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Effect of heat-clearing and detoxifying Chinese medicines combined with conventional therapy on mild hand, foot, and mouth disease with fever

An individual patient data meta-analysis

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Abstract

Background: In China, heat-clearing and detoxifying Chinese medicines combined with conventional therapy are commonly applied to treat the mild hand, foot, and mouth disease (HFMD). However, there is lack of solid evidence on the efficacy and safety of such therapies.

Methods: We conducted a pooled analysis with individual patient data from 5 strictly randomized controlled clinical trials to assess the efficacy and safety of this combination therapy for mild HFMD. An intention-to-treat analysis was performed. A 2-stage meta-analysis method was adopted to analyze the pooled effect size.

Results: In total, 947 patients were included. Compared with conventional therapy, the combination therapy significantly reduced the progression rate of HFMD from mild to severe (odds ratio [OR] 0.43, 95% confidence interval [CI]: 0.22 to 0.83, $P=.01$). Meanwhile, the healing time of skin rash and oral ulcer in the combination therapy group was significantly shorter than that of conventional therapy. The overall hazard ratio (HR) of healing time of the skin rash or oral ulcer was 1.22 (95%CI: 1.04 to 1.43; $P=.02$). However, except Jinlianqingre effervescent tablets, the combination therapy cannot shorten the time to fever resolution (HR 1.12, 95% CI: 0.97 to 1.29, $P=.14$). Because of the heterogeneity, Jinlianqingre effervescent tablets were analyzed separately and the HRs of the time to fever resolution and the healing time of skin rash or oral ulcer were 3.88 (95%CI: 3.19 to 4.72; $P<.0001$) and 3.79 (95%CI: 2.81 to 5.11; $P<.0001$), respectively. There were 30 adverse events reported in total; 2 cases were related to Chinese medicines.

Conclusion: In conclusion, the heat-clearing and detoxifying Chinese medicines on top of conventional therapy can effectively reduce the progressive rate of mild HFMD and improve healing of skin and oral mucosal lesions. More studies are needed for the time to fever resolution.

Abbreviations: CFDA = Chinese Food and Drug Administration, CI = confidence interval, HFMD = hand, foot, and mouth disease, HR = hazard ratio, ITT = intention-to-treat, JET = Jinlianqingre effervescent tablets, JOS = Jinzhen oral solution, KOS = Kangbingdu oral solution, OR = odds ratio, RCT = randomized controlled trial, RI = Reduning injection, XI = Xiyanping injection.

Keywords: hand, foot, and mouth disease, individual patient data, pooled analysis, traditional Chinese medicine

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1. Introduction

Hand, foot, and mouth disease (HFMD), accompanied with clinical symptoms of prodromal fever and followed by pharyngitis, mouth ulcers, and rashes on hands and feet, is a common infectious disease among infants and young children.[1,2] HFMD has been widespread in Asia-Pacific regions for more than 30 years. Australia, Korea, India, Singapore, Malaysia, and China have reported the epidemic profile of HFMD.[2–6] In China, several large outbreaks of HFMD occurred in recent years, notably the latest in 2008.[7–9] Considering the severity of the outbreak, HFMD was included in the national class C infectious diseases by the Ministry of Health of China, and was monitored through the direct network reporting system. Since 2008, regional outbreaks of HFMD have been reported frequently in China.[10–14] According to the annual incidence reported by the Ministry of Health of China,[8] the incidence of HFMD is increasing in recent years.[15] As a consequence, more and more studies focus on the epidemic profile of HFMD. In 2014, 2 vaccines for HFMD have been approved by the Chinese Food and Drug Administration; however, they are not widely applied in the clinical practice.[16,17] Until now, there is no effective treatments available for HFMD, although symptom-relieving conventional therapies, especially Paracetamol and adequate fluid intake which are recommended by the World Health Organization, are widely adopted in the treatment of mild HFMD.[18]

In China, it is common practice to treat mild HFMD with heat-clearing and detoxifying Chinese medicines combined with conventional therapy. Many studies have shown that the combination therapy is effective against the mild HFMD. It can shorten the course of the disease and alleviate symptoms without obvious adverse effects.[19–22] In 2010, the Ministry of Health of China issued the "Guideline for the Diagnosis and Treatment of HFMD", and recommended a number of Chinese medicines in the treatment of mild HFMD.[18] In this guideline, the mostly recommended Chinese medicines are those with heat-clearing and detoxifying effects. All these medicines are proprietary drugs which are widely applied in clinical practice. Although most of these medicines were approved by Chinese Food and Drug Administration (CFDA) many years ago, few publications regarding their clinical efficacy on mild HFMD are available. The majority of existing studies on these medicines was observational with limitations including: inappropriate or even no control group, small sample size, lack of appropriate randomization and blinding design, and poor efficacious outcome measurements.[23] Randomized controlled trials (RCT) started to appear recently and this study aims to combine the individual data from 5 RCTs to assess the efficacy and safety on HFMD.

2. Methods

2.1. Data sources

The 5 RCTs included in this study are all sponsored by the State Administration of Traditional Chinese Medicine of China Support Project (No. 200907001) under the research program – "Research on clinical treatment program and diagnosis rule of traditional Chinese medicine against mild HFMD." This is the first project to conduct a number of RCTs to study the efficacy and safety of Chinese medicines for treating mild HFMD in China. The Chinese medicines used in the 5 RCTs were Kangbingdu oral solution (KOS), Jinzhen oral solution (JOS), Reduning injection (RI), Xiyanping injection (XI), and Jinlianqingre effervescent tablets (JET). The protocols of the 5 RCTs were similar, especially with respect to their inclusion and exclusion criteria of patients, diagnostic criteria of mild HFMD, conventional treatment arrangements, outcomes, follow-up points, and duration of treatment. Strict quality control measures were used in data management and processing. All 5 trials used the central randomization system of the institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences to randomize participants based on block randomization. JOS and JET adopted double blinding (dummy of JOS or JET) and the other trials were open label trials.

This study was an individual data meta-analysis, and it did not provide any intervention to patients or collect any patients' data. In addition, all 5 the clinical trials had approved by the institutional review board of their investigation hospitals. Therefore, the ethical review was waived.

2.2. Intervention

In all 5 trials, all participants received an identical conventional therapy and on top of the conventional therapy 1 of the 5 medications (ie, KOS, JOS, RI, XI, or JET) was added in the treated group. The exact herbal components of each 5 medications were showed in Table 1. According to the guideline for the diagnosis and treatment of HFMD,[18] the treatment regimens in conventional therapy included oral care, skin care, reduction of temperature by applying physical cooling paste or warm bathing and vitamin B, vitamin C. Depending on physician's judgment, participants received the Ibuprofen suspension if body temperature was higher than 38.5°C.

The patients from both control and treated groups received their study therapy for 7 days. Data were recorded every day during the treatment period. All participants' informed consents were written by their guardians.

Table 1

The components of 5 analyzed Chinese medicines.

KOS	JOS	RI	XI	JET
Isatis root, gypsum, reed root, raw rehmannia, tulip, anemarrhena, acorus tatarinowii, patchouli, forsythia	Antelope horn, fritillaria, rhubarb, scutellaria, gypsum, artificial bezoar, liquorice	Artemisia annua, honeysuckle and gardenia	Total ester sulfonate of andrographolide	Antelope horn, fritillaria, rhubarb, scutellaria, bezoar, bluestone, gypsum, liquorice

JET = Jinlianqingre effervescent tablets, JOS = Jinzhen oral solution, KOS = Kangbingdu oral solution, RI = Reduning injection, XI = Xiyanping injection.

2.3. Inclusion criteria and data collection

As the main cooperating institution of the project, the institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences provided the logistic support for the whole project, which included randomization, drug blinding, data entry, data verification and data analysis. So the 5 datasets were checked and verified by the same standard operation procedure of data cleaning and integrity. Patients were diagnosed according to the Guideline for the Diagnosis and Treatment of HFMD.[18] The inclusion criteria were:

1) children aged from 1 to 13 years;
2) presentation of fever between 37.4°C and 39.0°C;
3) skin rash;
4) within 48 hours from the beginning of the HFMD syndromes.

The following data were extracted from the individual dataset of 5 trials and pooled together to be analyzed: age, sex, body temperature, skin rash and oral mucosal lesions at baseline and every day's visit; progression of HFMD, treatment group, use of Ibuprofen suspension, and any adverse event recorded. All the 5 trials used the standardized data collection methods and questionnaire.

2.4. Endpoints

The primary outcome was progression rate defined as the proportion of HFMD participants progressed from mild to severe condition during the follow-up. The severity of HFMD was assessed by investigator according to the guideline for the diagnosis and treatment of HFMD in the 5 studies.[18] The assessment was blinding for the investigator in JET and JOS, and it was not blinding in KOS, RI, and XI. The clinical diagnostic of mild HFMD was established, if the patient had at least 1 of the following symptoms accompanied or not accompanied by fever: maculopapular of vesicular rash on the palms and/or soles and vesicles and/or ulcers in the mouth. Severe HFMD was diagnosed if the patient had any of the following additional symptoms involving the nervous system: lethargy, weakness, agitation, irritability, headache, vomiting, limb weakness, acute flaccid paralysis, myoclonic jerks, ataxia, nystagmus, and oculomotor palsies. In this guideline, fever is a typical symptom of mild HFMD. Fever resolution was defined as body temperature below 37°C for 24 hours after the first intake of the treatment. Time to fever resolution was calculated as the time elapsed between the first intake of the treatment and fever resolution. The severity of skin rash (on hands, feet, hip, chest, back, limbs, and Coccyx area) and of oral mucosal lesions was recorded daily by using a symptom score (1 = absent, 2 = mild, 3 = moderate, and 4 = severe). The healing time of skin rash or oral ulcer was defined as the time elapsed between the first intake of the treatment and skin rash or oral ulcer completely disappearance.

2.5. Statistical analysis

The individual patient data of the 5 trials was pooled together and analyzed. An intention-to-treat (ITT) analysis was performed. Baseline characteristics of patients were compared within each trial and in combination. A 2-stage meta-analysis method was adopted to analyze the pooled effect size.[24] The q-test was used to test the heterogeneity among different trials. If the P value was less than .10, a random effects model (DerSimonian–Laird method) was applied. Otherwise, the fixed-effect model (Mantel–Haenszel method) was used.

All tests were performed by using a 2-sided significance level at 0.05. Review Manager (RevMan) version 4.2 for Windows, which is provided by the Nordic Cochrane Centre (Nordic Cochrane Collaboration, 2003) in Copenhagen, was used for testing heterogeneity and pooling the data. For other analyses, Statistical Analysis System (SAS, version 9.4, SAS Institute, Cary, NC) was used.

3. Results

A total 947 patients were included. Patient demographic and baseline characteristics for the 5 RCTs are shown in Table 2. The characteristics were similar and no significant among 5 trials. The Figure 1 described the different features of 5 Chinese medicines on the 3 outcomes with their odds ratios (OR)/hazard ratios (HR) point estimates based on the individual patient data. Except JET, the effects of the remaining trials were close on the 3 outcomes, so we conducted pooled analyses to explore the overall effects. The estimates of the time of fever resolution and the healing time of the skin rash or oral ulcer almost overlap among the 5 trials.

3.1. The progressive rate of HFMD

JET was not included because there was no patient progressed to the severe HFMD. No heterogeneity was detected ($P = .45$) among other 4 trials. The progressive rate of HFMD was significantly lower in the combination therapy than conventional therapy alone; the pooled OR was 0.43 (95%CI: 0.22 to 0.83; $P = .01$) (Fig. 2).

3.2. Time to fever resolution

Because of heterogeneity ($I^2 = 97\%$, $P < .001$), JET was not included in the pooled analysis. For the remaining 4 trials, the overall time to fever resolution was no significance between combination therapy and conventional therapy; the pooled HR was 1.12 (95%CI: 0.97 to 1.29; $P = .14$) (Fig. 3). The HR of JET was 3.88 (95%CI: 3.19 to 4.72; $P < .0001$).

3.3. The healing time of the skin rash or oral ulcer

Similar with the outcome above, JET was not included in the pooled analysis because of the heterogeneity ($I^2 = 97\%$, $P < .001$). The pooled analysis showed that the overall HR of healing time of the skin rash or oral ulcer in 4 trials was 1.22 (95%CI: 1.04 to 1.43; $P = .02$) (Fig. 4). The HR of JET was 3.79 (95%CI: 2.81 to 5.11; $P < .0001$).

3.4. Safety analysis

With respect to safety, 30 adverse events were reported in the 5 RCTs, including 11 (2.26%) in the combination therapy groups and 19 (4.13%) in the conventional therapy group ($P = .1365$, Table 3). No serious adverse event was reported. One case of right radial fracture was reported in RI trial. Two diarrhea cases were mentioned in the combination group of XI, which is possibly related to XI. Nine and 18 adverse events were reported in combination and conventional therapy group of JOS, respectively; these cases were not related to JOS, following the

Table 2

Patient characteristics and baseline information.

Items	N	KOS		RI		XI		JOS		JET	
		Combination	Conventional	Combination	Conventional	Combination	Conventional	Combination	Conventional	Combination	Conventional
Starting and ending dates		May to October, 2010		May to September, 2010		June to October, 2010		July to November, 2010		June to July, 2011	
N (%)	**947**	63 (44.68)	78 (55.32)	97 (47.78)	106 (52.22)	64 (44.76)	79 (55.24)	93 (54.10)	79 (45.90)	144 (50.00)	144 (50.00)
Mean age (SD), yr	**2.55 (1.41)**	2.77 (1.55)	2.60 (1.24)	2.53 (1.43)	2.58 (1.57)	2.42 (1.11)	2.33 (0.95)	2.41 (1.42)	2.47 (1.34)	3.47 (2.36)	3.72 (2.69)
Male, n (%)	**308 (63.24)**	36 (57.14)	44 (56.41)	61 (62.89)	68 (64.15)	43 (67.19)	56 (70.89)	55 (59.14)	57 (72.15)	82 (56.94)	100 (69.44)
Mean temperature (SD), °C	**38.11 (0.51)**	38.20 (0.74)	38.06 (0.65)	38.15 (0.57)	38.25 (0.53)	38.15 (0.54)	38.13 (0.50)	38.05 (0.45)	38.05 (0.49)	38.12 (0.32)	38.03 (0.34)
Temperature, n (%)											
37.4–38.5°C	**377 (77.41)**	46 (73.02)	58 (74.36)	78 (78.79)	70 (75.27)	58 (80.56)	67 (77.91)	73 (78.49)	65 (82.28)	134 (93.06)	133 (92.36)
38.5–39.0°C	**110 (22.59)**	17 (26.98)	20 (25.64)	21 (21.21)	23 (24.73)	14 (19.44)	19 (22.09)	20 (21.51)	14 (17.72)	10 (6.94)	11 (7.64)
Median symptom score† (IQR)	**11 (10-12)**	11 (10-12)	11 (10-12)	11 (10-12)	12 (10-13)	10 (9-11)	10 (9-12)	13 (10-15)	11 (9-14)	10 (10-11)	10 (10-11)
Typical symptom, *n (%)*											
Hands	**449 (95.88)**	60 (94.24)	74 (94.87)	87 (89.69)	101 (95.28)	56 (87.50)	71 (89.87)	77 (82.80)	66 (83.54)	139 (96.53)	140 (97.22)
Feet	**433 (93.44)**	55 (87.30)	73 (93.59)	82 (84.54)	97 (91.51)	58 (80.62)	68 (86.08)	77 (82.80)	62 (78.48)	125 (86.81)	134 (83.06)
Oral mucosal lesions	**449 (98.47)**	55 (87.30)	71 (91.03)	94 (96.91)	100 (94.34)	60 (93.75)	69 (88.46)	92 (98.82)	75 (94.84)	144 (100.0)	144 (100.0)
Chest, back, and Limbs	**63 (12.94)**	15 (23.81)	14 (27.95)	4 (4.12)	13 (12.26)	6 (9.37)	11 (13.92)	4 (4.30)	4 (5.06)	6 (4.17)	6 (4.17)
Coccyx area	**109 (22.38)**	8 (12.70)	11 (14.10)	20 (20.62)	43 (40.57)	12 (18.75)	15 (18.89)	25 (26.91)	17 (21.52)	20 (13.89)	24 (16.67)
Hip	**289 (59.34)**	34 (53.97)	40 (51.28)	65 (67.01)	76 (71.70)	29 (45.31)	45 (56.86)	47 (50.54)	40 (50.63)	49 (34.03)	37 (25.69)

IQR=interquartile range, JET = Jinlianqingre effervescent tablets, JOS = Jinzhen oral solution, KOS = Kangbingdu oral solution, RI = Reduning injection, XI = Xiyanping injection.

† Symptoms were hands, feet, oral mucosa lesions, chest, back and limbs, coccyx area, and hip. Each symptom was scored as 0 (none), 1 (mild), 2 (moderate), or 3 (severe).

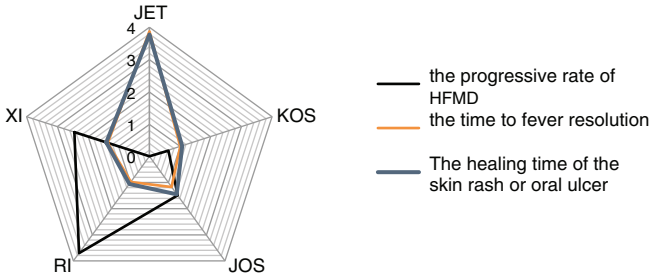

Figure 1. The effects of 5 Chinese medicines on the 3 outcomes.

judgment of the doctor. No adverse event was reported in JET and KOS.

4. Discussion

Our study indicated that the heat-clearing and detoxifying therapy can reduce the progressive rate of mild HFMD and healing time of skin rash or oral ulcer, compared with the conventional therapy. The principle of treatment and methods of treatment are the basic principle which are followed in the TCM clinical practice. The methods of treatment in TCM actually represents a kind of drugs with similar pharmacological properties or a kind of prescriptions with similar efficacy. Heat-clearing and detoxifying therapy is a main and common method of treatment and have anti-inflammatory and antimicrobial effects. Heat-clearing and detoxifying therapy usually applied as a complementary treatment against acute infectious diseases, for instance, influenza, mumps, meningitis and HFMD, as well in China and is mostly recommended by the "Guideline for the Diagnosis and Treatment of HFMD," which was issued by the Ministry of Health of China. However, there is no verified clinical evidence of their efficacy on HFMD. A meta-analysis showed that Chinese medicines may have an effect on reducing the fever clearance time, rash subsidence time, and healing times of oral symptoms.[19] However, the methodological quality of the included clinical studies was generally poor. In addition, the efficacy outcome was subjective and classified into 4 grades ("curative", "markedly effective", "effective" or "ineffective").[20–24] In our study, the individual patient data was pooled and analyzed from 5 strictly high-quality RCTs which were conducted under similar protocols and produced datasets built with the same structure. Compared with the surrogate endpoints classified 4 grades ("curative", "markedly effective", "effective" or "ineffective"), the progressive rate of HFMD is more objective and can directly reflect the true effect of the treatment. Our study suggested the progressive rate of HFMD was significantly lower under the combination therapy than the conventional therapy. No previous clinical study reported the progressive rate of

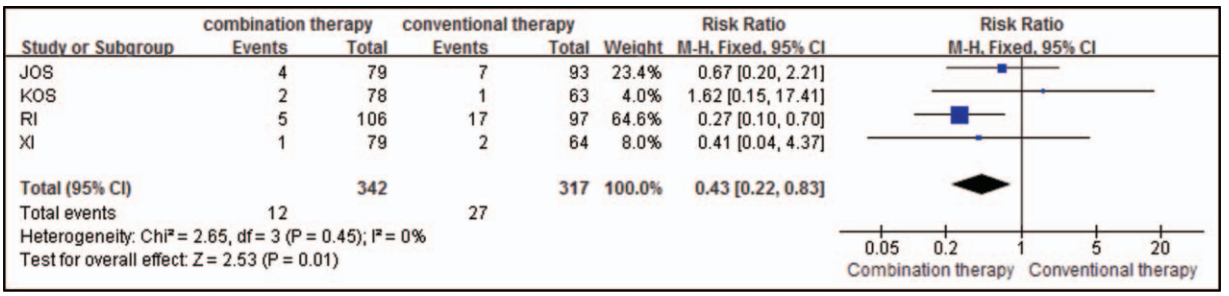

Figure 2. Forest plot of the progressive rate of hand, foot, and mouth disease.

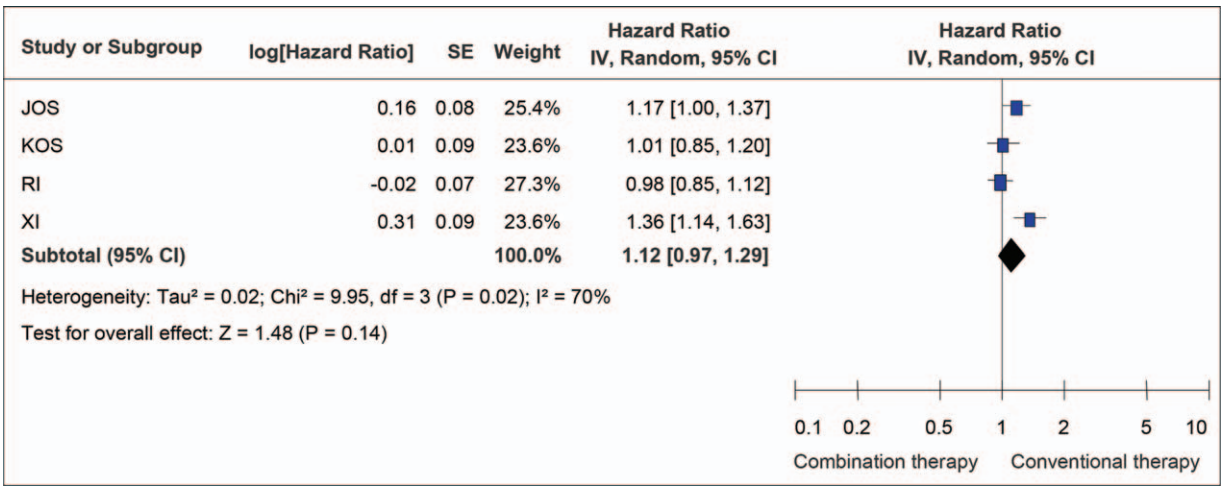

Figure 3. Forest plot of the time to fever resolution.

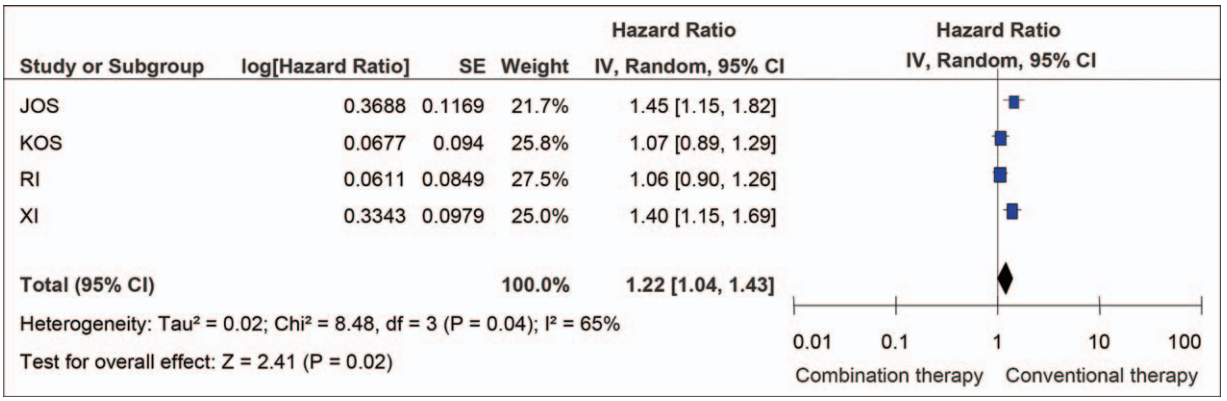

Figure 4. Forest plot of the healing time of the skin rash or oral ulcer.

HFMD, which was used here for the first time as primary outcome in the trials of Chinese medicines administered to treat HFMD.

Several studies have demonstrated that fever is an important endpoint and the total duration of fever ≥ 3 days, peak temperature ≥ 38.5°C, and history of lethargy were identified as risk factors for the neurological involvement in mild HFMD.[22,23,25,26] Our results suggested that the combination therapy in JET can significantly shorten the time to fever resolution; while JOS, KOS, RI, and XI had no effect on the fever resolution. This might be explained with the ingredients in the medicine. Although there is gypsum (SHIGAO) in KOS, JOS, and JET, have antipyretic effect and commonly used to the treatment of febrile diseases in traditional Chinese medicine,[27,28] the remaining components are not completely same in the 3 drugs. For JET, the further study about the antipyretic mechanic is needed.

With regarding to the healing time of skin rash or oral ulcer, our results indicated that the combination therapy can shorten the healing time, compared with the conventional therapy. For JET, although it was not included in the pooled analysis, the separate results showed that it can shorten the time to fever resolution and the healing time of skin rash or oral ulcer and its effects were greater than the overall estimates of the remaining trials.

In general, heat-clearing and detoxifying Chinese medicines combined with conventional therapy can reduce the progression rate of mild HFMD and shorten the healing time of skin rash or oral ulcer. For JET, it also can shorten the time to fever resolution. These findings are consistent with previous observational studies and clinical trials.[22,23,25,26] The safety analysis suggested that the 5 Chinese medicines were safe. The diarrhea cases in XI might be related to the cooling function with its component, andrographis paniculata. Compared with the previous studies, our results were based on individual patient data from 5 strictly randomized controlled trials and adopted more objective outcomes; it could provide strong evidences in favor of the efficacy of heat-clearing and detoxifying Chinese medicines combined with conventional therapy on treating mild HFMD. However, this study also has some limitations. First of all, because all patients were febrile cases, the efficacy of heat-clearing and detoxifying Chinese medicines on the afebrile mild HFMD calls for further researches. Secondly, for the effects on fever, more studies are needed. Thirdly, this study depended on the 'guideline for the diagnosis and treatment of HFMD' of China when determining the inclusion criteria, the progression rate of HFMD, and the cure of HFMD. However, the guideline was not the one accepted worldwide. And as the primary outcome, the progression rate of HFMD was not widely used for the severity and improvement degree of HFMD. Its significance need be proved in the future. Finally, the mechanic of heat-clearing and detoxifying Chinese medicines treatment on mild HFMD is unconcern and needed to be explored in the further study.

Table 3

Adverse events of the 5 trials.

Trials	Conventional therapy	Combination therapy
KOS	0	0
XI		
Diarrhea	2	0
RI		
Right radial fracture	0	1
JET	0	0
JOS		
Bronchopneumonia	1	1
Encephalitis	4	8
Enteritis	0	1
Symptomatic sinus tachycardia	0	1
Transiently increased lactate dehydrogenase	4	5
Transiently increased alanine transaminase	0	2
Total	11	19

JET = Jinlianqingre effervescent tablets, JOS = Jinzhen oral solution, KOS = Kangbingdu oral solution, RI = Reduning injection, XI = Xiyanping injection.

5. Conclusion

The heat-clearing and detoxifying Chinese medicines combined with conventional therapy can reduce the progressive rate of HFMD from mild to severe and shorten the healing time of skin rash or oral ulcer. For JET, it also can shorten the time of fever resolution. This study provides a good choice for doctors to treat mild HFMD.

Author contributions

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Supervision: Baoyan Liu.
Writing – original draft: Shiyan Yan.
Writing – review & editing: Ying Lu.

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