Original Article

Evaluation on Common Hand, Foot, and Mouth Disease Treated by Integrative Traditional Chinese Medicine and Western Medicine

Guo-liang Zhang¹, Jian-bo Ding², Shuang-jie Li³, Xi Zhang⁴, Yi Xu⁵, Hua-sheng Yang², Dan Wei⁶, Qin Li⁷, Qing-sheng Shi⁸, Qing-xiong Zhu⁹, Tong Yang¹⁰, Zi-qiang Zhuo¹¹, Yi-mei Tian², Hao-jie Zheng¹², Liu-ping Tang¹³, Xin-ying Zou¹⁴, Tao Wen^{15*} and Xiu-hui Li^{2*}

Objective To evaluate the efficacy and safety of traditional Chinese medicine (TCM) combined with Western medicine in the treatment of patients with common hand, foot and mouth disease (HFMD) by conducting a prospective, controlled, and randomized trial.

Methods A total of 452 patients with common HFMD were randomly assigned to receive Western medicine alone (n = 220) or combined with TCM (Reduning or Xiyanping injections) (n = 232). The primary outcome was the incidence rate of rash/herpes disappearance within 5 days, while secondary outcomes included the incidence rate for fever, cough, lethargy, agitation, and vomiting clearance within 5 days.

Results The rash/herpes disappearance rate was 45.5% (100/220) in Western medicine therapy group, and 67.2% (156/232) in TCM and Western medicine combined therapy group, with significant difference ($P < 0.001$). Moreover, TCM remarkably increased the incidence rate of secondary disappearance, which was 56.4% in Western medicine therapy group and 71.4% in TCM and Western medicine combined therapy group ($P = 0.001$). No drug-related adverse events were observed.

Conclusions It's suggested that the integrative TCM and Western medicine therapy achieved a better therapeutic efficacy. TCM may become an important complementary therapy on relieving the symptoms of HFMD.

Key words: Hand, foot and mouth disease; Traditional Chinese medicine; Treatment; Reduning injection; Xiyanping injection

Hand, foot and mouth disease (HFMD) is a common infectious disease among children, which is commonly caused by enterovirus 71 (EV71) or coxsackievirus type A 16 (CVA16).¹⁻³ The clinical manifestations of HFMD always begin with typical fever, sore throat, headache, myalgia, tiredness

and anorexia. One or two days later, blisters appear in the mouth, and rashes develop on the cheeks, gums and tongue.^{4,5} In recent years, HFMD has become more common in Asia-Pacific region, and especially in China.⁶ A report by the Ministry of Health of China in 2010 documented that there were over one million

¹Department of Infectious Diseases, Anhui University of Traditional Chinese Medicine, Hefei, Anhui Province 230031, China

²Department of Integrated TCM and Western medicine, Beijing Youan Hospital affiliated to Capital Medical University, Beijing 100069, China

³Department of Communicable Diseases, Children's Hospital of Hunan Province, Changsha, Hunan Province 410007, China

⁴Department of Pediatrics, Kaifeng Children's Hospital, Kaifeng, Henan Province 475003, China

⁵Department of Pediatrics, Guangzhou Medical Center for Women & Children, Guangzhou, Guangdong Province 510623, China

⁶Department of Pediatrics, First Hospital affiliated to Guangxi Medical University, Nanning, Guangxi Province 530021, China

⁷Department of Infectious Diseases, Fuzhou Infectious Diseases Hospital, Fuzhou, Fujian Province 350025, China

⁸Handan Maternal and Child Health Hospital, Handan, Hebei Province 056001, China

⁹Children's Hospital of Jiangxi Province, Nanchang, Jiangxi Province 330006, China

¹⁰The People's Hospital of Liuzhou, Liuzhou, Guangxi Province 545006, China

¹¹Department of Pediatrics, Quanzhou Children's Hospital, Quanzhou, Fujian Province 362017, China

¹²Department of TCM, the Fifth Hospital in Shijiazhuang, Shijiazhuang, Hebei Province 050025, China

¹³Department of Pediatrics, Liuzhou Worker's Hospital, Liuzhou, Guangxi Province 545005, China

¹⁴Department of Pediatrics, Shenzhen Maternal and Child Health Hospital, Shenzhen, Guangdong Province 518017, China

¹⁵Beijing Institute of Hepatology, Beijing Youan Hospital affiliated to Capital Medical University, Beijing 100069, China

Correspondence: Xiu-hui Li, MD, E-mail: lixiuhui@sohu.com; Tao Wen, PhD, E-mail: wentao5281@163.com

Department of Integrated TCM and Western medicine, Beijing Youan Hospital affiliated with Capital Medical University, Beijing 100069, China

HFMD cases annually and more than 2 000 HFMD-associated deaths in China over the past 3 years.⁷ Commonly, HFMD is mild and self-limiting, with relief of symptoms within 7-10 days, but viruses can be detected in the stool for weeks after the symptoms dissipate.^{4,8} There are no specific treatments for HFMD at present. The most common treatment is to relieve symptoms by supportive therapy and the application of antivirals, antibiotics and immunopotentiators.^{5,8} According to the guidelines issued by the Ministry of Health of China,⁹ HFMD should be paid enough attention during the first five days in case it progress into severe conditions without immediate and effective intervention. Traditional Chinese medicine (TCM) was highly recommended by Ministry of Health of China for HFMD treatment.⁹ Previous reports showed that treatment with TCM could significantly alleviate disease symptoms.^{10,11} Reduning and Xianping injections have been widely used in clinical practice to alleviate the fever and inflammation associated with HFMD.^{12,13} In present study, we conducted a well designed prospective clinical trial with a sufficient sample size to observe the efficacy and safety of TCM in conjunction with conventional therapy in treating HFMD.

PATIENTS AND METHODS

Study design

A prospective, randomized, controlled and multicenter trial was conducted during the HFMD epidemic at 14 medical centers in China. A total of 452 eligible children with common HFMD were recruited. The study was conducted in accordance with the Declaration of Helsinki, approved by local ethics committees and institutional review boards as appropriate. All patients and their guardians agreed and provided signed written informed consent forms before enrollment.

Patient enrollment

The diagnosis of common HFMD was established according to the guidelines for the diagnosis and treatment of HFMD issued by the Ministry of Health of China in 2010.⁹ In addition, the following inclusion criteria were considered: aging 1-14 years old; no more than 48 hours after the occurrence of rash/herpes or fever symptoms.

Patients were excluded if they had other primary diseases such as congenital heart disease, chronic

hepatitis, acute or chronic nephritis, and blood diseases; with a history of allergy to herbal medicine; participating in other clinical studies on HFMD; with any condition that could interfere with the evaluation of our study's objectives.

In addition, enterovirus isolation and identification were performed in Clinical Test Center of Beijing Youan Hospital. Human EV71, Coxsackievirus A16 and enterovirus general type nucleotide acid detection kit were applied for the identification. During the recruitment phase, this notification was collated by assistants at each collaborating practice and reviewed by the trial investigators to exclude children who did not fulfill the eligibility criteria.

Sample size and randomization

Given that the previous clinical trials on evaluating Chinese herbal medicines in the treatment of HFMD were so limited, mostly due to small size of samples and no formal power calculations were obtained, and we therefore designed this study to recruit more samples ($n = 452$) from multiple centers in China to ensure a sufficient sample size and draw objective conclusions.^{13,14}

Participants were randomly assigned into two treatment groups using a web-based randomization system provided by China Academy of Chinese Medical Sciences, which adopted the computer telephone integration technology to integrate computer, internet and telecom.¹³ After eligibility had been determined and consent had been obtained, the trial identification number, date of birth and trial center name were entered into this randomization system. The random number list was generated by a statistician who was not involved in data collection or analysis. The researcher immediately informed a coordinator at each center who was blinded to the participants' characteristics to assign the participants to treatment. The participants were also blinded to the treatment assignment.¹³

Randomization was stratified by 14 medical centers, locating in Beijing, Anhui Province, Hunan Province, Henan Province, Guangdong Province, Guangxi Province, Fujian Province, Hebei Province and Jiangxi Province in China, which were selected to ensure broad geographic spread and representation of HFMD.¹³

Drug administration

Western medicine therapy was administered to patients

in both two groups according to the guidelines for the diagnosis and treatment of HFMD (China, 2010).⁹ In the integrated TCM and Western medicine therapy group, patients received Western medicine therapy combined with Reduning or Xiyanping injections. Reduning injection that consists of the following three herbs, qinghao (*Herba artemisia annua*), jinyinhua (*Lonicera japonica Thunb*), and zhizi (*Gardenia jasminoides Ellis*), is manufactured by GMP-certified Jiangsu Kangyuan Pharmaceutical, Inc., China. Xiyanping injection was light yellow to orange clear liquid, which is composed of total andrographolide sulfonate (manufactured by GMP-certificated Jiangxi Qingfeng Pharmaceutical, Inc., China). The criteria for the quality of Reduning or Xiyanping injections were in accordance with the Chinese pharmacopoeia (2005).¹⁵ Reduning injection was administered to patients at $0.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ by intravenous infusion (in 5% dextrose) whereas andrographolide sulfonate was administered $5\text{-}10 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ for intravenous infusion (in 5% dextrose).

Patients in two groups were followed-up every day during treatment period and for 3 days in post-treatment period.

Assessment of clinical outcomes

During the course of study, the presence of HFMD symptoms and drug-associated side effects were recorded routinely. Primary clinical outcome was the incidence rate of rash/herpes disappearance within 5 days, while secondary outcomes included the incidence rate for fever, cough, runny nose, lethargy and weakness, agitation or irritability, and vomiting clearance within 5 days. The intervention-related side effects were also recorded.

Statistical analysis

Categorical variables were expressed as percentages and analyzed by chi-squared test. Continuous variables were analyzed by unpaired *t*-test. All tests were in two-tailed, and *P* values less than 0.05 was considered statistically significant. All statistical procedures were performed with SAS software (version 9.2; SAS Institute, Inc., Cary, NC, USA).

RESULTS

Participants' characteristics

Total of 466 participants from 14 medical centers in 8 provinces in China were recruited, 14 of whom were

excluded due to no informed consents or not meeting inclusion criteria. In total, 452 participants were randomly assigned into two groups and included in a full analysis set (FAS).

The baseline demographic characteristics including gender, age, height, body weight and body temperature were similar between the two groups (Table 1), with no statistical differences, and thus were comparable.

Clinical outcomes

The study showed TCM and Western medicine combined therapy could effectively alleviate HFMD-associated symptoms compared with Western medicine therapy alone. With respects to the primary clinical outcome, the incidence rate of rash/herpes disappearance within 5 days was 45.5% (100/220) in Western medicine therapy group, and 67.2% (156/232) in TCM and Western medicine combined therapy group, with significant difference ($P < 0.001$) (Table 2). As for secondary clinical outcomes, TCM remarkably increased the incidence rate of fever, cough, lethargy and weakness, agitation or irritability disappearance within 5 days, which was 56.4% in the Western medicine therapy group and 71.4% in the TCM and Western medicine combined therapy group ($P = 0.001$) (Table 2).

In addition, Reduning or Xiyanping injections were both well tolerated. During the treatment, there were no drug-related side effects or adverse events observed in both groups.

DISCUSSION

Several clinical trials have assessed the efficacy and safety of TCM in treatment of HFMD,^{12,14} also with certain limitations. First, most trials were restricted to a small sample size, which yielded bias and did not reflect the general population of patients. Second, the findings of these trials were mostly reported in Chinese journals without translation into English and thus cannot be well recognized around the world. This is one of the first prospective, randomized and controlled trials to evaluate the efficacy and safety of herbal medicines, such as Reduning or Xiyanping injections, in the treatment of common HFMD. In conjunction with Western medicine, administration of TCM (Reduning or Xiyanping injections) significantly increased the rate of rash/herpes disappearance within 5 days after the onset of illness as well as relieving

Table 1. Characteristics for participants with common HFMD

Characteristic	Western medicine therapy group (n = 220)	TCM plus Western medicine therapy group (n = 232)	Statistical values	P values
Male, n (%)	144 (62.60)	156 (65.80)	$\chi^2 = 0.525$	0.469
Mean $\pm$ SD, years	1.97 $\pm$ 1.26	2.04 $\pm$ 1.43	$t = 0.582$	0.561
Body temperature (SD)	37.78 (0.73)	37.95 (0.72)	$t = 1.712$	0.088
Height (SD), cm	88.97 (13.94)	89.56 (13.52)	$t = 0.439$	0.661
Body weight (SD), kg	13.04 (3.77)	13.02 (3.5)	$t = 0.049$	0.961

Table 2. Analysis on the rates of rash/herpes or secondary outcomes disappearance in common HFMD

		Western medicine therapy group (n = 220)	TCM and Western medicine combined therapy group (n = 232)	χ^2	P values
The rates of rash/ herpes disappearance	Disappearance, n (%)	100 (45.5)	156 (67.2)	21.284	0.000
	Non-disappearance, n (%)	120 (54.5)	76 (32.8)		
The rates of secondary outcomes disappearance	Disappearance, n (%)	124 (56.4)	165 (71.4)	11.110	0.001
	Non-disappearance, n (%)	96 (43.6)	66 (28.6)		

other symptoms such as fever, cough, fatigue and irritation related to HFMD. Based on these clinical observations, we may suggest that TCM in the form of Reduning or Xiyanping injections is a complementary medication in HFMD treatment.

Reduning injection, one of the famous traditional Chinese preparations, consists of three herbs, *Herba artemisia annua*, *Lonicera japonica* Thunb, and *Gardenia jasminoides* Ellis.¹² The mechanism of Reduning injection in treatment of HFMD is yet to be elucidated. It has been reported that artemisia annua has numerous biological functions such as antimicrobial and antiparasitic properties.¹⁶ *Lonicera japonica* Thunb and *Gardenia jasminoides* are known for their abilities to remove heat and toxic materials and to relieve inflammation.¹⁷ These herbs are widely used as important components in TCM formulas in clinical settings. It is speculated that the synergy of the three individual herbs is responsible for the therapeutic efficacy of Reduning injection in the treatment of common HFMD.

The main bioactive compound in Xiyanping injection is herb-derived compound andrographolide sulfonate, which is obtained from a popular Chinese herb *andrographis paniculata* (Burm) Nees.¹³ Andrographolide sulfonate is known to have many types of bioactivity, such as declining body temperature and relieving inflammation.¹⁸ It has an effectively antithermic and antibacterial role to infections caused by various virus and bacteria.^{13,18} It is likely that this mechanism is responsible for the clinical improvement that is observed in our study. More rigorous studies are needed to clarify the mechanisms of TCM in treating HFMD.

In summary, our study provides evidence that

TCM, in the form of both Reduning and Xiyanping injections, can be safely used in the treatment of common HFMD. TCM can serve as a complementary medication to Western medicine, which accelerates the resolving symptoms of HFMD and should be highlighted in clinical settings.

Competing interests

The authors declare that they have no competing interests.

Acknowledgement

This work was supported by State Administration of Traditional Chinese Medicine of China Research Project (200907001-3).

REFERENCES

1. Fan X, Jiang J, Liu Y, Huang X, Wang P, Liu L, et al. Detection of human enterovirus 71 and Coxsackievirus A16 in an outbreak of hand, foot, and mouth disease in Henan Province, China in 2009. *Virus Genes* 2013;46(1):1-9.
2. Wu Y, Yeo A, Phoon MC, Tan EL, Poh CL, Quak SH, et al. The largest outbreak of hand, foot and mouth disease in Singapore in 2008: the role of enterovirus 71 and coxsackievirus A strains. *Int J Infect Dis* 2010;14(12):e1076-1081.
3. Zhu J, Luo Z, Wang J, Xu Z, Chen H, Fan D, et al. Phylogenetic analysis of enterovirus 71 circulating in Beijing, China from 2007 to 2009. *PLoS One* 2013; 8(2):e56318.
4. Zhang J, Sun J, Chang Z, Zhang W, Wang Z, Feng Z. Characterization of hand, foot, and mouth disease in China between 2008 and 2009. *Biomed Environ Sci* 2011;24(3):214-221.
5. Zhou H, Guo S, Zhou H, Zhu Y, Zhang L, Zhang W. Clinical characteristics of hand, foot and mouth disease in Harbin and the prediction of severe cases. *Chin Med J (Engl)* 2012;125(7):1261-1265.
6. Zhu Q, Hao Y, Ma J, Yu S, Wang Y. Surveillance of hand, foot,

- and mouth disease in mainland China (2008-2009). *Biomed Environ Sci* 2011;24(4):349-356.
7. Ministry of Health of The People's Republic of China. Report of epidemic situation of infectious disease in China from January of 2010 to January of 2011. <http://www.moh.gov.cn/publicfiles/business/htmlfiles/mohjbyfkzj/s3578/201102/50646.htm>.
 8. Tian H, Yang QZ, Liang J, Dong SY, Liu ZJ, Wang LX. Clinical features and management outcomes of severe hand, foot and mouth disease. *Med Princ Pract* 2012;21(4):355-359.
 9. The Ministry of Health of the People's Republic of China, Guideline for the Diagnosis and Treatment of Hand Foot and Mouth Disease, Beijing, China, 2010.
 10. Xue B, Yao Z, Yu R. Studies on anti-EV71 virus activity of traditional Chinese medicine and its clinical application in treatment of HFMD. *Zhongguo Zhong Yao Za Zhi (Chin)* 2011;36(23):3366-3370.
 11. Lin TY, Liu YC, Jheng JR, Tsai HP, Jan JT, Wong WR, et al. Anti-enterovirus 71 activity screening of chinese herbs with anti-infection and inflammation activities. *Am J Chin Med* 2009;37(1):143-158.
 12. Mu Y, Chen X, Zhang A. Effect of reducing injection on HFMD in children: a randomized controlled trial. *Zhongguo Zhong Xi Yi Jie He Za Zhi (Chin)* 2011; 31(9):1209-1212.
 13. Li X, Zhang C, Shi Q, Yang T, Zhu Q, Tian Y, et al. Improving the efficacy of conventional therapy by adding andrographolide sulfonate in the treatment of severe hand, foot, and mouth disease: a randomized controlled trial. *Evid Based Complement Alternat Med* 2013; 2013:316250.
 14. Cao HJ, Liu ZL, Steinmann P, Mu YJ, Luo H, Liu JP. Chinese herbal medicines for treatment of hand, foot and mouth disease: A systematic review of randomized clinical trials. *Eur J Integr Med* 2012; 4(1):e85-e111.
 15. Pharmacopoeia Committee of People's Republic of China, Chinese Pharmacopoeia, Chemical Industry Press, Beijing, China, 2005 edition, 2005.
 16. Wang C, Cao B, Liu QQ, Zou ZQ, Liang ZA, Gu L, et al. Oseltamivir compared with the Chinese traditional therapy maxingshigan-yinqiaosan in the treatment of H1N1 influenza: a randomized trial. *Ann Intern Med* 2011;155(4):217-225.
 17. Zu M, Zhou D, Gao L, Liu A, Du G. Evaluation of Chinese traditional patent medicines against influenza virus in vitro. *Yao Xue Xue Bao (Chin)* 2010; 45(3):408-412.
 18. Lu C, Liu X, Ding X, Chen X, Fan H, Liu Y, et al. A metabolomics profiling study in hand-foot-and-mouth disease and modulated pathways of clinical intervention using liquid chromatography/quadrupole time-of-flight mass spectrometry. *Evid Based Complement Alternat Med* 2013; 647452.