect myocardial cells, and regulate immunity (Cho and Leung, 2007a; 2007b; Fu *et al*., 2011; Liu *et al*., 2011). Bear bile, with its main pharmacological component ursodeoxycholic acid (UDCA, 3α,7β-dihydroxy-5β-cholan-24-oic acid), has been used in TCM for thousands of years. Modern investigations have shown that it contains a wide range of pharmacological actions with little toxicological side effects (Boatright *et al*., 2009). Based on the mentioned pharmacologic functions, both medicaments were used in the study to evaluate their efficacy on treating JRP.

2 Materials and methods

This study was conducted from 2007 to 2010 in the Department of Stomatology, Children's Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang Province, China, which covers the whole provincial population of over 7 million who is under the age of 18. One hundred fifty-one children were enrolled in this research for three years, including 99 males and 52 females, with an average age of 5.61 years. The distribution of ages among the three groups revealed no significant differences (Table 1).

Table 1 Age distribution between these three groups*

Group	Average age (year)	Age range (year)
A (n=50)	5.74±2.43	1.33–11.92
B (n=49)	5.68±2.33	1.92–13.00
C (n=52)	5.41±2.40	1.67–12.33

n: case number. *F=0.286, P=0.752, no statistical difference between the three groups

All participants displayed recurrent symptoms of soreness, a swollen parotid gland with or without snowflake-like purulent secretion, and with or without fever. The number of recurrences was at least twice (including the present time). Each year the recurrences before treatment were noted by the patients' parent(s), from which the total number of recurrences per patient was calculated. The patients who only suffered one episode of parotitis or whose B ultrasonography images showed stone in their salivary gland were excluded. All the patients received anti-inflammatory therapy during the acute period. Before the treatment, a bacterial sample was taken from the parotid duct of every patient. A bacterial culture and antimicrobial susceptibility test was done. If the treatment was not functioning as expected, we changed the antibiotics according to the test results.

A B-mode ultrasonography was performed twice. Ultrasonic inspection was performed during the first visit to confirm if there were stones in the parotid glands and to explore their swollen dimensions. If there were stones in the parotid glands, the patient was excluded from the study. Once pain and swelling

wore off after anti-inflammatory therapy, an ultrasonography was performed again to determine whether the glands recovered from the inflammation, which the echo of the ultrasonic image showed to be homogeneous.

Whilst the acute symptoms were under control, the patients were divided into three groups in order of their visit: Groups A, B, and C. Here, Group A served as a control group for Groups B and C receiving the studied medicines. In Group A the 50 patients were advised to have their parotid region massaged 5 to 6 times for 2 to 3 min daily, and those of 6 years old and over to keep vitamin C melting gradually in their mouth 3 times daily and those of under 6 years to taste vinegar 3 to 4 times daily to stimulate salivation. Forty-nine children in Group B took one bear bile capsule (0.25 g per capsule containing 0.05 g bear bile powder, Guangzhou Yongfutang Pharmaceuticals Ltd.) thrice daily if they were 6 years old or over or twice daily if they were under 6 years old. At the same time, the Group B patients took one packet of Huangqi granule (sugar-free, 4 g per packet and its main ingredient is Huangqi extract, Sichuan Baili Pharmaceuticals Ltd.) twice daily for children of 6 years old and over and once daily for children under 6 years old. The foresaid dosages of the Chinese medicines used are recommended by the manufacturers. The 52 children in Group C had their parotid massaged, kept vitamin C melting gradually in their mouth (the same usage as Group A), and took a bear bile capsule and Huangqi granule (the same usage as Group B). Each child was treated by this protocol for one month and their follow-up period was from 1.0 to 3.5 years [(2.47±0.74) years]. Whenever the patient's parotid glands became sore and swollen again, they were required to come to the clinic for an emergency treatment in which time the number of recurrence was calculated. The emergency treatment was antibiotic therapy for 3 to 5 d until the symptoms disappeared. No concomitant medications were used during the entire follow-up period except for the emergency therapy with antibiotics.

According to the recurrence numbers recorded during the whole follow-up period, the children were categorized into three groups at the end of this research: recovery, improvement, and invalidity. Recovery: no relapse during observation period. Improvement: recurrence frequency was between one to four times per year. Invalidity: recurrence frequency was more than five times per year. Two kinds of indicators were introduced, the total recurrence number and a cure rate, to compare the effectiveness among these three groups. The cure rate was calculated as the number of recovered children over the total number of children in that group, while the total recurrence number represented the total number of recurrence frequency during the follow-up period.

At the beginning of the study a description of the complete procedure and precautions was given to the children's parents/guardians and an informed consent was also received. This study's protocol was reviewed and approved by the Medical Ethics Committee at the Children's Hospital, School of Medicine, Zhejiang University, Hangzhou, China.

All data was entered into a computer database and SPSS 10.0 for Windows (Statistics Package for Social Science, SPSS Inc., Chicago, IL, USA) was used to perform the statistical analysis. The differences of the parotitis recurrence frequency between pre- and post-treatment and the differences of the follow-up period after treatment among the three groups were tested with one-way analysis of variance (ANOVA). The differences of treatment effectiveness among the three groups were tested by Ridit analysis (Liu and Su, 2005). Significance was established at a 5% level.

3 Results

All the patients displayed good compliance and completed the observation at the end of the study. No subjects dropped out during the follow-up period and no complications or side effects were observed.

There was a significant reduction of average recurrence frequency in all three groups (Fig. 1), especially for Groups B and C. As displayed on Table 2, the average recurrence frequency of Group A after treatment had statistically decreased to 2.68 compared to 4.32 before treatment (P=0.012). The medications of Group B decreased the average recurrence frequency significantly from 3.98 before treatment to 0.98 after treatment (P=0.000). In Group C, the average recurrence before treatment was 4.15, and after treatment, it significantly decreased to 1.31 (P=0.000).

As shown in Table 2 and Fig. 1, the average recurrence frequency before treatment for each group was about 4 yearly without significant difference among the three groups (P>0.05). After treatment, the difference between pre- and post-treatment for all three groups was found to be statistically significant with Groups B and C displaying a greater significance than Group A (P<0.001). After treatment a significant statistical difference existed between Groups A and B (P<0.001) and Groups A and C (P<0.05), whereas Groups B and C showed no statistical significance (P>0.05).

Table 2 Recurrence comparison among the three groups after different therapies

Group	n_{tr}		Average recurrence	
	Before treatment	After treatment	Before treatment	After treatment
A (n=50)	216	134	4.32	2.68
B (n=49)	195	48	3.98	0.98
C (n=52)	216	68	4.15	1.31

n: case number; n_{tr}: total number of recurrences. The results revealed significant difference among the three groups after different therapies

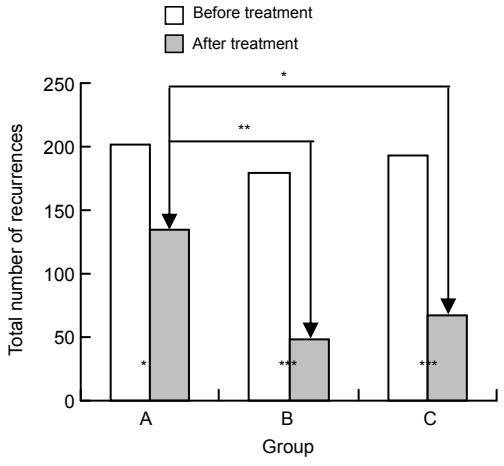

Fig. 1 Recurrence comparison among the three groups
* P<0.05, ** P<0.01, *** P<0.001, significant reduction of recurrence frequency

The cure rate of Group A was 28.00% (14/50), of Group B was 63.27% (31/49), and of Group C was up to 59.62% (31/52). The invalidity rate of Group A was 22.0% (11/50) and significantly higher than that of Group B, which was 8.16% (4/49), and Group C, which was 9.62% (5/52) (Fig. 2). According to the Ridit analysis, there existed a statistical difference between Groups A and B (P=0.001) and between Groups A and C (P=0.003). However, no statistical difference existed between Groups B and C (P= 0.701). Nevertheless, the cure rate was greatest and the invalidity rate lowest in Group B.

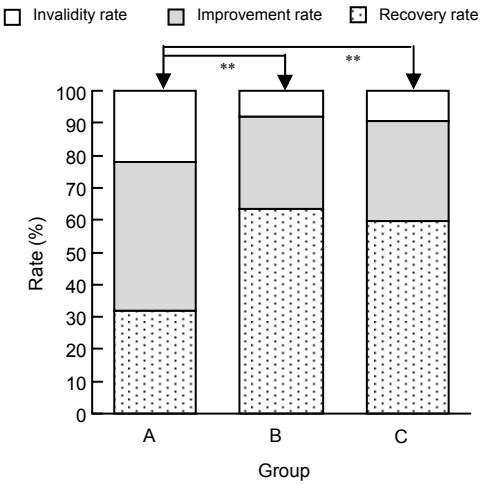

Fig. 2 Comparison of the recovery, invalidity, and improvement rates among the three groups after different therapies
There existed a significant difference (Ridit analysis) between Groups A and B, Groups A and C (** P<0.01), whereas no statistical difference existed between Groups B and C (P>0.05)

4 Discussion

JRP is defined as a recurrent parotid inflammation in children, a non-obstructive disease with episodes of mostly painful swelling of the gland, and with an etiology that remains an enigma. It is speculated that immunologic abnormality (Ruan *et al*., 2010), genetic factors, and duct malformations as well as bacterial infections (Zenk *et al*., 2010) comprise the main etiology. Vinagre *et al.* (2003) had excluded the main known respiratory viruses as the principal etiologic agents. Currently, there are three ways to treat parotitis: administration of antibiotics, treatment by sialography, and treatment under sialendoscopy. Taking antibiotics or non-steroid anti-inflammatory drugs via oral or other approaches is the basic method to treat this infection and it is always effective when used at the acute stage. However, due to the recrudescent characteristics of JRP, antibiotics are not always recommended to treat this disease, and

furthermore, drug resistance can be inevitable after repeated usage. Sialography is the basic method before the emergence of sialendoscopy. Lipiodol was injected into the duct and parotid tissue where it would remain for up to 28 months in the periphery of the gland (Schortinghuis *et al*., 2009) and exert the anti-bacterial properties of iodine. Katz *et al*. (2009) actively recommended this method due to its atraumatic and painless procedure after treating 840 patients. Even so, the process of injecting lipiodol is unacceptable in young children. On one hand, they are afraid of needle-type injections by nature, and on the other hand, the swollen pain they felt would be insufferable, which directly leads to their refusal unless under general anesthesia. As a novel instrument, sialendoscopy has become an important device for diagnosis and treatment. Sialendoscopy has not only cleared myxoma, pus, and epithelial cell debris that block the parotid duct but can also assist in rinsing that area with normal saline or other drugs. It can also extract stones that block the duct, which helps the recurrent inflammation to diminish (Martins-Carvalho *et al*., 2010; Konstantinidis *et al*., 2011). However, it would be very difficult to apply these methods to young children except if general anesthesia, or at least local anesthesia for older children, was administered (Martins-Carvalho *et al*., 2010). Unfortunately, general anesthesia is often refused by Chinese parents because of the possibility of side effects and unforeseen risks. And with the earliest onset age in this study being 1.3 years of age, it was imperative that a safe, simple, and convenient therapeutic method be found. Thus, the use of TCM was thought of and has confirmed to be effective on treating this kind of disease.

Thus far, the largest study (840 cases) was done by Katz *et al*. (2009), who observed 100% effectiveness for the children with first episode. However, for those who experienced a second recurrence or multiple recurrences, 98% acquired the recurrent symptoms during the follow-up period of 5.5 years with the number of recurrences ranging from 1 to 4 (average 2.5). This study results showed that bear bile capsule and Huangqi granule can significantly decrease the recurrent frequency and statistically increase the cure rate of the recurrent salivary gland inflammation. Over 63% of the patients recovered from the disease during the long observation period. This cure rate almost equaled 77.78% (14/18) rate reported by Martins-Carvalho *et al*. (2010) who applied sialendoscopy to JRP by means of general anesthesia. Bear bile had a positive effect on smooth muscle contraction while Huangqi promoted secretions from the gland tissue as well as stimulated the immune system (Cho and Leung, 2007a; 2007b; Liu *et al*., 2011). The cooperative use of bear bile and Huangqi, which unblocked the salivary duct and increased the secretions of saliva, can reconstruct the self-cleaning effect of the parotid gland. Once this process was accomplished, recovery was inevitable.

Although JRP has a tendency to resolve by age, usually in puberty, children with recurrent parotitis come to our clinic to seek for a better treatment for agony due to this disease. Hereby, Group A in this study was employed as a control group. In our understanding, massaging the children's parotid region and stimulating salivary secretion are helpful to the recovery of chronic parotitis. In fact, our research showed that the treatment in Group A can significantly decrease the recurrences. Compared to Group A, however, Group B produced greater pharmacological effects on the treatment of JRP. It can statistically decrease the recurrent numbers and increase the cure rate. The cure rate in Group B, up to 63%, was the highest among the three groups and this result indicated bear bile and Radix Astragali can be a better method to treat JRP. Due to lack of a placebo control group, further study should be done to rule out the potential role of placebo effect.

In the previous hypothesis, local massage and the stimulation of vitamin C were hypothesized to be a good addition with bear bile and Huangqi because of its ability to increase secretions and flush out the parotid gland. Thus, we postulated that Group C should be the best among the three groups. However, the results were not altogether conclusive. Group C did not show statistical significance over Group B and its recovery rate was even less than that of Group B (Fig. 2). One possible explanation could be the tissue destruction within the parotid gland. Ußmüller and Donath (1999) reported that a large amount of lymphocyte infiltration was found to affect the parotid gland tissue. It is these lymphocytes that replace the normal gland tissue, which leads to the loss of the gland's ability to secrete. In the researchers' opinion, the acid, i.e., vitamin C, stimulated the secretion of

saliva only when the gland tissue of the parotid was normal. As to a diseased parotid gland like recurrent parotitis, the same stimulation may result in aggravating the original disease instead. The researchers theorized that local massage and vitamin C would be effective only when the gland tissue started recovering or the recurrences were seldom, which implied less destruction of the glandular parenchyma.

5 Conclusions

The cooperative use of bear bile and Huangqi could statistically reduce the recurrence frequency and significantly increase the cure rate. This treatment protocol provided a good alternative way in the treatment of JRP.

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