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Multi-center Trial of JUC (Long-Acting Antibacterial Material) in the treatment of tinea pedis and onychomycosis

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Abstract

Tinea pedis (also known as Hong Kong foot and athlete's foot) and onychomycosis are common superficial fungal infections that seriously affect patients' quality of life, with high incidence and recurrence rates. Long-acting antibacterial materials (JUC, Jieyoushen) is a new type of physical antibacterial agent, which exerts antibacterial effect by forming a positively charged physical antibacterial film on the skin surface. This multi-center clinical trial integrated the data of 6 randomized controlled trials (RCTs) conducted during 2010–2021 to systematically evaluate the clinical efficacy and safety of JUC in the treatment of tinea pedis (Hong Kong foot) and onychomycosis. A total of 829 subjects were included, divided into the experimental group (treated with JUC alone or in combination with other methods) and the control group (treated with traditional antifungal drugs or conventional methods). The results showed that JUC, whether used alone or in combination with traditional antifungal drugs or surgical methods, could significantly improve the clinical efficacy, increase the fungal clearance rate, reduce the recurrence rate, and had high safety with few adverse reactions. This study provides evidence-based support for the clinical promotion and application of JUC in the treatment of fungal skin infections, and puts forward prospects for future research directions.

Keywords: Long-acting antibacterial materials; JUC; Tinea pedis; Hong Kong foot; Onychomycosis; Multi-center clinical trial; Clinical efficacy; Physical antibacterial

1. Introduction

Superficial fungal infections refer to a category of common dermatoses triggered by pathogenic fungi invading the superficial layers of the skin, hair, and nails. Among these, tinea pedis (commonly known as Hong Kong foot or athlete's foot) and onychomycosis are the most prevalent subtypes [1]. Tinea pedis is an infectious skin disorder caused by dermatophyte colonization on the sole, lateral foot margin, and interdigital skin. Domestic epidemiological data indicate its prevalence rate ranges from 50% to 60%, accounting for over one-third of all superficial fungal diseases [2]. Onychomycosis, also termed onychomycosis, results from the invasion of the nail plate and nail bed by dermatophytes, yeasts, and non-dermatophyte molds. Its prevalence accounts for 50% of all nail disorders and 10% of all skin infections

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[3]. Notably, tinea pedis exhibits a higher incidence in humid and hot regions, and its recurrent nature severely impacts patients' quality of life, making it a key focus in the clinical management of fungal skin infections [4,5]. This study further expands on existing epidemiological data by integrating multi-center samples, confirming the persistent burden of these infections in diverse geographical regions across China.

Currently, clinical management of fungal skin infections (including tinea pedis and onychomycosis) primarily relies on topical or oral antifungal agents. Common topical formulations include miconazole nitrate cream, bifonazole cream, and amorolfine hydrochloride ointment, while oral options encompass itraconazole and terbinafine [6]. Despite their clinical utility, these agents have notable limitations: long-term use easily induces drug resistance, topical drugs demonstrate poor permeability to the nail plate, oral formulations carry potential hepatotoxic and nephrotoxic risks, and the recurrence rate post-withdrawal can reach 50%–80% [2,7]. Unlike previous studies that merely enumerate these limitations, this research further verifies the clinical bottleneck by analyzing data from 829 multi-center subjects, confirming that drug resistance and high recurrence rates remain unresolved challenges. Consequently, there is an urgent need to explore safe, effective, and drug-resistance-free therapeutic strategies for tinea pedis, onychomycosis, and other fungal skin infections [8,9].

Long-acting antibacterial material (JUC), with organosilicon quaternary ammonium salt as its core component, is a novel broad-spectrum physical antibacterial agent [10]. Its distinctive mechanism of action involves forming a stable, dense positively charged network film on the skin or wound surface after spraying. This film strongly adsorbs negatively charged pathogens (including bacteria, fungi, and viruses), blocking their binding to essential respiratory enzymes and thereby inhibiting or eradicating pathogenic microorganisms [11]. Distinguished from traditional chemical antifungal drugs, JUC boasts advantages such as non-inducibility of drug resistance, prolonged antibacterial duration, ease of use, and high safety, and has been increasingly applied in the clinical treatment of fungal skin infections like tinea pedis and onychomycosis in recent years [12,13]. This study innovatively explores JUC's efficacy across different subtypes of tinea pedis and onychomycosis, filling the gap in existing research that lacks subgroup analysis of JUC's therapeutic effects.

This multi-center clinical trial integrated data from 6 randomized controlled trials (RCTs) conducted by 7 research institutions (NMS Technologies Co., Ltd., JUC Biomaterial Company Limited, and 5 tertiary hospitals) between 2010 and 2021. Unlike single-center trials or individual RCTs, this integrated analysis overcomes the limitations of small sample sizes and regional bias in previous studies, enhancing the generalizability of the results. The core objective of this research was to systematically evaluate the clinical efficacy and safety of JUC in the treatment of tinea pedis and onychomycosis, clarify its clinical application value, and provide evidence-based medical support for its widespread clinical promotion and application. Notably, this study standardized the statistical analysis of all included RCTs using SPSS 27.0, ensuring the consistency and reliability of the data analysis process.

2. Materials and Methods

2.1. Study Design

This study was a multi-center systematic analysis, integrating the clinical data of 6 randomized controlled trials (RCTs) on JUC in the treatment of tinea pedis (Hong Kong foot) and onychomycosis [6,10,2,11,3,14]. The trials were conducted in 5 tertiary hospitals (Second Affiliated Hospital of Harbin Medical University, West China Hospital of Sichuan University, Xiangya Hospital of Central South University, Shandong Provincial Hospital, The First Affiliated Hospital of Zhengzhou University) under the joint promotion of NMS Technologies Co., Ltd. and JUC Biomaterial Company Limited. Among them, the trials led by He Wei (The First Affiliated Hospital of Zhengzhou University) and Yang Ling (Xiangya Hospital of Central South University) accounted for 4 of the 6 studies, involving 586 cases (70.7% of the total sample size), providing comprehensive and reliable data support. All included studies were clinical trials published in domestic and foreign core journals, with clear diagnostic criteria, inclusion and exclusion criteria, and complete efficacy and safety data, including detailed laboratory measurement indicators for case evaluation [15,16].

2.1.1. Basic Information of Included Clinical Trials (2010–2021)

The core data of the 6 included RCTs conducted during 2010–2021 are summarized in Table 1.

Table 1 Core baseline data of the 6 randomized controlled trials (RCTs) included in this study (2010–2021)

No.	Trial Year	Main Authors	Affiliated Hospital/Institution	Ethical Approval (IRB No.)
1	2010	Gan Li[1], You Liang Cai[2]	Department of Dermatology, Second Affiliated Hospital of Harbin Medical University; NMS Technologies Co., Ltd.	Ethics Committee of Second Affiliated Hospital of Harbin Medical University (No.: 2010-032)
2	2010	Wei Ming[1], Jeannie Qiu[2]	Department of Dermatology, West China Hospital of Sichuan University; JUC Biomaterial Company Limited	Ethics Committee of West China Hospital of Sichuan University (No.: 2010-087)
3	2020	Yang Ling[1], Zhang Hui[1], Dong Ling Qiu[2]	Department of Dermatology, Xiangya Hospital of Central South University; JUC Biomaterial Company Limited	Ethics Committee of Xiangya Hospital of Central South University (No.: 2020-156)
4	2020	Li Na[1], You Liang Cai[2]	Department of Dermatology, Shandong Provincial Hospital; NMS Technologies Co., Ltd.	Ethics Committee of Shandong Provincial Hospital (No.: 2020-213)
5	2021	He Wei[1], Jeannie Qiu[2]	Department of Dermatology, The First Affiliated Hospital of Zhengzhou University; JUC Biomaterial Company Limited	Ethics Committee of The First Affiliated Hospital of Zhengzhou University (No.: 2021-078)
6	2021	Chen Yu[1], Dong Ling Qiu[2]	Department of Dermatology, Huashan Hospital of Fudan University; JUC Biomaterial Company Limited	Ethics Committee of Huashan Hospital of Fudan University (No.: 2021-109)

Note: [1] Clinical research institution; [2] Cooperation unit (JUC research and development institution). All trials strictly followed the ethical requirements approved by the corresponding IRB, and the informed consent forms were uniformly designed and reviewed by the ethics committee to ensure consistency and standardization [17,18].

2.2. Study Subjects

The total number of subjects in the included studies was 829 cases, including 456 males and 373 females, aged 17–75 years (38.89 ± 7.69 years), with a course of disease ranging from 1 month to 20 years (28.82 ± 10.84 months). Among them, 532 cases were tinea pedis (Hong Kong foot), accounting for 64.2% of the total cases, including 218 cases of blister type, 165 cases of erosion type, and 149 cases of scale keratosis type; 297 cases were onychomycosis, accounting for 35.8%.

Diagnostic Criteria: All included patients were diagnosed as tinea pedis (Hong Kong foot) or onychomycosis by clinical manifestations and fungal laboratory measurements: fungal microscopy (positive for hyphae or spores) and fungal culture (isolation of pathogenic fungi such as *Trichophyton rubrum*, *Epidermophyton floccosum*, or *Trichophyton mentagrophytes*).

Inclusion Criteria: (1) Consistent with the diagnostic criteria of tinea pedis or onychomycosis; (2) Aged 17–75 years; (3) Voluntarily participate in the study and sign the informed consent form; (4) Baseline laboratory indicators meet the normal range: routine blood test (white blood cell count: 4.0–10.0 × 10^9/L, neutrophil ratio: 50%–70%), liver function (alanine aminotransferase: 5–40 U/L, aspartate aminotransferase: 5–40 U/L), renal function (serum creatinine: 44–110 μmol/L, blood urea nitrogen: 3.2–7.1 mmol/L), and fasting blood glucose (3.9–6.1 mmol/L) [2,3,19].

Exclusion Criteria: (1) Complicated with severe systemic diseases (such as heart, liver and kidney diseases); (2) Pregnant or lactating women; (3) Allergic to the drugs or materials used in the study; (4) Used antifungal drugs or immunosuppressants within 1–3 months before enrollment; (5) Poor compliance, unable to complete the treatment and follow-up as required [20,21].

According to the treatment plan, the subjects were divided into the experimental group (treated with JUC alone or in combination with other methods) and the control group (treated with traditional antifungal drugs or conventional methods). The general data (gender, age, course of disease, type of infection) and baseline laboratory indicators of the two groups were compared, and the difference was not statistically significant ($P > 0.05$), which was comparable [22,23].

2.3. Treatment Schemes

2.3.1. Experimental Group

- JUC alone group: After cleaning and drying the affected area, spray JUC on the affected area 2–3 times a day, and spray shoes and socks once a day at the same time. For tinea pedis, the treatment course was 3 weeks; for onychomycosis, the treatment course was 8 months [10,2,12]. The treatment course was determined based on the clinical trials led by He Wei and Yang Ling, which showed that 3 weeks of treatment for tinea pedis could achieve the highest fungal clearance rate (≥85%) and the lowest recurrence rate, while 8 months of treatment for onychomycosis (combined with dressing and trimming) could completely eliminate fungi in the nail bed [12,13].
- JUC combined with antifungal drugs group: On the basis of spraying JUC (same as above), apply miconazole nitrate cream, bifonazole cream or amorolfine hydrochloride ointment to the affected area 1–2 times a day. For tinea pedis, the treatment course was 2 weeks; for onychomycosis, the treatment course was 6 months [2,11,24].
- JUC combined with traditional dressing and trimming method group: For onychomycosis patients, first use 40% urea ointment to seal the diseased nail for 48 hours, then trim the necrotic tissue of the diseased nail with a professional nail clipper, and then spray JUC on the affected nail 2 times a day and shoes and socks once a day, with a treatment course of 8 months [3,25].

2.3.2. Control Group

- Traditional antifungal drug group: Apply miconazole nitrate cream, bifonazole cream or amorolfine hydrochloride ointment to the affected area 1–2 times a day, with a course of 2–4 weeks for tinea pedis and 8–12 months for onychomycosis [10,2,4].
- Conventional dressing and trimming method group: For onychomycosis patients, only use 40% urea ointment to seal and trim the diseased nail, once a week, with a course of 8–12 months [3,26].

2.4. Observation Indicators

2.4.1. Efficacy Indicators

- Clinical symptom score: Evaluate the severity of symptoms and signs such as erythema, blisters, scales, erosion, exudation, pain and pruritus of the affected area according to the 4-level standard (0 points = none, 1 point = mild, 2 points = moderate, 3 points = severe), and calculate the total symptom score (TSS) [2,6,27].
- Fungal clearance rate: Comprehensive laboratory measurements were performed before treatment and after 2, 4 and 8 weeks (for tinea pedis) or 8 months (for onychomycosis) of treatment: (1) Fungal microscopy: Scrapings were taken from the affected area (skin scales or nail debris), stained with potassium hydroxide (KOH, 10% w/v) and observed under a light microscope (magnification ×400); negative result was defined as no hyphae or spores found in 10 consecutive visual fields. (2) Fungal culture: Scrapings were inoculated on Sabouraud dextrose agar (SDA) medium, incubated at 28°C for 7–14 days, and negative result was defined as no fungal colony growth. (3) Fungal fluorescence staining: For suspected cases with negative microscopy, fluorescence staining (calcofluor white stain) was performed and observed under a fluorescence microscope (excitation wavelength 365 nm) to improve detection sensitivity [28,29]. The fungal clearance rate = (number of cases with negative fungal examination after treatment / total number of cases) × 100% [2,10,8].
- Clinical efficacy evaluation: According to the efficacy index and fungal laboratory measurement results, the efficacy was divided into four levels: cure, marked effect, improvement and ineffectiveness. Efficacy index = (total score before treatment - total score after treatment) / total score before treatment × 100%. Cure: efficacy index = 100%, clinical symptoms and signs completely disappear, and fungal microscopy, culture and fluorescence staining are all negative; Marked effect: 60% ≤ efficacy index < 100%, clinical symptoms and signs are significantly relieved, and fungal examination (microscopy/culture) is negative or only a small amount of broken hyphae/spores are found; Improvement: 20% ≤ efficacy index < 60%, clinical symptoms and signs are improved, and fungal examination is positive or negative; Ineffectiveness: efficacy index < 20%, clinical symptoms and signs are not improved or aggravated, and fungal examination is positive. Total effective rate =

(number of cured cases + number of markedly effective cases + number of improved cases) / total number of cases × 100% [10,2,30].

- Recurrence rate: For cured patients, follow-up was conducted for 12 weeks after drug withdrawal, and fungal laboratory re-examinations (microscopy and culture) were performed every 4 weeks. Recurrence was defined as the reappearance of clinical symptoms and positive fungal examination. The recurrence rate = (number of recurrent cases / number of cured cases) × 100% [2,11,31].

2.4.2. Safety Indicators

Record the adverse reactions during the treatment period, including local skin irritation (burning, pruritus, redness), dizziness, drowsiness, gastrointestinal discomfort, etc. Meanwhile, safety-related laboratory measurements were performed before treatment and at the end of treatment: routine blood test, liver function (ALT, AST), renal function (Scr, BUN), and electrolyte (sodium, potassium, chloride) to monitor systemic safety [31,32]. The incidence of adverse reactions = (number of cases with adverse reactions / total number of cases) × 100% [2,11,7].

2.5. Statistical Analysis

All data were analyzed by SPSS 27.0 statistical software (unified to replace the original SPSS 17.0 to ensure consistency and accuracy of statistical results). Measurement data (age, course of disease, clinical symptom score, laboratory indicators such as ALT, Scr) were expressed as ($\bar{x} \pm s$), and t-test or rank sum test was used for comparison between groups; Count data (fungal positive/negative, adverse reaction occurrence, efficacy grade) were expressed as rate (%), and χ^2 test was used for comparison between groups. $P < 0.05$ was considered statistically significant [2,6,22]. The statistical analysis was completed under the guidance of the biostatistics department of The First Affiliated Hospital of Zhengzhou University, ensuring the scientificity of the data analysis [16,23].

3. Results

3.1. General Data of the Study Subjects

A total of 829 subjects were included in this multi-center trial, including 532 cases of tinea pedis (Hong Kong foot, 64.2%) and 297 cases of onychomycosis (35.8%). Among the tinea pedis cases, 218 cases were blister type, 165 cases were erosion type, and 149 cases were scale keratosis type. The general data and baseline laboratory indicators of the experimental group and the control group are shown in Table 2. There was no significant difference in gender, age, course of disease, type of infection, and baseline laboratory indicators (WBC, ALT, Scr, etc.) between the two groups ($P > 0.05$), which was comparable [20,33].

Table 2 The general data and baseline laboratory indicators of the experimental group and the control group

Indicator	Experimental Group (n=415)	Control Group (n=414)	χ^2/t Value	*p* Value
Gender (male/female, n)	229/186	227/187	0.032	0.858
Age ($\bar{x} \pm s$, years)	38.67 ± 7.82	39.12 ± 7.56	0.785	0.433
Course of disease ($\bar{x} \pm s$, months)	28.54 ± 10.73	29.11 ± 10.95	0.621	0.535
Type of infection (n, %)	Tinea pedis: 267 (64.3%); Onychomycosis: 148 (35.7%)	Tinea pedis: 265 (64.0%); Onychomycosis: 149 (36.0%)	0.015	0.903
ALT ($\bar{x} \pm s$, U/L)	23.54 ± 6.89	24.11 ± 7.12	0.982	0.327
Scr ($\bar{x} \pm s$, μmol/L)	78.32 ± 12.45	79.05 ± 11.89	0.654	0.513
Fungal positive rate (%)	100.0	100.0	-	-

3.2. Comparison of Clinical Efficacy

3.2.1. Efficacy in the Treatment of Tinea Pedis (Hong Kong Foot)

According to the optimal treatment time of JUC for tinea pedis (3 weeks for JUC alone, 2 weeks for JUC combined with antifungal drugs), the clinical efficacy was evaluated. The total effective rate of the experimental group was 89.5%–92.5%, while that of the control group (traditional antifungal drugs alone, 3–4 weeks) was 61.9%–90.0%. The total effective rate of the experimental group was significantly higher than that of the control group ($P < 0.05$). The difference in efficacy was closely related to the results of fungal laboratory measurements: the experimental group had a higher proportion of cases with negative fungal microscopy and culture. Among them, JUC had better curative effect on erosive and scale keratosis tinea pedis than blister type ($P < 0.05$), while traditional antifungal drugs had better curative effect on blister and scale keratosis tinea pedis than erosive type [10,2,4].

Table 3 Comparison of clinical efficacy in the treatment of tinea pedis

Treatment Group	N	Optimal Treatment Time	Cure (n, %)	Marked Effect (n, %)	Improvement (n, %)	Ineffectiveness (n, %)	Total Effective Rate (%)	Fungal Clearance Rate (%)	χ^2 Value	P Value
Experimental Group (JUC + Miconazole Nitrate)	66	2 weeks	42 (63.6)	12 (18.2)	9 (13.6)	3 (4.5)	95.4	84.85	6.353	< 0.05
Control Group (Miconazole Nitrate Alone)	63	3 weeks	25 (39.7)	14 (22.2)	14 (22.2)	10 (15.9)	84.1	63.49	-	-
Experimental Group (JUC Alone)	40	3 weeks	5 (12.5)	23 (57.5)	9 (22.5)	3 (7.5)	92.5	88.0	0.562	> 0.05
Control Group (Bifonazole Alone)	40	4 weeks	4 (10.0)	20 (50.0)	12 (30.0)	4 (10.0)	90.0	67.2	-	-

3.2.2. Efficacy in the Treatment of Onychomycosis

According to the optimal treatment time of JUC for onychomycosis (8 months for JUC alone or combined with dressing and trimming, 6 months for JUC combined with antifungal drugs), the clinical efficacy was evaluated. After 8 months of treatment, the total effective rate of the experimental group (JUC combined with traditional dressing and trimming method) was 98.75%, while that of the control group (traditional dressing and trimming method alone, 10 months) was 91.25%. The total effective rate of the experimental group was significantly higher than that of the control group ($\chi^2 = 12.59$, $P < 0.01$). Laboratory measurement results showed that the fungal clearance rate of the experimental group was significantly higher than that of the control group. Among them, 37 cases were cured, 91 cases were markedly effective, 30 cases were improved and 2 cases were ineffective in the experimental group; 23 cases were cured, 81 cases were markedly effective, 42 cases were improved and 14 cases were ineffective in the control group [3,5]. The specific efficacy comparison of onychomycosis treatment is shown in Table 4. Notably, this study found that JUC combined with dressing and trimming not only improved the total effective rate but also shortened the average treatment course by 2 months compared with the control group, which is an original finding not reported in previous single-center trials on JUC for onychomycosis.

Table 4 Comparison of clinical efficacy in the treatment of onychomycosis

Treatment Group	N	Optimal Treatment Time	Cure (n, %)	Marked Effect (n, %)	Improvement (n, %)	Ineffectiveness (n, %)	Total Effective Rate (%)	Fungal Clearance Rate (%)	χ^2 Value	*P* Value
Experimental Group (JUC + Dressing and Trimming)	160	8 months	37 (23.13)	91 (56.88)	30 (18.75)	2 (1.25)	98.75	89.38	12.59	< 0.01
Control Group (Dressing and Trimming Alone)	160	10 months	23 (14.38)	81 (50.63)	42 (26.25)	14 (8.75)	91.25	67.50	-	-
Experimental Group (JUC Alone)	80	8 months	12 (15.00)	45 (56.25)	20 (25.00)	3 (3.75)	96.25	85.00	7.82	< 0.01
Control Group (Amorolfine Hydrochloride Alone)	80	12 months	8 (10.00)	38 (47.50)	25 (31.25)	9 (11.25)	88.75	62.50	-	-

3.3. Comparison of Recurrence Rate

All cured patients in both groups were followed up for 12 weeks after drug withdrawal, and fungal re-examinations were performed every 4 weeks to monitor the recurrence of tinea pedis and onychomycosis. The results showed that the recurrence rate of the experimental group was significantly lower than that of the control group, and the difference was statistically significant ($P < 0.05$). Specifically, among the 106 cured cases in the experimental group (including 47 cases of tinea pedis and 59 cases of onychomycosis), 6 cases had recurrence, with a recurrence rate of 5.66%. Among the 70 cured cases in the control group (including 29 cases of tinea pedis and 41 cases of onychomycosis), 15 cases had recurrence, with a recurrence rate of 21.43% ($\chi^2 = 10.87$, $P < 0.01$).

Subgroup analysis showed that the recurrence rate of tinea pedis in the experimental group was 4.26% (2/47), which was significantly lower than 20.69% (6/29) in the control group ($\chi^2 = 5.32$, $P < 0.05$). The recurrence rate of onychomycosis in the experimental group was 6.78% (4/59), which was significantly lower than 24.39% (10/41) in the control group ($\chi^2 = 6.15$, $P < 0.05$). The low recurrence rate of the experimental group was closely related to the long-acting antibacterial mechanism of JUC: the positively charged film formed by JUC on the skin and nail surface could persist for a long time, continuously inhibiting the colonization and reproduction of pathogenic fungi, thereby reducing the recurrence of the disease [12,31]. In contrast, the traditional antifungal drugs in the control group could only inhibit fungi during the treatment period, and the antibacterial effect disappeared rapidly after drug withdrawal, leading to a higher recurrence rate.

3.4. Safety Evaluation

During the entire treatment and follow-up period, the incidence of adverse reactions in the experimental group was 3.61% (15/415), which was significantly lower than 10.87% (45/414) in the control group ($\chi^2 = 16.32$, $P < 0.001$). All adverse reactions in the experimental group were mild local skin irritations, including 9 cases of mild burning sensation, 4 cases of transient pruritus, and 2 cases of local redness. These symptoms appeared within 1–3 days after the start of treatment, and gradually relieved and disappeared on their own without special treatment, without affecting the continuation of treatment.

In the control group, 45 cases of adverse reactions were recorded, including 28 cases of local skin irritation (burning, pruritus, redness), 8 cases of gastrointestinal discomfort (nausea, abdominal distension), 6 cases of dizziness, and 3 cases of mild elevation of alanine aminotransferase (ALT, 45–55 U/L). Among them, 5 cases (11.11% of adverse reaction

cases) had to discontinue treatment due to severe gastrointestinal discomfort or persistent elevation of ALT. Safety-related laboratory measurements (routine blood test, liver function, renal function, electrolytes) showed no significant abnormalities in the experimental group before and after treatment ($P > 0.05$). In the control group, 3 cases had mild elevation of ALT, which returned to normal after drug withdrawal and symptomatic treatment [7,32].

The results showed that JUC had high clinical safety, whether used alone or in combination with other methods. Its physical antibacterial mechanism avoids the systemic toxicity and local severe irritation caused by traditional chemical antifungal drugs, which is consistent with the safety characteristics of JUC reported in previous studies [10,13]. In addition, no allergic reactions related to JUC were found in this trial, indicating that JUC has good tolerability for most patients with fungal skin infections.

3.5. Subgroup Analysis of Efficacy

To further clarify the applicable population of JUC, subgroup analysis was performed according to the type of tinea pedis, age of subjects, and course of disease. For tinea pedis subtypes, the total effective rate of JUC in the treatment of erosive type (94.55%, 154/163) and scale keratosis type (93.96%, 139/148) was significantly higher than that of blister type (88.07%, 192/218) ($P < 0.05$). This may be because the blister type tinea pedis has intact skin barrier, and the penetration of JUC is slightly affected, while the erosive and scale keratosis types have damaged skin barrier, which is more conducive to the formation of JUC antibacterial film on the skin surface [4,24].

According to age grouping, the total effective rate of JUC in the treatment of subjects aged 17–40 years (94.29%, 264/280) was slightly higher than that of subjects aged 41–75 years (90.12%, 129/143), but the difference was not statistically significant ($P > 0.05$), indicating that JUC has stable efficacy in different age groups. According to the course of disease grouping, the total effective rate of JUC in the treatment of patients with course of disease ≤ 2 years (95.31%, 244/256) was significantly higher than that of patients with course of disease > 2 years (88.68%, 149/168) ($\chi^2 = 7.23$, $P < 0.01$). This suggests that early intervention with JUC can achieve better therapeutic effects, which is of great guiding significance for the clinical treatment of fungal skin infections.

4. Discussion

This multi-center clinical trial integrated data from 6 RCTs involving 829 subjects, systematically evaluating the clinical efficacy and safety of JUC in the treatment of tinea pedis and onychomycosis, and the results further confirm the clinical value of JUC as a novel physical antibacterial material in the treatment of superficial fungal infections. The core findings of this study are consistent with the preliminary single-center trial results of JUC [10,12,13], but it also makes up for the limitations of small sample size and regional bias in previous studies through multi-center integration, and innovatively conducts subgroup analysis to clarify the applicable population of JUC, providing more comprehensive evidence-based medical support for its clinical promotion.

The results of this study show that JUC, whether used alone or in combination with traditional antifungal drugs or dressing and trimming methods, can significantly improve the total effective rate and fungal clearance rate, and reduce the recurrence rate, which is closely related to its unique physical antibacterial mechanism. Different from traditional chemical antifungal drugs that rely on inhibiting fungal cell wall synthesis or cell metabolism to exert effects [6,7], JUC forms a stable positively charged antibacterial film on the surface of the skin and nails. This film can strongly adsorb negatively charged pathogenic fungi (such as *Trichophyton rubrum* and *Epidermophyton floccosum*), block their respiratory process, and thus achieve the effect of inhibiting or killing fungi [11,12]. This physical antibacterial mode not only avoids the drug resistance caused by long-term use of chemical antifungal drugs, but also has a long-acting antibacterial effect—after spraying, the antibacterial film can persist on the skin surface for a long time, continuously inhibiting the colonization and reproduction of fungi, which is the key reason why the recurrence rate of the experimental group is significantly lower than that of the control group (5.66% vs. 21.43%).

In terms of clinical efficacy, this study found that JUC has different therapeutic effects on different subtypes of tinea pedis: the total effective rate on erosive and scale keratosis tinea pedis is significantly higher than that on blister type ($P < 0.05$). This may be due to the intact skin barrier of blister type tinea pedis, which slightly affects the adhesion and penetration of JUC, making it difficult to form a uniform antibacterial film on the skin surface; while the skin barrier of erosive and scale keratosis tinea pedis is damaged, which is more conducive to the adsorption of JUC and the formation of antibacterial film, thus exerting a better therapeutic effect [4,24]. This finding provides important clinical guidance for the targeted application of JUC: for patients with blister type tinea pedis, it is recommended to use JUC combined with traditional antifungal drugs to improve the therapeutic effect, while for erosive and scale keratosis tinea pedis, JUC alone can achieve a good therapeutic effect.

Subgroup analysis also shows that the total effective rate of JUC in the treatment of patients with course of disease ≤ 2 years is significantly higher than that of patients with course of disease > 2 years (95.31% vs. 88.68%, P < 0.01), indicating that early intervention with JUC can effectively control the progression of the disease and improve the therapeutic effect. This is because in the early stage of fungal infection, the pathogenic fungi mainly colonize the superficial layer of the skin or nail surface, and the damage to the skin and nail tissue is relatively mild, which is conducive to the full play of JUC's antibacterial effect; while in the later stage of the disease, the fungi may invade the deep layer of the skin or nail bed, and the tissue damage is more serious, which increases the difficulty of treatment [3,25]. Therefore, for patients with tinea pedis and onychomycosis, it is necessary to intervene as early as possible, and JUC can be used as a preferred intervention measure to improve the prognosis of patients.

In terms of safety, the incidence of adverse reactions in the experimental group (3.61%) is significantly lower than that in the control group (10.87%, P < 0.001), and all adverse reactions in the experimental group are mild local skin irritations, which can be relieved spontaneously without special treatment, without affecting the continuation of treatment. In contrast, the control group has not only local skin irritation, but also systemic adverse reactions such as gastrointestinal discomfort and elevated ALT, and even some patients have to discontinue treatment due to severe adverse reactions. This difference is mainly due to the physical antibacterial mechanism of JUC: it does not enter the human body through the skin barrier, does not participate in the metabolic process of the human body, and thus avoids the systemic toxicity caused by chemical antifungal drugs [10,13]. In addition, no allergic reactions related to JUC are found in this trial, indicating that JUC has good tolerability and is suitable for most patients with fungal skin infections, including elderly patients and patients with mild liver and kidney function abnormalities (excluded in this study due to inclusion criteria).

This study also has certain limitations. First, the included RCTs are all conducted in China, and the subjects are all Chinese populations, which may limit the generalizability of the results to other ethnic groups. Second, the follow-up time of this study is 12 weeks after drug withdrawal, which is relatively short, and the long-term recurrence rate and safety of JUC need to be further verified by long-term follow-up studies. Third, this study does not compare the therapeutic effect of JUC with that of oral antifungal drugs (such as itraconazole and terbinafine), and the position of JUC in the clinical treatment system of tinea pedis and onychomycosis needs to be further clarified through head-to-head trials. Fourth, the mechanism of JUC's antibacterial effect is only analyzed at the clinical level, and its molecular mechanism (such as the specific binding site with fungal cells) needs to be further studied through in vitro experiments.

In conclusion, this multi-center clinical trial confirms that JUC has significant clinical efficacy and high safety in the treatment of tinea pedis and onychomycosis. It can significantly improve the total effective rate and fungal clearance rate, reduce the recurrence rate, and has the advantages of no drug resistance, long-acting antibacterial effect and good tolerability. It provides a new safe and effective therapeutic option for the clinical treatment of tinea pedis and onychomycosis. In the future, we need to carry out multi-center, large-sample, long-term follow-up trials involving different ethnic groups, compare the therapeutic effect of JUC with that of oral antifungal drugs, and further explore its molecular antibacterial mechanism, so as to provide more sufficient evidence for its widespread clinical application. At the same time, it is also necessary to strengthen the popularization of JUC's clinical application, guide clinicians to use JUC reasonably according to the subtype of the disease, course of disease and age of patients, so as to maximize its clinical value.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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