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CLINICAL STUDY

Reduning injection for fever, rash, and ulcers in children with mild hand, foot, and mouth disease: a randomized controlled clinical study

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Abstract

OBJECTIVE: To assess the efficacy and safety of Reduning injection for fever, rash, and ulcers in children with mild hand, foot, and mouth disease (HFMD).

METHODS: A stratified-block randomized, double-blind, parallel-controlled, and multicenter clinical trial was conducted with 360 patients in five hospitals across China: Quanzhou Children's Hospital, Shijiazhuang No. 5 Hospital, Shanghai Public Health Centre, Hunan Provincial Children's Hospital, and Kaifeng Children's Hospital. Patients were randomized into three groups with 120 in each. Group A was treated with Western Medicine, group B with Reduning injection, a Chinese herbal medicine, and group C with both Reduning injection and Western Medicine. Results were compared for treatment efficacy and safety on HFMD. The clinical outcomes were observed as follows: fever and onset time of antifebrile effect (time to bring the body temperature down ≥0.5℃ after medication); cumulative time for fever recovery (body temperature recovering to normal and lasting more than 24 h without medication); cumulative time for rash disappearance (without new rashes or ulcers appearing and the original ones fading away); and cumulative time for mouth ulcer disappearance.

RESULTS: For the onset time of the antifebrile effect, there was no statistical difference between groups A and B (P>0.05) and groups B and C (P> 0.05). However, there was a statistical difference between groups A and C (P<0.05), and the effect in

group C was the best. For the cumulative time for rash disappearance, there was no statistical difference between groups A and B (P>0.05). There were statistical differences between groups A and C, and groups B and C (P<0.05), and the effect in group C was the best. For the cumulative time for mouth ulcers disappearance, there were no statistical differences among the three groups (P>0.05).

CONCLUSION: Reduning injection with Western Medicine for symptomatic treatment is most effective for mild HFMD. No adverse reactions were observed.

Key words: Hand, foot and mouth disease; Symptomatic therapy; Randomized controlled trial; Treatment outcome; Reduning injection

INTRODUCTION

Worldwide, hand, foot, and mouth disease (HFMD) outbreaks have occurred frequently since its first report in 1958, posing a threat to public health, especially to children in the Asia-Pacific region.[1-6] The disease can be caused by more than 20 different enteroviruses, and its main manifestations are fever, rashes, and ulcers in areas such as the oral mucosa and the hands, feet and buttocks. The majority of HFMD cases are mild and self-limited, but some will experience severe complications, including aseptic meningitis, encephalitis, pneumonia, myocarditis, brain-stem encephalitis, acute flaccid paralysis, and even death. Unfortunately, the definition and standards of the warning index system for severe cases does not exist. Studies show that high fever (body temperature >39.1℃) correlates with patients' condition.[7] Therefore, it could be used as a positive indicator. Acute onset and rapid progression have made early intervention and detailed observation decisive for HFMD prognosis. At present, there is no vaccine available for HFMD treatment. According to the 2010 edition of the Chinese Ministry of Health guidelines,[8] the clinical treatment for mild cases of HFMD is symptomatic relief with Western Medicine and some Chinese patent medicines such as Reduning injection (Jiangsu Kanion Pharmaceutical LLC., Nanjing, China) to clear heat, dispel wind, and remove toxins. We studied the clinical efficacy and safety of Reduning injection on mild HFMD.

METHODS

Subjects

This study was an ongoing clinical trial that enrolled 360 participants in five hospitals across China (Chengdu Infectious Disease Hospital, Shenzhen Infectious Disease Hospital, Hangzhou Infectious Disease Hospital, Wuhan Infectious Disease Hospital, Anhui Provincial Children's Hospital). Trial registration: International clinical research registration number NCT 01175915. The protocols in this study were approved by the Frist Affiliated Hospital of Anhui University of Chinese Medicine Ethics Committee (Hefei, China) (Approval ID: 2010-01). Informed consent was obtained from all participants or their guardians.

Inclusion criteria: (a) met the diagnostic criteria in the Guideline of mild HFMD (2010 Edition) issued by Chinese Ministry of Health;[8] (b) symptoms of fever and skin lesions appearing in less than 24 h; (c) aged 1-14 years.

Exclusion criteria: (a) those with congenital organic diseases, such as significant cardiovascular abnormalities, chronic hepatitis, chronic nephritis, or blood system diseases; (b) those with a history of allergies to herbal medicines; (c) those suffering from with a family history of mental illness; (d) those participating in other clinical trials for HFMD; (e) other unpredictable factors that might cause the participant to become lost to follow-up.

Elimination criteria: (a) participants who refused to be randomized into any group; (b) participants who successfully enrolled but were later found not conform to standard; (c) participants who failed to offer any data after enrollment; (d) participants who were reluctant to comply with the medication (using the experimental drugs less than three times).

The trial would be stopped if the disease rapidly deteriorated, posing life-threatening risks for the participants, or participants developed some serious complications and specific physiological changes which were considered not appropriate to continue the experiment. The trial was ended if patients were intolerant or had adverse drug reactions.

Grouping

The study was a stratified-block randomized, double-blind, parallel-controlled, and multicenter clinical trial. All patients were randomized and administrated by the Central Randomization System of China Academy of Chinese Medical Sciences in Beijing. Each group had 120 patients.

Treatment

All treatments were made consulting the Guidelines on HFMD and detailed records were kept in the aforementioned hospitals. Patients were separated from each other to avoid cross-infection and ensure proper rest. Patients ate lightly and intensive nursing of the skin and oral cavity was given.

Treatment for group A: (a) vitamin B and C, orally; (b) if body temperature is less than or equal to 38.5℃, give a tepid bath or use gel sheets for physical cooling; if the body temperature is greater than or equal to 38.5℃, give ibuprofen granules (peros, 20 g/kg, taking in two

times within one day).

Treatment for group B: (a) for patients 1-3 years old, Reduning injection was given at 0.5 mL/kg per day with a maximal dosage of 10 mL. Reduning injection was diluted into 80-100 mL 5% glucose injection or 0.9% sodium chloride injection and given intravenously at 20-30 drops per min, once per day. (b) for patients 3-5 years old, Reduning injection was given at 0.5 mL/kg per day with a maximal dosage of 10 mL. Reduning injection was diluted into 50-100 mL 5% glucose injection or 0.9% sodium chloride injection and given intravenously at 30-40 drops per min, once per day. (c) for patients 6-10 years old, 10 mL Reduning injection was given, once per day. Reduning injection was diluted into 100-200 mL 5% glucose injection or 0.9% sodium chloride injection and given intravenously at 30-60 drops per min, once per day. (d) for patients 11-13 years old, 15 mL Reduning injection was given, once per day. Reduning injection was diluted into 200-250 mL 5% glucose injection or 0.9% sodium chloride injection and given intravenously at 30-60 drops per min, once per day.

Treatment for group C: both Reduning injection and symptomatic treatment with Western Medicines.

Ibuprofen suspension was produced by Shanghai Johnson & Johnson Pharmaceuticals (Shanghai, China). Reduning injection was made by Jiangsu Kanion Pharmaceutical (Nanjing, China).

Course: a course of treatment lasted for 3-7 days with a 3-day follow-up.

Data analysis

There is no acknowledged consensus on objective index for the treatment at present. Therefore, the changes in patients' main clinical outcomes after treatments were compared. The antifebrile working time (time to bring body temperature down more than 0.5℃ after medication) and the time for full fever recovery (the body temperature recovered to lower than 37℃ and lasted for more than 24 h without medication) were especially important. Vanishing-time of the rashes and ulcers on different parts of the body was also recorded (recovery of skin was considered when there were no rashes or ulcers emerging and the original rash disappeared).

Data analysis was conducted using the SAS software (Ver. 9.1.3 SAS Institute, Chicago, IL, USA). Discrete variables are expressed as counts (percentages) and constituent ratio, continuous variables are expressed as median and means ± standard deviation (*SD*). Differences in the demographic and clinical characteristics of the patient groups were assessed using the *Chi*-squared test and one-way ANOVA for categorical variables. Log-rank test, Kaplan-Meier estimates and corresponding 95% confidence intervals (*CI*) for covariates were applied for the final data. $P<0.05$ was considered statistically significant.

RESULTS

Demographic characteristics and clinical manifestations

Complete baseline data were available for 335 of 349 participants (96%). Thirteen participants were excluded: 3 from group A (1 for age of 6 months, 2 for hormone use), 6 from group B (1 for antiviral medications, 5 for hormone use), and 5 from group C (1 for age of 9 months, 3 for hormone use, 1 for being suspended for observation). There were no significant differences among the three groups ($P>0.05$). Patients were 1-11 years old, with slightly more boys than girls. Those from rural areas had a higher incidence (Table 1). The flow diagram of the trial is shown in Figure 1.

Clinical indicators

Antifebrile working time: there was no significant difference between groups A and B in statistics ($P>0.05$), and there was no significant difference between groups B and C in statistics ($P>0.05$). There was a significant difference between groups C and A ($P<0.05$). Group C was superior to other groups (Table 2, 3). The Kaplan-Meier estimate of antifebrile effect rate revealed that group C displayed an obvious advantage over the other two groups (Table 4, Figure 2).

Cumulative time for body temperature recovery

The log-rank test of cumulative time for body temperature recovery revealed that there was a distinct difference among the groups ($P=0.045$). The cumulative time in group C (censored=36.0 h) was significantly less than that in group A (censored=48.0 h) ($P=0.020$). The cumulative time in group C (censored=36.0 h) was also significantly less than that in group B (censored=43.0 h) ($P=0.042$) (Table 5, 6). Similar results were also concluded from the Kaplan-Meier estimate of body temperature recovery rate at any time-point: group C was superior to groups B and A (Table 7, Figure 3).

Cumulative time for rash disappearance

The log-rank test of the cumulative time for rash disappearance showed that there was a remarkable difference among the groups ($P=0.004$). The cumulative time in group C (censored=108.0 h) was superior to that in group A (censored=120.0 h), and the difference was significant ($P=0.010$). The cumulative time in group C (censored=108.0 h) was also significantly less than that in group B (censored=120.0 h) ($P=0.003$) (Table 8, 9). In the Kaplan-Meier estimate of rash disappearance rate at any time-point, group C was superior to groups A and B (Table 10, Figure 4).

Cumulative time for ulcer disappearance

The log-rank test of the cumulative time for ulcer disappearance showed that there was no significant difference among the three groups ($P>0.05$) (Tables 11-13, Figure 5).

Table 1 Comparison of general information of the three groups

Item		Group A	Group B	Group C
Gender [*n* (%)]	Male	71 (60.7)	69 (60.0)	73 (63.5)
	Female	46 (39.3)	46 (40.0)	42 (36.5)
Age (years)	*n*	117	115	115
	Mean±*SD*	2.1±1.5	2.2±1.7	2.1±1.5
	95% *CI* (L-H)	1.82-2.37	1.89-2.51	1.82-2.39
	Min-Max	1.00-8.00	1.00-11.00	1.00-10.00
	Median	2.00	2.00	2.00
Height (cm)	*n*	105	102	98
	Mean±*SD*	90.5±14.3	90.1±12.4	90.8±12.4
	95% *CI* (L-H)	87.73-93.27	87.66-92.53	88.27-93.27
	Min-Max	65.00-158.00	65.00-135.00	64.00-140.00
	Median	88.00	88.50	88.50
Weight (kg)	*n*	116	114	115
	Mean±*SD*	13.4±4.4	13.6±3.6	13.1±3.2
	95% *CI* (L-H)	12.56-14.19	12.91-14.27	12.51-13.71
	Min-Max	7.00-45.00	8.00-26.00	8.50-30.00
	Median	12.00	12.75	12.50
Residence [*n* (%)]	Urban area	23 (19.7)	19 (16.5)	16 (14.0)
	Township	30 (25.6)	36 (31.3)	35 (30.7)
	Rural area	64 (54.7)	60 (52.2)	63 (55.3)
	Others	0 (0.0)	0 (0.0)	0 (0.0)
Living status [*n* (%)]	Diaspora	93 (79.5)	87 (76.3)	97 (84.3)
	Nursery	21 (17.9)	24 (21.1)	15 (13.0)
	Pupil	3 (2.6)	3 (2.6)	2 (1.7)
	Junior	0 (0.0)	0 (0.0)	0 (0.0)
	Others	0 (0.0)	0 (0.0)	1 (0.9)
Exposure history within 7 days [*n* (%)]	None	92 (79.3)	89 (78.8)	88 (77.2)
	Exist	24 (20.7)	24 (21.2)	26 (22.8)
Highest fever temperature (℃)	*n*	116	114	115
	Mean±*SD*	38.5±0.6	38.4±0.6	38.4±0.6
	95% *CI* (L-H)	38.39-38.59	38.33-38.57	38.33-38.57
	Min-Max	37.30-40.00	37.50-40.00	37.50-40.80
	Median	38.50	38.50	38.40
Medication history [*n* (%)]	Chinese medicine	1 (0.9)	0 (0.0)	0 (0.0)
	Western Medicine	25 (21.7)	22 (19.5)	21 (18.6)
	Others	1 (0.9)	1 (0.9)	0 (0.0)
	Treatment-naive	88 (76.5)	90 (79.6)	92 (81.4)
Allergic history [*n* (%)]	None	113 (97.4)	111 (96.5)	114 (99.1)
	Once or more	3 (2.6)	4 (3.5)	1 (0.9)
Past medical history [*n* (%)]	None	117 (100.0)	111 (96.5)	114 (99.1)
	Exit	0 (0.0)	4 (3.5)	1 (0.9)
Temperature (℃)	*n*	111	111	104
	Mean±*SD*	38.0±0.7	38.0±0.6	38.1±0.7
	95% *CI* (L-H)	37.89-38.15	37.92-38.13	37.98-38.23
	Min-Max	36.10-40.00	36.50-40.00	36.50-40.00
	Median	38.00	38.00	38.00

Table 1 Comparison of general information of the three groups (continued)

Item		Group A	Group B	Group C
Pulse (times/min)	*n*	117	115	114
	Mean±*SD*	118.8±13.5	118.6±13.4	117.6±12.4
	95% *CI* (L-H)	116.39-121.32	116.10-121.05	115.31-119.90
	Min-Max	80.00-146.00	88.00-150.00	80.00-155.00
	Median	120.00	120.00	118.00
Respiration (times/min)	*n*	117	115	114
	Mean±*SD*	27.0±4.5	27.1±4.4	26.8±4.0
	95% *CI* (L-H)	26.20-27.85	26.27-27.89	26.10-27.59
	Min-Max	19.00-40.00	20.00-42.00	18.00-40.00
	Median	26.00	28.00	26.50
Systolic pressure (mm Hg)	*n*	107	108	111
	Mean±*SD*	90.4±8.1	88.8±7.2	90.3±7.5
	95% *CI* (L-H)	88.82-91.93	87.39-90.13	88.85-91.67
	Min-Max	72.00-119.00	69.00-120.00	79.00-120.00
	Median	90.00	88.50	90.00
Diastolic pressure (mm Hg)	*n*	107	108	111
	Mean±*SD*	57.2±7.3	56.1±7.1	56.4±7.7
	95% *CI* (L-H)	55.85-58.65	54.72-57.42	54.98-57.87
	Min-Max	38.00-85.00	39.00-88.00	38.00-90.00
	Median	60.00	57.50	56.00

Notes: gender, residence, living status, exposure history within 7 days, medication history, allergic history and past medical history are calculating by *Chi*-square test; age, height, weight, highest fever temperature, temperature, pulse, respiration, systolic pressure and diastolic pressure are calculating by *Chi*-square test; group A: symptomatic treatment with Western Medicines; group B: Reduning injection; group C: both Reduning injection and symptomatic treatment with Western Medicine. The three groups were no significant difference in gender, age, height, weight, residence, living status, exposure history within 7 days, highest fever temperature, medication history, allergic history, past medical history, temperature, pulse, respiration, systolic pressure and diastolic pressure (P>0.05). P values are 0.848, 0.851, 0.934, 0.631, 0.740, 0.561, 0.922, 0.879, 0.754, 0.410, 0.070, 0.557, 0.750, 0.910, 0.221 and 0.484.

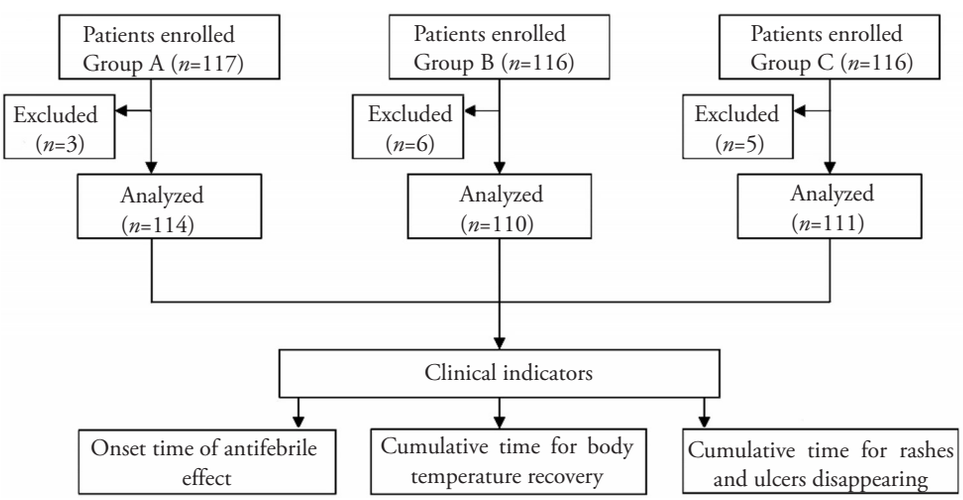

Figure 1 Flow diagram of the trial clinical indicators

Adverse events and safety analysis

There was an adverse event in one patient from group A. There were no adverse events in groups B and C. There was no statistical difference in comparisons among the three groups (P>0.05). There were no adverse reactions in all three groups (Tables 14, 15).

DISCUSSION

Some herbs and their compounds can be effective when used to prevent and cure infectious diseases. However, their clinical application is extremely limited because of few evidence-based clinical trials.

There is an increasing number of studies on clinical

Table 2 Quartiles of onset time (h) of antifebrile effect

Item	Group A	Group B	Group C
n	97	104	93
Censored (%)	9 (9.3)	16 (15.4)	5 (5.4)
25% (95% *CI*)	1.0 (0.5-1.0)	0.5 (0.5-1.0)	0.5 (0.5-1.0)
50% (95% *CI*)	3.0 (2.0-4.0)	2.0 (1.0-2.0)	1.0 (1.0-2.0)
75% (95% *CI*)	8.0 (4.0-24.0)	6.0 (4.0-50.0)	4.0 (2.0-8.0)

Notes: group A: symptomatic treatment with Western Medicines; group B: reduning injection; group C: both Reduning injection and symptomatic treatment with Western Medicines.

Table 3 Log-rank test of onset time (h) of antifebrile effect

Item	Statistic	DF	*P*
Group A∶B∶C	4.889	2	0.087
Group A∶B	0.017	1	0.895
Group A∶C	4.308	1	0.038
Group B∶C	3.178	1	0.075

Notes: DF: dickey-fuller. Group A: symptomatic treatment with Western Medicines; group B: reduning injection; group C: both Reduning injection and symptomatic treatment with Western Medicines.

Table 4 Kaplan-Meier estimate of antifebrile effect rate

Item	Group A (%)	Group B (%)	Group C (%)
8	79.4	76.0	84.9
16	81.4	80.8	88.2
24	85.6	82.7	92.5
32	87.6	82.7	93.5
40	87.6	82.7	93.5
48	88.7	82.7	94.6
56	88.7	83.7	94.6
64	88.7	83.7	94.6
72	90.7	83.7	94.6

Notes: group A: symptomatic treatment with Western Medicines; group B: reduning injection; group C: both Reduning injection and symptomatic treatment with Western Medicines.

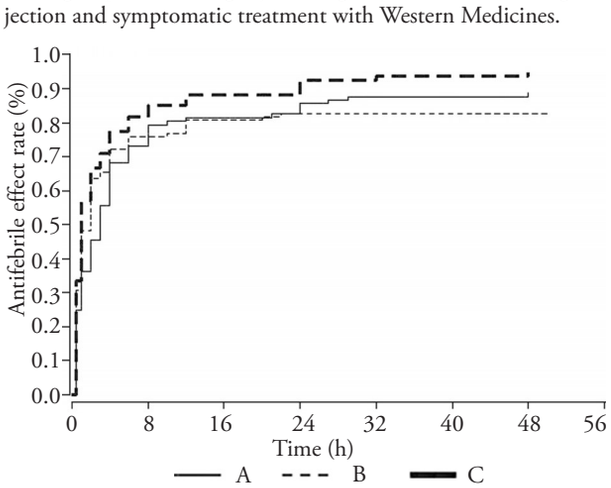

Figure 2 Kaplan-Meier estimate of antifebrile effect rate
A: symptomatic treatment with Western Medicines; B: Reduning injection; C: both Reduning injection and symptomatic treatment with Western Medicines.

Table 5 Quartiles of cumulative time (h) for body temperature recovery

Item	Group A	Group B	Group C
n	97	104	93
Censored (%)	17 (17.5)	22 (21.2)	6 (6.5)
25% (95% *CI*)	28.0 (24.0-35.0)	12.0 (6.0-24.0)	6.0 (4.0-24.0)
50% (95% *CI*)	48.0 (41.0-60.0)	43.0 (29.0-52.0)	36.0 (27.0-48.0)
75% (95% *CI*)	96.0 (71.0-100.0)	105.0 (72.0-100.0)	72.0 (58.0-86.0)

Notes: group A: symptomatic treatment with Western Medicines; group B: reduning injection; group C: both Reduning injection and symptomatic treatment with Western Medicines.

Table 6 Log-rank test of cumulative time (h) for body temperature recovery

Item	Statistic	DF	*P*
Group A∶B∶C	6.216	2	0.045
Group A∶B	0.057	1	0.811
Group A∶C	5.371	1	0.020
Group B∶C	4.147	1	0.042

Notes: DF: dickey-fuller. Group A: symptomatic treatment with Western Medicines; group B: reduning injection; group C: both Reduning injection and symptomatic treatment with Western Medicines.

treatments for HFMD using Traditional Chinese Medicine (TCM). According to Chinese medicine theory, the recognized pathogenesis of this disease lies in the invasion of damp-heat and epidemic toxin co-existing with the deficiency of anti-pathogenic *Qi*. For treatment, expelling pathogenic heat, dissolving dampness, and detoxifying should be emphasized.[9-12] Reduning injection is a state-level new drug in Category Ⅲ (approval number: Z20050217) with efficacy meeting these TCM treatment criteria. It is a Chinese herbal compound composed of three antiviral herbs, namely, Qinghao (*Herba Artemisiae Annuae*), Jinyinhua (*Flos Lonicerae*), and Zhizi (*Fructus Gardeniae*).

Prior in vitro fundamental research indicated that Reduning injection could inhibit the activities of Enterovirus 71 (EV 71) and coxsackie A16 (CA 16). This research provides the first comparative analysis on prevailing therapies among people with mild untreated HFMD in China. Our study is unique because its data

Table 7 Kaplan-Meier estimate of body temperature recovery rate at any time-point (%)

Item	Group A	Group B	Group C
12	15.5	26.0	26.9
24	20.6	35.6	35.5
36	36.1	47.1	50.5
48	52.6	57.7	60.2
60	60.8	64.4	68.8
72	70.1	66.3	78.5
84	73.2	71.2	82.8
96	75.3	73.1	86.0
108	79.4	76.9	88.2
120	79.4	77.9	90.3
132	80.4	77.9	90.3
144	81.4	78.8	91.4
156	82.5	78.8	92.5
168	82.5	78.8	93.5

Notes: DF: dickey-fuller. Group A: symptomatic treatment with Western Medicines; group B: reduning injection; group C: both Reduning injection and symptomatic treatment with Western Medicines.

Table 8 Quartiles of the cumulative time (h) for rash disappearance

Item	Group A	Group B	Group C
n	117	115	115
Censored (%)	18 (15.4)	24 (20.9)	9 (7.8)
25%	96.0	96.0	82.0
(95% *CI*)	(96.0-112.0)	(92.0-96.0)	(72.0-96.0)
50%	120.0	120.0	108.0
(95% *CI*)	(118.0-132.0)	(110.0-134.0)	(96.0-120.0)
75%	144.0	179.0	144.0
(95% *CI*)	(140.0-168.0)	(144.0-168.0)	(123.0-148.0)

Notes: group A: symptomatic treatment with Western Medicines; group B: reduning injection; group C: both Reduning injection and symptomatic treatment with Western Medicines.

Table 9 Log-rank test of the cumulative time (h) for rash disappearance

Item	Statistic	DF	*P*
Group A:B:C	10.98	2	0.004
Group A:B	0.254	1	0.615
Group A:C	6.588	1	0.010
Group B:C	8.996	1	0.003

Notes: DF: dickey-fuller. Group A: symptomatic treatment with Western Medicines; group B: reduning injection; group C: both Reduning injection and symptomatic treatment with Western Medicines.

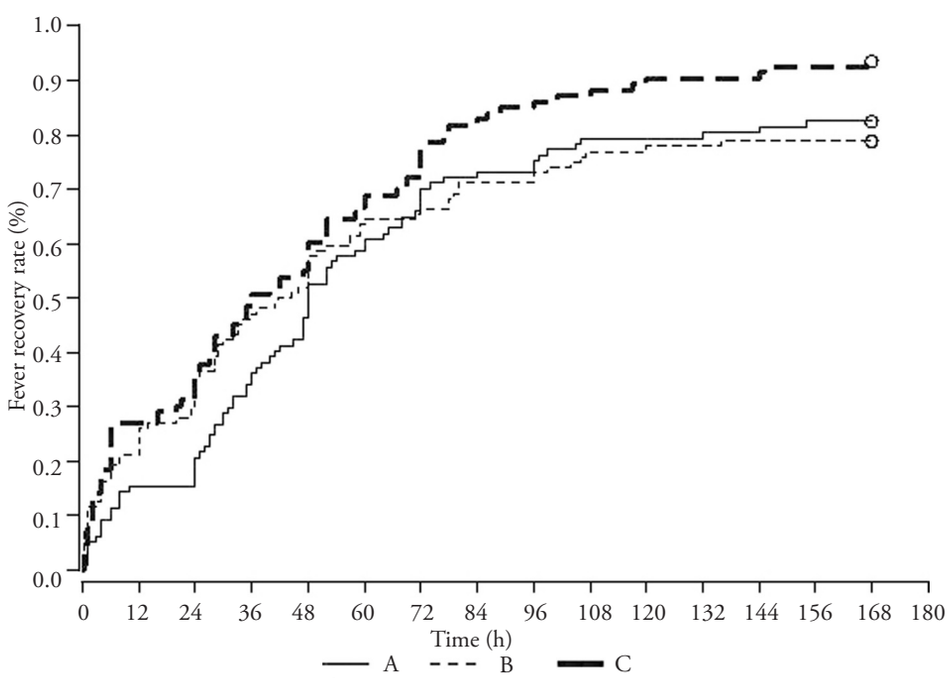

Figure 3 Kaplan-Meier estimate of body temperature recovery rate at any time-point
A: symptomatic treatment with Western Medicines; B: Reduning injection; C: both Reduning injection and symptomatic treatment with Western Medicines.

were collected prospectively from treatment-naïve individuals at the time of entry into a clinical trial in five cities in different geographic settings, and the therapies were recommended by the Guidelines on HFMD. Because the participants were required to meet the uniform inclusion and exclusion criteria before study entry, the study population was more homogeneous across geographic areas than independent cohorts.

We found that children aged 2-4 years may be most susceptible to HFMD, perhaps because of profound changes occurring in the body, instability of the immune system, boundless energy, and outgoing personality. This may be one of the main ways of the disease. As instability of the immune system, resistance is rela-

Table 10 Kaplan-Meier estimate of rash disappearance rate at any time-point (%)

Item	Group A	Group B	Group C
12	0.0	0.0	0.0
24	0.0	0.0	0.0
36	0.0	0.0	0.0
48	0.9	2.6	6.1
60	1.7	2.6	7.8
72	7.7	10.4	21.7
84	9.4	13.0	26.1
96	26.5	36.5	43.5
108	31.6	39.1	50.4
120	53.8	57.4	66.1
132	59.8	58.3	71.3
144	75.2	67.8	80.9
156	78.6	69.6	86.1
168	82.9	73.0	91.3

Notes: Group A: symptomatic treatment with Western Medicines; group B: reduning injection; group C: both Reduning injection and symptomatic treatment with Western Medicines.

tively weak, so easy to be infected. Meanwhile, children do not pay attention to personal hygiene, so easy. Our study also discovered that this disease tended to prevail in rural areas. China is currently a mostly agricultural state, and rural residents account for the majority of the total population. This population also lacks awareness about the related prevention and isolation of HFMD.

Table 11 Quartiles of the cumulative time (h) for ulcer disappearance

Item	Group A	Group B	Group C
n	112	110	105
Censored (%)	0 (0.0)	0 (0.0)	1 (1.0)
25% (95%CI)	77.0 (69.0-96.0)	72.0 (70.0-88.0)	82.0 (72.0-90.0)
50% (95%CI)	115.0 (98.0-120.0)	98.0 (96.0-114.0)	108.0 (96.0-120.0)
75% (95%CI)	136.0 (129.0-144.0)	131.0 (120.0-140.0)	132.0 (120.0-144.0)

Notes: group A: symptomatic treatment with Western Medicines; group B: Reduning injection; group C: both Reduning injection and symptomatic treatment with Western Medicines.

Table 12 Log-rank test of the cumulative time (h) for ulcer disappearance

Item	Statistic	DF	*P*
Group A∶B∶C	0.845	2	0.655
Group A∶B	0.640	1	0.424
Group A∶C	0.004	1	0.950
Group B∶C	0.571	1	0.450

Notes: DF: Dickey-Fuller. Group A: symptomatic treatment with Western Medicines; group B: reduning injection; group C: both Reduning injection and symptomatic treatment with Western Medicines.

Body temperature was selected as a primary outcome because it was a significant sign of deterioration of the disease. Interestingly, we found that Reduning injection could optimize the efficacy of the drugs for symptomatic treatment, since integrated therapy performed better statistically than others. The effects included a re-

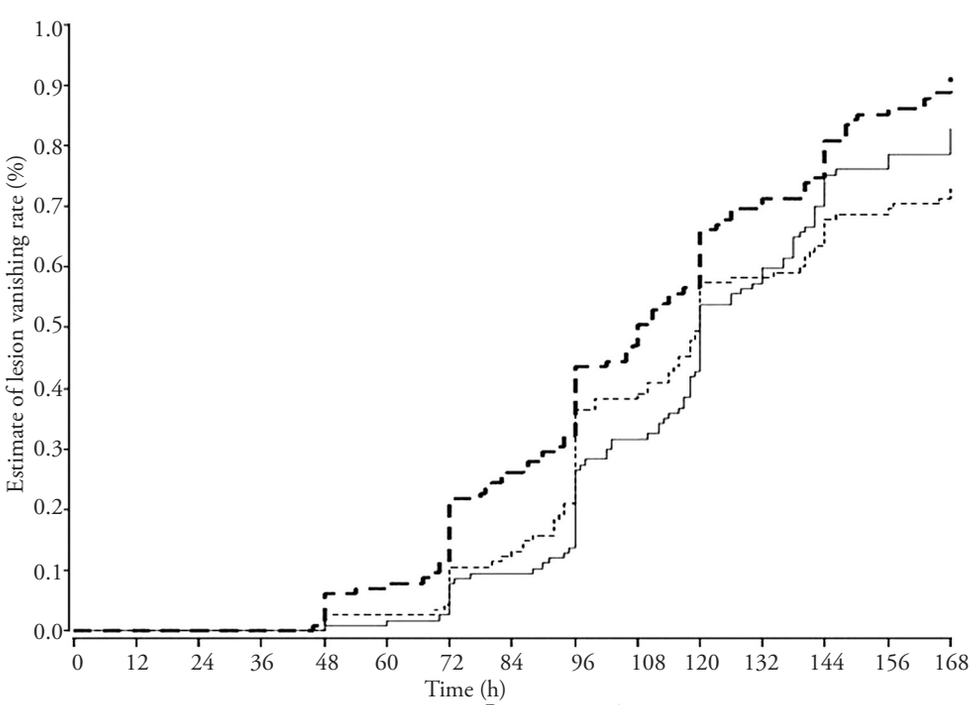

Figure 4 Kaplan-Meier estimate of rash disappearance rate at any time-point
A: symptomatic treatment with Western Medicines; B: reduning injection; C: both Reduning injection and symptomatic treatment with Western Medicines.

Table 13 Kaplan-Meier estimate of ulcer disappearance rate at any time-point (%)

Item	Group A	Group B	Group C
12	0.0	0.0	0.0
24	0.9	0.9	0.0
36	1.8	1.8	1.9
48	11.6	8.2	5.7
60	13.4	10.0	6.7
72	23.2	27.3	21.9
84	28.6	32.7	30.5
96	39.3	49.1	43.8
108	47.3	55.5	52.4
120	63.4	70.9	69.5
132	70.5	76.4	76.2
144	85.7	89.1	87.6
156	89.3	90.0	90.5
168	96.4	97.3	94.3
180	98.2	98.2	97.1
192	100.0	99.1	99.0
204	100.0	99.1	99.0
216	100.0	100.0	99.0
228	100.0	100.0	99.0
240	100.0	100.0	99.0
252	100.0	100.0	99.0

Notes: group A: symptomatic treatment with Western Medicines; group B: Reduning injection; group C: both Reduning injection and symptomatic treatment with Western Medicines.

Table 14 Adverse events [*n* (%)]

Item	Group A	Group B	Group C
Exist	1 (0.8)	0 (0.0)	0 (0.0)
None	117 (99.2)	116 (100.0)	115 (100.0)
Total number	118	116	115

Notes: group A: symptomatic treatment with Western Medicines; group B: Reduning injection; group C: both Reduning injection and symptomatic treatment with Western Medicines. The three groups were no significant difference in Adverse events (P=0.376).

Table 15 Adverse reactions [*n* (%)]

Item	Group A	Group B	Group C
Exist	0 (0.0)	0 (0.0)	0 (0.0)
None	118 (100.0)	116 (100.0)	115 (100.0)
Total number	118	116	115

Notes: group A: symptomatic treatment with Western Medicines; group B: Reduning injection; group C: both Reduning injection and symptomatic treatment with Western Medicines. The three groups were no significant difference in Adverse reactions (P=1.000).

duction in onset time of antifebrile effect, an acceleration of body temperature recovery, and a stability of body temperature after fever reduction.

The cumulative times for rash and ulcer disappearance were consistent with the previous results. Group C always showed superiority over other groups. The herbal medicines might have ingredients that act synergistically in ways we do not yet understand. Nevertheless, this study provides an opportunity to compare the efficacy of different treatments on patients with mild HFMD.

This study also has several limitations. The major indicators of efficacy should be accurate and directional.

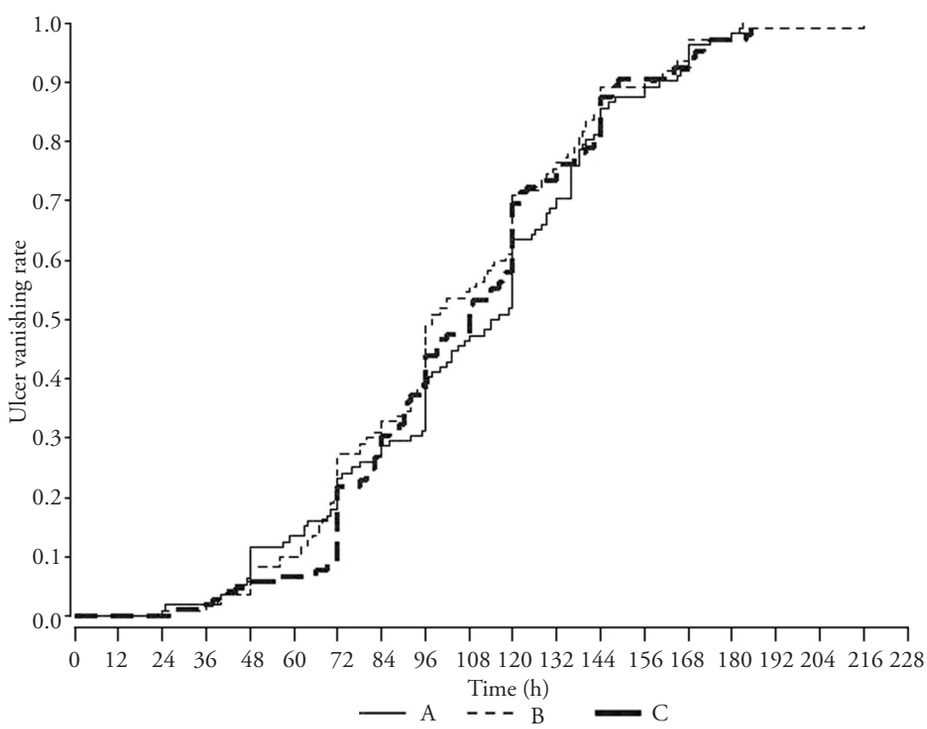

Figure 5 Kaplan-Meier estimate for ulcer disappearance rate at any time-point
A: symptomatic treatment with Western Medicines; B: Reduning injection; C: both Reduning injection and symptomatic treatment with Western Medicines.

Therefore body temperature, rash, and ulcers were selected for observation because those symptoms have the advantages of being simple, convenient, easily operated with strong controllability. Each symptom was an essential prerequisite for carrying out a multicenter clinical trial. However, there were no before-and-after laboratory indices of the patients, as there are no recognized biochemical markers for HFMD. Finally, we lack discussion about the mechanisms of action and interaction between Western Medicine and Reduning injection.
Despite these limitations, this study provides evidence that the prevalence of mild HFMD is independently related to factors such as age, gender, and residence. Therefore, integrated treatment could be the best choice for children. These findings have significance for the improvement of various clinical treatment programs, especially in the resource-limited countryside.

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