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Original Article

A multicentered, randomized, open study on efficacy and safety of Meifute® antifungal solution of optimal application time in moccasin-type tinea pedis

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Abstract: Objective: This study aimed to evaluate the efficacy and safety of the Meifute® antifungal solution on moccasin-type tinea pedis with optimal application time. Methods: A multicentered, randomized and open clinical trial was conducted by enrolling 267 patients with moccasin-type tinea pedis from 10 centers. 91 of these patients were treated with regimen A (foot bath twice per 7 days, 2 hours each time), 87 with regimen B (foot bath twice per 7 days, 1 hour each time) and 89 with regimen C (foot bath twice per 7 days, 0.5 hour each time). The evaluation of mycological effect, clinical efficacy and the overall therapeutic effect were achieved using fungus microscopic examination, fungus culture method and total symptom score. The initial valuation data were recorded as the baseline and further data were collected 1 week after the first administration (V1), 1 week after the second administration (V2) and 2 weeks after the withdrawal (V3). Results: At V3, the number of eligible patients in group A, B and C were 69, 78 and 80, respectively. There was no statistically significant difference in the fungal clearance rates (84.1%, 88.5% and 76.3%, respectively), clinical effective rate (14.5%, 28.2% and 24.1%, respectively) or integral effective rate (49.3%, 61.5% and 56.3%, respectively) among three groups. The adverse events including transient pain (31 cases, 11.6%), pain (20 cases, 7.5%), erosion (17 cases, 6.4%), pruritus (10 cases, 3.7%), burning (6 cases, 2.2%) and swelling (3 cases, 1.1%) be alleviated without any treatment. The incidence of pain and erosion in group A was significantly higher than that in group B and C. The only case of ulcer happened in group A which was cured after one-week application of Bactroban, Bifonazole, and Hirudoid. Because of the different incident of adverse reactions, there were significant difference in the dropout rates among group A, B and C (9.9%, 2.3% and 0.0%, respectively). Conclusion: The therapeutic efficacy of a 0.5 h treatment with antifungal liquid was found to be the same as that of standard application time of 2 hours. On the other hand, 0.5 h treatment protocol could reduce the incidence of adverse reactions and therefore improve the compliance of patients.

Keywords: Meifute, application time, moccasin-type tinea pedis, antifungal

Introduction

Tinea pedis was one of the most common superficial fungal infection diseases, characterized by interdigital skin involvement [1, 2]. Acute phase tinea pedis showed interdigital erythema and dipping and might be accompanied by painful blisters, such as interdigital-type tinea pedis. The more common type was the moccasin-type tinea pedis, the chronic phase of the tinea pedis, primarily manifested as plantar and lateral hyperkeratosis, erythema and scale [3]. While taking a long period of time [4], the treatment with traditional topical agent had poor permeability, efficacy and patient compliance. The treatment with oral antifungal

medication has been proved to be effective in the treatment of moccasin-type tinea pedis, but there might be some potential adverse reactions [5].

As a new type of antifungal agent, Meifute® antifungal solution has been proved effective for the treatment of the moccasin-type tinea pedis by previous researches [6, 7]. However, Meifute® antifungal solution has also found to be causing local irritation and therefore resulted in declined compliance. In order to improve compliance and to ensure the efficacy, this study enrolled selected patients with moccasin-type tinea pedis for evaluation of the efficacy and safety of Meifute® antifungal solution of different application time.

Subjects and methods

Case selection

The patients were selected from dermatology clinic of 10 hospitals, including the Third Affiliated Hospital of Sun Yat-sen University, the First Affiliated Hospital of Sun Yat-sen University, Sun Yat-sen Memorial Hospital of Sun Yat-sen University, Nanfang Hospital of Southern Medical University, Guangdong Provincial Dermatology Hospital, Guangdong General Hospital, Guangzhou Institute of Dermatology, the Second Affiliated Hospital of Guangzhou Medical University, Shenzhen People's Hospital, and Peking University Shenzhen Hospital. The applied inclusion criteria were: (1) male and female aged 18- 65 years; (2) presented symptoms in accordance with the clinical diagnosis of moccasin-type tinea pedis, tested positive by fungal direct microscopy and the total symptom score (TSS) were > 8 points; (3) voluntary participation with informed consent signed for this clinical observation trial; (4) effective contraceptive measures were taken by female subjects of childbearing age during this trial. Patients were excluded if they: (1) had severe local bacterial infection or other dermatosis that can interfere the diagnosis or therapy of tinea pedis; (2) had onychomycosis; (3) had foot eczema; (4) were allergic with the agent used in the study; (5) had severe heart diseases, liver diseases, kidney diseases, diabetes and psychosis; (6) had systemic corticosteroids or immune suppressants therapy in three months; (7) had systemic antifungal therapy during the past 3 months, or local antifungal therapy during the past 2 weeks (8) were female in pregnancy or lactation period.

Randomization

Random numbers generated by stratified randomization were obtained from the Statistics Analysis System 6.12 programmed by the Department of Medical Statistics and Epidemics at north campus of Sun Yat-sen University. Each involved subject was assigned a random number from the random center sequence according to the enrollment date. The random number would then determine the regimen allocations, including regimen A (foot bath twice per 7 days, 2 hours each time); regimen B (foot bath twice per 7 days, 1 hour each time) and regimen C (foot bath twice per 7 days, 0.5 hour each time).

Agent and administration methods

Meifute® antifungal solution [Hu Wei Xiao Zi (2014) No. 0021] was provided by Shanghai Meifute Biotechnology Limited Company (Lot: 20150403/20150505). The usage was as follows: (1) put the infected foot into the fluid collecting bag; (2) add in Meifute® antifungal solution of proper amount, which was about half of a bottle of per foot; (3) a different duration was specified for each group; (4) wash the treated foot with clean water after application.

Observed indicators and efficacy evaluation

Indicator observation and efficacy evaluation: The evaluation of mycological effect, clinical efficacy and the overall therapeutic effect were achieved using fungus microscopic examination, fungus culture method and total symptom score (TSS). The initial valuation data were recorded as the baseline (V0) and further data were collected 1 week after the first administration (recorded as V1), 1 week after the second administration (recorded as V2) and 2 weeks after the withdrawal (4 weeks after first administration, recorded as V3). The primary evaluation point of therapeutic efficacy was 2 weeks after withdrawal (V3) and the secondary evaluation point was 1 week after the second administration (v2). All of the adverse events during the trail were documented. The indica-

Table 1. The baseline characteristic of 267 patients with moccasin-type tinea pedies

Character	Total (n = 267)	Groups of different application time			χ^2	*P*
		Group A (n = 91)	Group B (n = 87)	Group C (n = 89)		
Age, years *mean ± sd*	40.94±11.10	40.55±10.68	41.66±10.86	40.65±11.83	0.265	0.767
Sex [*n* (%)]						
Male	153 (57.3)	52 (57.1)	52 (59.8)	49 (55.1)	0.401	0.818
Female	114 (42.7)	39 (42.9)	35 (40.2)	40 (44.9)		
Disease duration, days *Median (Q25, Q75)*	1132 (730, 2920)	1095 (545, 2400)	1095 (395, 2920)	1460 (730, 3650)	4.503	0.105
Lesions [*n* (%)]						
Left foot alone	22 (8.2)	9 (9.9)	7 (8.0)	6 (6.7)	1.110	0.893
Right foot alone	15 (5.7)	5 (5.5)	6 (6.9)	4 (4.5)		
Both feet	230 (86.1)	77 (84.6)	74 (85.1)	79 (88.8)		
TSS *Median (Q25, Q75)*	11 (9, 13)	11 (9, 13)	11 (10, 13)	11 (9, 14)	0.696	0.706

Table 2. The summary table of the dropout rate in groups of different application time in V2

The type of dropout	Total	Groups of different application time			χ^2	*P*
		Group A (n = 91)	Group B (n = 87)	Group C (n = 89)		
All dropout cases	37 (13.9)	22 (24.2)	9 (10.3)	6 (6.7)	12.791	0.002
Caused by adverse reaction	10 (3.7)	8 (8.8)	2 (2.3)	0 (0.0)	-	0.004*
Caused by other reasons	27 (10.1)	14 (15.4)	7 (8.0)	6 (6.7)	4.304	0.116

*Hypothesis tested by Fisher's exact test.

Table 3. The comparison of the fungal clearance rate in groups of different application time in V2

Groups of different application time	Case of fungal clearance (n)	Fungal clearance rate (%)	χ^2	*P*
Group A (n = 68)	23	33.8	4.798	0.091
Group B (n = 78)	40	51.3		
Group C (n = 83)	33	39.8		
Total (n = 229)	96	41.9		

tors of clinical efficacy evaluation were as follows. Patients with TSS variation rate = 100% were evaluated as cured, 100% > TSS variation rate ≥ 60% greatly improved; 60% > TSS variation rate ≥ 20% improved, TSS variation rate < 20% not changed; Indicators of integral efficacy were as follows. Patients were evaluated as cured when their TSS variation rate = 100% and have negative results in both fungal direct microscopy and fungal culture; greatly improved when 100% > TSS variation rate ≥ 60% and have negative results in both fungal direct microscopy and fungal culture, improved when 60% > TSS variation rate ≥ 20% and negative results in both fungal direct microscopy and fungal culture or when TSS variation rate ≥ 20% and have positive result in fungal direct microscopy and/or fungal culture and not changed when TSS variation rate < 20% and have positive or negative results in fungal direct microscopy and/or fungal culture. The effective rate is the total of cured rate and greatly improved rate.

Statistical methods

Statistical analysis was performed using SPSS version 18.0 software, and *P* value of ≤ 0.05 was considered statistically significant. Baseline analysis, fungal clearance, clinical efficacy and integral efficacy were compared by the Chi-square test and the rank sum test. The datasets of statistical analysis included a Per Protocol Set (PPS), Full Analysis Set (FAS), and Safety Analysis set (SAS). The PPS included those subjects who met protocol requirements (the set of qualified cases). The FAS included the PPS and those subjects who were lost to follow-up but received at least once treatment in study (the set of qualified cases and the set of dropout cases). The SAS included the study subjects who received the treatment in study, attended at least once follow-up visit, and provided partial safety data [8]. In this study, the baseline data was analyzed in the FAS, and the efficacy data was analyzed in the PPS and safety was evaluated in the SAS.

Table 4. The Comparison of clinical efficacy in groups of different application time in V2 period [n (%)]

Groups of different application time	The evaluation of clinical efficacy				χ^2	*P*
	Cured	Greatly improved	Improved	No change		
Group A (n = 69)	0 (0.0)	10 (14.5)	39 (56.5)	20 (29.0)	8.176	0.017
Group B (n = 78)	1 (1.3)	21 (26.9)	44 (56.4)	12 (15.4)		
Group C (n = 83)	1 (1.2)	19 (22.9)	52 (62.7)	11 (13.3)		
Total (n = 230)	2 (0.9)	50 (21.7)	135 (58.7)	43 (18.7)		

Table 5. The Comparison of integral efficacy among groups of different application in V2 period [n (%)]

Groups of different application time	The evaluation of integral efficacy				χ^2	*P*
	Cured	Greatly improve	Improved	Not changed		
Group 1 (n = 68)	0 (0.00)	6 (8.8)	43 (63.2)	19 (27.9)	7.538	0.023
Group 2 (n = 78)	1 (1.3)	16 (20.5)	49 (62.8)	12 (15.4)		
Group 3 (n = 83)	1 (1.2)	8 (9.6)	63 (75.9)	11 (13.3)		
Total (n = 229)	2 (0.9)	30 (13.1)	155 (67.7)	42 (18.3)		

Results

Baseline characteristics

All 267 patients (153 males, 114 females) with moccasin-type tinea pedis (accorded with FAS and SAS) were enrolled from 10 hospitals with an average age of 40.94±11.10 years, an average duration of 1132 days. 22 of these patients had their left foot involved (8.2%), 15 Right foot involved (5.7%), 230 both feet involved (86.1%) and the average TSS score of all enrolled patients was 11. There was no statistically significant difference in age, sex, disease duration, lesion distribution, and TSS among the groups (**Table 1**).

Analysis of minor therapeutic efficacy (V2)

The summary of the dropout cases among groups of different application Time: At V2, chi-square test presented statistically significant difference (χ^2 = 12.791, *P* = 0.002 < 0.05) in the dropout rates among three groups, where group A had the highest dropout rate (24.2%) while group C had the lowest (6.7%). Hypothesis was put forward that the dropout rate was linked with adverse reactions and significant difference (*P* = 0.004 < 0.05) in dropout rates of the groups was observed by a Fisher's exact test. Adverse reactions resulting in a dropout rate of 8.8% in group A, ranking the highest in all groups. And 0 dropout rate was caused by adverse reactions in group C, which ranked lowest in all groups. A chi-square test was performed to find out dropout rate caused by other reasons and no significant difference was found (χ^2 = 4.304, *P* = 0.116 > 0.05). It was therefore considered that the ratio of dropout rate caused by other reasons in all three groups was the same (**Table 2**). In addition, the fungal test data of one of the case was lost, making it impossible to obtain data of fungal clearance rate and integral efficacy. Therefore, there is one more data of clinical efficacy (230) than that of fungal clearance rate (229) and integral efficacy (229).

The comparison of the fungal clearance rate among groups of different application time: In 229 eligible patients, 96 (41.9%) were considered to be clear of fungus, with 23 (33.8%) from group A, 40 (51.3%) from group B and 33 (39.8%) from group C. There was no statistically significant difference in the fungal clearance rate among different groups (χ^2 = 4.798, *P* = 0.091 > 0.05) (**Table 3**).

The comparison of the clinical efficacy among groups of different administration time: In 230 qualified cases, 2 cases (0.9%) were evaluated as cured, 50 cases (21.7%) greatly improved, 135 cases (58.7%) improved and 43 cases (18.7%) not changed. The difference in percentages of cases evaluated as cured, greatly improved, improved and not changed in different groups was found to be of statistical significant, (χ^2 = 8.176, *P* = 0.017 < 0.05) (**Table 4**), and it suggested that there was difference in clinical efficacy among three groups. The further multiple comparisons showed that, at V2, there were significant difference (both *P* = 0.029) in clinical efficacy between group A and group B and that between group A and group C, while the difference of clinical efficacy between group B and group C was not statistically significant. Therefore, the clinical efficacy of both

Table 6. The summary table of the dropout rate in groups of different application time in V3

The type of dropout	Total	Groups of different application time			χ^2	*P*
		Group A (n = 91)	Group B (n = 87)	Group C (n = 89)		
All dropout cases	40 (15.0)	22 (24.2)	9 (10.3)	9 (10.1)	9.165	0.010
Caused by adverse reactions	11 (4.1)	9 (9.9)	2 (2.3)	0 (0.0)	-	0.001*
Caused by other reasons	29 (10.9)	13 (14.3)	7 (8.0)	9 (10.1)	1.866	0.393

*Hypothesis tested by Fisher's exact test.

Table 7. The comparison of the fungal clearance rate in groups of different application time in V3

Groups of different application time	Cases of fungal clearance cases (n)	Fungal clearance rate (%)	χ^2	*P*
Group 1 (n = 69)	58	84.1	4.246	0.120
Group 2 (n = 78)	69	88.5		
Group 3 (n = 80)	61	76.3		
Total (n = 227)	188	82.8		

group B and group C were considered to be of the same level, both of which were better than that of group A. On the other hand, with the clinical effective rate of group A, B and C being 14.5%, 28.2% and 24.1%, respectively and the chi-squared test presenting $\chi^2 = 4.099$ and $P = 0.129 > 0.05$, no significant difference in clinical effective rates was found among three groups.

The comparison of the integral efficacy among groups of different application time: In 229 qualified cases, 2 cases (0.9%) were evaluated as cured, 30 cases (13.1%) greatly improved, 155 cases (67.7%) improved and 42 cases (18.3%) not changed. There were significant differences in the percentages mentioned above ($\chi^2 = 7.538$, $P = 0.023 < 0.05$) (**Table 5**). Further multiple comparisons showed a significant difference in integral efficacy distribution between group A and group B ($P = 0.020$). However, there was no statistically significant difference between other two groups. The integral efficacy of group B was the best among all the groups after when the two-week treatments. The integral effective rate of group A, B and C were 8.8%, 21.8% and 10.8%, respectively and chi-squared test found that the difference in integral effective rates among three groups were statistically significant ($\chi^2 = 6.146$, $P = 0.046 < 0.05$). While group A has the lowest the integral effective rate, group B achieved the highest integral effective rate, with was consistent with the result of integral efficacy.

Analysis of major efficacy (V3)

The summary of the dropout cases among groups of different application time: At V2, the difference of dropout rate among three groups was found statistically significant ($\chi^2 = 9.165$, $P = 0.010 < 0.05$) by a chi-square test. Group A had the highest dropout rate (24.2%), while group C had the lowest (10.1%). Hypothesis was put forward that the dropout rate was linked with adverse reactions and significant difference ($P = 0.001 < 0.05$) in dropout rates of the groups was found by a Fisher's exact test. Adverse reactions resulting in a dropout rate of 9.9% in group A, ranking the highest in all groups. And 0 dropout rate was caused by adverse reactions in group C, which ranked lowest in all groups. A chi-square test was performed on the dropout rates caused by other reasons and no significant difference was found ($\chi^2 = 1.866$, $P = 0.393 > 0.05$) in the rates of different groups. It was therefore considered that the ratio of dropout rate caused by other reasons in all three groups was the same (**Table 6**).

The comparison of the fungal clearance rate among groups of different application time: The fungal microscopy result of all 267 enrolled patients was positive and the positive rate of fungal culture was 78.76% including 65.04% of isolation positive rate of dermatophytes (mainly including Trichophyton rubrum and Trichophyton mentagrophytes) and 13.72% of other non-dermatophytes (mainly including candida and aspergillosis etc). In 227 qualified cases, 188 cases were evaluated as fungal cleared (82.8%), of which 58 cases (84.1%) were from group A, 69 cases (88.5%) from group B and 61 cases (76.3%) from group C. The difference in fungal clearance among the three groups were no statistically significant ($\chi^2 = 4.246$, $P = 0.120 > 0.05$) (**Table 7**).

Table 8. The comparison of clinical efficacy in groups of different application time in V3 period [n (%)]

Groups of different application time	The evaluation of clinical efficacy				χ^2	*P*
	Cured	Greatly improved	Improved	Not changed		
Group 1 (n = 69)	12 (17.4)	27 (39.1)	26 (37.7)	4 (5.8)	2.206	0.332
Group 2 (n = 78)	6 (7.7)	46 (59.0)	24 (30.8)	2 (2.6)		
Group 3 (n = 80)	14 (17.5)	41 (51.2)	25 (31.3)	0 (0)		
Total (n = 227)	32 (14.1)	114 (50.2)	75 (33.0)	6 (2.6)		

Table 9. The Comparison of integral efficacy in groups of different application in V3 period [n (%)]

Groups of different application time	The evaluation of integral efficacy				χ^2	*P*
	Cured	Greatly improved	Improved	Not changed		
Group 1 (n = 69)	12 (17.4)	22 (31.9)	31 (44.9)	4 (5.8)	0.971	0.615
Group 2 (n = 78)	6 (7.7)	42 (53.8)	28 (35.9)	2 (2.6)		
Group 3 (n = 80)	14 (17.5)	31 (38.8)	35 (43.8)	0 (0)		
Total (n = 227)	32 (14.1)	95 (41.9)	94 (41.4)	6 (2.6)		

The comparison of the clinical efficacy in groups of different administration time: Among the 227 qualified cases, 32 cases (14.1%) were evaluated as cured, 114 cases (50.2%) greatly improved, 75 cases (33.0%) improved and 6 cases (2.6%) not changed. There were significant differences in the percentages listed above (χ^2 = 2.206, *P* = 0.332 > 0.05) (**Table 8**). On the other hand, there was no difference in the clinical efficacy among all the groups with different application time, with the clinical effective rates of group A, B and C being 56.5%, 66.7% and 68.8%, respectively. There was no significant difference in the clinical efficacy rate among three groups (chi-squared test, χ^2 = 4.099 and *P* = 0.259 > 0.05).

The comparison of the integral efficacy in groups of different application time: Among 227 qualified cases, 32 cases (14.1%) were evaluated as cured, 114 cases (50.2%) greatly improved, 75 cases (33.0%) improved and 6 cases (2.6%) not changed. Significant differences were observed in the percentages listed above (χ^2 = 0.971, *P* = 0.615 > 0.05) (**Table 9**). However, no significantly different in the integral efficacy was found among different groups (χ^2 = 0.971, *P* = 0.615 > 0.05) (**Table 9**). With the integral effective rate of group A, B and C being 49.3%, 61.5% and 56.3%, respectively, no significant difference in the integral effective rates was found among these groups (chi-squared test, χ^2 = 2.239 and *P* = 0.327 > 0.05).

Safety analysis

As shown in **Table 10**, 31 cases of transient pain (11.6%), 20 cases of pain (7.5%), 17 cases of erosion (6.4%), 10 cases of pruritus (3.7%), 6 cases of burning (2.2%), and 3 cases of swelling (1.1%) were reported during the study. All these adverse events could be alleviated without any treatment. The incidence of pain and erosion in group A was significantly higher than that in group B and C. The only case of ulcer occurred in group A, which was cured after one-week application of *Bactroban, Bifonazole, and Hirudoid* (**Figure 1**). The dropout rates resulting from adverse reactions in group A, B and C were 9.9%, 2.3% and 0.0%, respectively, which were found to differed from each other significantly.

Discussion

Traditional topical drugs has poor penetration into lesions of moccasin-type tinea pedis, and therefore these topical drugs along fail to achieve the complete cure of the disease [9, 10]. A routine oral application of itraconazole is recommended in some countries for the treatment of moccasin-type tinea pedis [11-14]. It is also specified in the tinea pedis therapy guidelines in China that best efficacy could be achieved with application of itraconazole 200 mg/time and twice a day for 7 days on moccasin-type tinea pedis [15]. Nonetheless, oral antifungal medicines are not suitable for all patients with moccasin-type tinea pedis because of the induced gastrointestinal reactions, liver function abnormal, and many other adverse drug reactions [16-19]. As a new topical drug for tinea pedis, Meifute® antifungal solution contains nanosilver, Benzalkonium chloride, menthol, citric acid, lactic acid, glacial acetic acid and other effective ingredients. Nanosilver particles could directly penetrate into the bacteria and combine with the enzymes

Table 10. The incidence of different adverse reactions [n (%)]

Groups of different application time	Transient pain	Pain	Erosion	Pruritus	Burning	Swelling	Ulceration
Group A (n = 91)	9 (9.9)	12 (13.2)	13 (14.3)	5 (5.5)	2 (2.2)	2 (2.2)	1 (1.1)
Group B (n = 87)	10 (11.5)	2 (2.3)	4 (4.6)	1 (1.1)	1 (1.1)	1 (1.1)	0 (0.0)
Group C (n = 89)	12 (13.5)	6 (6.7)	0 (0.0)	4 (4.5)	3 (3.4)	0 (0.0)	0 (0.0)
Total (n = 267)	31 (11.6)	20 (7.5)	17 (6.4)	10 (3.7)	6 (2.2)	3 (1.1)	1 (0.4)

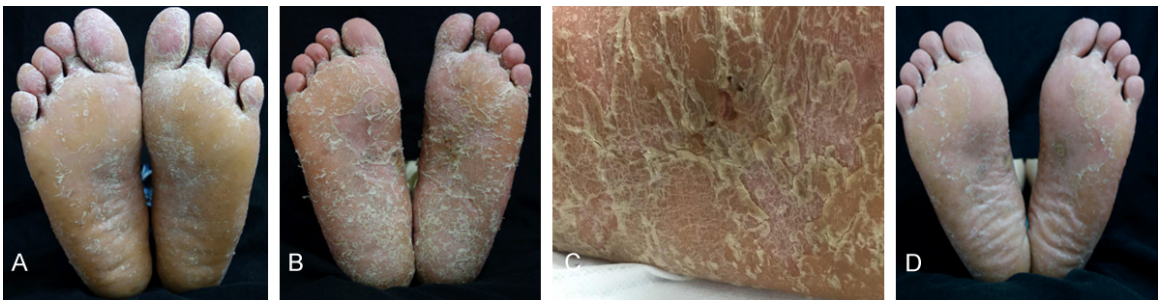

Figure 1. Patient 68A in group A with moccasin-type tinea pedis (A, before treatment) felt burning and pain 30 minutes after the first time of foot bath. His feet were swollen next day and were difficult to walk. The patient came back again after 1 week and the physical examination showed that there was a lot of scale in bilateral planta pedis, and three bean-size superficial ulcers (B, C) covered by little yellow or white purulent secretion in the medial lateral, and accompanied with slight tenderness. The diagnosis was considered to be *primary irritant contact dermatitis with infection,* prescribed *Bactroban, Bifonazole, Hirudoid* for external application, and the ulcers disappeared and scale greatly reduced (D) after one week.

of oxygen metabolism, leading to the asphyxia of bacteria. It could not only inhibit the growth or kill most of the bacteria and fungi, but also have antibacterial activity to drug-resistant pathogens. Benzalkonium chloride is a cationic surfactant, working with a non-oxidative mechanism and has highly effective bactericidal ability in a broad-spectrum. Menthol results in a feeling of coolness, relieves itchiness and pain and reduces the pruritus caused by tinea pedis and other discomfort like twinge or burning that are caused by the effective ingredients of the drug. Citric acid, a kind of alpha hydroxyl acid, functions to speed up the renewal of keratin layer. Lactic acid mainly acts as a drug carrier and pH regulator, which has an effect of antisepsis and bactericidal. Glacial acetic acid can regulate pH and effectively inhibit the growth or kill the fungal colonization on superficial skin. Meifute® antifungal solution with strong permeability can accelerate the renewal of keratin and effectively inhibit microbial reproduction. It can also combine with the protein molecules on the surface of fungi and split the proton pump, leading to the cracking of the fungal cell membrane and achieving the effect of fungicidal [7].

It was found by this multicenter clinical study that after four-week treatment on moccasin-type tinea pedis using Meifute® antifungal solution with different application time in (V3), the fungal clearance rate was 82.8%, clinical effective rate was 64.3%, and the integral effective rate was 56.0%. It was suggested by the data that Meifute® Antifungal Solution alone and effectively clear pathogens and achieve well therapeutic efficacy in the treatment of moccasin-type tinea pedis. Previous studies presented a fungal clearance rate of 96.5% [6] and integral effective rate of 88.71% [7] after weekly application of Meifute® antifungal solution with the application time being two hours each time. The fungal clearance rate and integral effective rate in previous studies are higher than that of this study, which was presumably due to the fact the application time of group B and group C in this study were shorter than that of the standard application time. Moreover, the stricter inclusion criteria and the hot weather and humid climate in southern China may also be the reasons of lower fungal clearance rate and integral effective rate in this study. For group B and C, the application time was shortened to 1 hour and 0.5 hour. No sta-

tistically significant difference were found amongbetween group B and C with group A (2 hours standard application time) in fungal clearance rate, clinical efficacy, clinical effective rate, integral efficacy, and integral effective rate after four-week treatment. But group B and C have significantly lower drop-out rates resulting from adverse reactions such as pain and erosion etc., when compared with group A. In group C, where the best compliance were observed, no incidence of adverse reactions such as erosion and swelling has occurred, and therefore has not resulted in dropout of the patients. It was found that a shortened application time of Meifute® antifungal solution to 0.5 hour could lead to less adverse drug reactions and thus greatly improve the compliance of patients. And the application time of 0.5h can achieve the same therapeutic efficacy as standard treatment for two hours does.

It is worth noting that the clinical efficacy of group B and group C were better than that of group A after the treatment for 2 weeks (V2), and the integral efficacy of group B was the best, with the highest clinical effective rate of 21.8%s being significantly higher than that of group A (8.8%). This is considered to be associated with the interference on TSS, which was caused by an increased incidence of scale, pruritus, and erosion after prolonged administration in group A. The latest research showed [20, 21] that the regimen of 2% naftifine hydrochloride gel alone administered once daily for 2 weeks was effective in the therapy of moccasin-type tinea pedis. And 4 weeks after withdrawal, the fungal clearance rate, the effective rate and the percentage of patient evaluated as cured were 65.8%, 51.4% and 19.2%, respectively. However, a treatment for 2 weeks (withdrawal) resulted in a cure rate of a mere 1.7%. The fungal clearance and effective rate of Meifute® antifungal solution at 2 weeks after withdrawal (V3) was slightly higher than that of 2% naftifine hydrochloride gel at 4 weeks after withdrawal. The results show that the efficacy of Meifute® antifungal solution applied on moccasin-type tinea pedis alone was equivalent to or better than that of 2% naftifine hydrochloride gel alone. It was also found in this study that the cured rate was only 0.9% when the applied Meifute® antifungal solution for 2 weeks, but the rate climbed up to 14.1% at 2 weeks after withdrawal. This change wa almost the same as that of 2% nifedipine hydrochloride gel when applied for 2 weeks and 4 weeks after withdrawal. It is therefore suggested that both of these two drugs have after-effect. The higher cured rate at 2 to 4 weeks after withdrawal when compared to that right after the withdrawal might also be associated with the exacerbation of drug-induced scale, itchiness or erosion. Also, this may be due to the fact that some of the dead fungus in the microscopy could be easily seen and mistakenly considered to be a positive result.

Throughout the entire study, in spite of the adverse reactions observed, there is no systematic adverse reactions reported any of the three groups and all of the adverse reactions were mild and can be alleviated without any treatment. The only case of ulcer which occurred in group A was cured with a topical drug treatment for 1 week. Transient pain and pain were the adverse reactions with highest incidence. These adverse reactions were observed to occurred most often within 10 min of foot bath and would significantly reduce or disappear about 15 min later. The adverse reaction of Transient pain and pain may be related to the small amount of glacial acetic acid (5.7-6.3%) in the Meifute® Antifungal Solution.

To conclude, the Meifute® Antifungal is effective, convenient and safe treatment for moccasin-type tinea pedis. According to the observation, desquamation would normally start in 1 week after application and lead to the fungi clearing and then the cure of tinea pedis. A shortened application time of the Meifute Antifungal to 0.5 hour could achieve the same therapeutic efficacy as that of the standard administration of 2 hours but reduce the incidence of adverse reactions, which could then greatly improve the compliance of patients.

Disclosure of conflict of interest

None.

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