ORIGINAL ARTICLE

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Clinical efficacy evaluation of crisaborole ointment in the treatment of vulvar leukoplakia

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SUMMARY

OBJECTIVE: The aim of this study was to evaluate the clinical efficacy of crisaborole ointment in the treatment of vulvar leukoplakia.
METHODS: A prospective, randomized controlled clinical trial was conducted, and a total of 100 patients with vulvar leukoplakia were divided into the observation group (n=50) treated with crisaborole ointment and the control group (n=50) treated with vitamin E. The symptom improvement and vulvar leukoplakia score after 2 weeks of treatment were analyzed, and the clinical efficacy of vulvar leukoplakia was evaluated by referring to the Guidelines for Clinical Research of New Drugs of Traditional Chinese Medicine (2018 Edition).
RESULTS: After 2 weeks of treatment, the overall score of lesions in the observation group decreased, and the total treatment efficiency of patients in the observation group was 92% (46/50), which was significantly higher than that of 52% (26/50) in the control group P<0.05).
CONCLUSION: Crisaborole ointment can effectively treat vulvar leukoplakia, improving the symptoms and pathological changes of the vulvar skin.
KEYWORDS: Leukoplakia. Nutrition disorders. Crisaborole. Clinical trial.

INTRODUCTION

Vulvar leukoplakia, as a common disease in women, refers to a localized chronic lesion of the vulvar mucosa caused by pigment changes and tissue degeneration due to nutritional disorders of the vulvar skin mucosa. The etiology of this disease is still unclear, and a large number of clinical studies suggest that this disease may be related to local humid stimulation of the vulva, autoimmune disorders (cellular immunity and humoral immunity), genetics, low hormone level, infection, and metabolic disorders. The mainstay of treatment includes topical drug therapy and physiotherapy[1]. The long-term efficacy and optimization parameters of physiotherapy require further observational studies. In comparison, topical drug therapy is more psychologically acceptable to patients. The active ingredient of crisaborole ointment is crisaborole, which is FDA-approved for atopic dermatitis in patients over 2 years old[2,3]. Crisaborole is a boron-based phosphodiesterase 4 (PDE-4) inhibitor that inhibits the PDE-4 enzyme, which is a key regulator of inflammatory cytokine production in the skin. Overactive PDE-4 has been shown to contribute to the signs and symptoms of atopic dermatitis. As a non-steroidal topical monotherapy, crisaborole mediates an anti-inflammatory effect on almost all inflammatory cells[4]. This study was conducted to evaluate the clinical efficacy of crisaborole ointment in the treatment of vulvar leukoplakia, and the results are reported as follows.

DATA AND METHODS

General data

A total of 100 patients with vulvar intraepithelial non-neoplastic lesions confirmed by vulvar biopsy sections who visited our gynecology clinic from September 2020 to September 2021 were selected. The pathological results of the vulvar biopsy were vulvar lichen simplex chronicus or vulvar lichen sclerosus. They were randomly divided into the control group (n=50) and the observation group (n=50). There were no statistical differences in age and disease duration between the two groups of patients participating in this study (p>0.05), which were comparable.

Inclusion and exclusion criteria

Inclusion criteria were as follows: ①symptoms: vulvar pruritus; ②signs: vulvar hypopigmentation; and ③pathological biopsy: pathological diagnosis of vulvar lichen simplex chronicus or vulvar lichen sclerosus. Exclusion criteria were as follows: ① combined malignant tumors; ② combined lactating and pregnant women; and ③ drug allergy.

Treatment

The observation group was given 2% crisaborole ointment (produced by Pharmacia and Upjohn Company LLC, specification

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30g/branch/box, HJ20200022) to be applied to the vulvar lesions twice a day. The control group was a placebo group, and vitamin E was given to be applied externally to the vulvar lesions by cutting small openings in the vitamin E and squeezing out the liquid from it to be applied externally to the vulvar lesions twice a day. The drug was discontinued during menstruation and applied after menstruation was cleared. Follow-up was conducted after 2 weeks of treatment. The patient was also instructed to keep the vulva clean and dry and to avoid eating allergic and spicy foods.

Evaluation indicators

Indicators for determining the treatment effect: With reference to the Guidelines for Clinical Research on New Chinese Medicines (2018 edition), the scores were based on skin color, lesion area, and itching scoring method. (1) Skin color: 0 points: normal color; 1 point: red skin; 2 points: pink skin; 3 points: white skin. (2) Lesion area: 0 points: no lesion area; 1 point: lesion area less than 30% of the vulva; 2 points: lesion area accounts for 30–50% of the vulva; 3 points: lesion area greater than 50% of the vulva. (3) Itching scoring method: the itching visual analog scale (VAS) evaluation method was used, which integrates the degree of itching, scratching behavior, and the impact on sleep for evaluation; scoring method: 1 point: no itching; 2 points: occasional slight itching; 3 points: itching, need to scratch gently to stop itching, does not affect sleep; 4 points: very itchy, cannot help scratching hard many times to stop itching, waking up itching at night, but can fall asleep after scratching hard; 5 points: intense itching, requiring a burst of non-stop scratching, even scratching the skin, difficult to fall asleep habitually, or waking up after sleep with repeated scratching and itching. Overall score=skin color score×lesion extent score+itching score.

Judgment of clinical efficacy

Clinical cure: ① the area of vulvar leukoplakia is reduced by more than 80%; ② the symptoms of vulvar itching disappear; and ③ the skin color and texture of the lesion return to the level of the surrounding normal skin. Significant effect: ① the area of vulvar leukoplakia is reduced by 50–80%; ② occasional vulvar itching; and ③ the skin color of the lesion turns pink or light brown. Improvement: ① 30–50% reduction in the area of vulvar leukoplakia; ② reduction in the degree of vulvar itching; and ③ improvement in the color and texture of the lesion area. Ineffective: ① the area of vulvar leukoplakia is not significantly reduced; ② the degree of vulvar itching is not reduced. Cure, significant effect, and improvement are all considered effective.

Statistical methods

The SPSS19.00 statistical software was selected to collate the relevant experimental data, and the measurement data were expressed as percentages (%), using χ^2 validation; a t-test was used for the comparison between the two groups with normal distribution, a non-parametric test was used for those with non-normal distribution, and a chi-square test was used for the count data. P<0.05 indicates a statistically significant difference.

RESULTS

Comprehensive score of two groups of patients after 2 weeks of treatment: As shown in Table 1, the lesion overall score before treatment was 2.29±0.85 in the observation group and 2.28±1.14 in the control group. There was a 0.45 reduction in lesion overall scale score from baseline in the observation group (p<0.05) and a 0.25 decrease from baseline in the control group (p>0.05). The difference in the observation group statistically indicates that the crisaborole treatment was effective. Comparison of adverse reactions between the two groups: No serious side effects were observed during and after treatment in both groups.

Comparison of the efficiency of the two groups: The effective rate was 92% in the observation group and 52% in the control group. After one course of treatment, the efficiency of the observation group was higher than that of the control group, and the difference was statistically significant (p<0.001).

Comparison of adverse reactions and recurrence conditions: Common adverse reactions of external drugs outside the vulva include local allergy, redness, pain, and even ulceration. There are two cases in the observation group with local pain and ulceration, and the local adverse reactions subsided after timely withdrawal, with an incidence of 2/50 (4%). The control group had no adverse effects at 0%. The incidence of adverse effects between the control and observation groups was statistically significant (P<0.05), as shown in Table 2.

DISCUSSION

Vulvar leukoplakia is a vulvar skin disease with pruritus as the main symptom and vulvar skin hypopigmentation as the main sign, including vulvar lichen simplex chronicus and vulvar lichen sclerosus. The common pathology is hyperkeratosis of the epidermis with inflammatory cell infiltration in the dermis[4-6].

At present, the main treatments for vulvar leukoplakia include topical drug therapy[7] and physiotherapy, and physiotherapy

Table 1. Comparison of skin color scores before and after treatment between two groups of patients.

		Skin color score (points)	Lesion extent score (points)	Itching score (points)	Overall score (points)
Observation group (50n=case)	Before treatment	2.45±0.76	2.29±0.85	2.76±0.73	11.19±6.46
	After treatment	1.62±0.16 D*	1.84±0.41 D*	0.64±0.56 D*	4.94±6.45 D*
Control group (50n=case)	Before treatment	2.44±0.69	2.28±1.14	2.75±0.84	11.89±4.35
	After treatment	2.24±0.28Δ	2.03 ±1.36D	2.45±0.11 D	10.44±4.86 D

Comparison between the observation group and the control group, DP>0.05; compared with the same group before treatment, DP<0.05; compared with the control group after treatment, *P<0.05.

Table 2. Comparison of clinical efficacy between the two groups.

Group	Number of cases	Cure	Significant effect	Improvement	Ineffective	Effective rate	χ^2	p
Observation group	50	21	15	10	4	92%	27.71	<0.001
Control group	50	5	7	14	24	52%		

includes focused ultrasound[8], photodynamic therapy[9], and microablative fractional radiofrequency (MFR), of which MFR was an innovative, easy-to-use intervention to be considered the first therapeutic option or complement medical treatments for vulvar leukoplakia[10].

Topical drug therapy mainly includes glucocorticoids, testosterone propionate cream, progesterone cream, and topical immunosuppressants[11]. However, previous studies on drug treatment for vulvar leukoplakia are inadequate. Among them, glucocorticoids are effective in improving pruritus, but the recurrence rate is high after stopping the drug, and long-term use has the side effects of skin atrophy, skin pigmentation changes, and easy infection[12], so they are only used as short-term drugs. Testosterone propionate cream is not effective in improving pruritus, and long-term use has the side effect of causing masculinization[13,14]. Progesterone cream has few side effects but not effective. Some studies found that the efficacy of testosterone propionate ointment and progesterone ointment in the treatment of vulvar leukoplakia was similar to that of placebo[14]. Long-term use of topical immunosuppressants has the potential to induce vulvar cancer[15]. These drawbacks reduce patients' compliance and limit the long-term use of these drugs. In addition, the irregular treatment causes some patients to have poor results with the above drugs, leading to chronic prolongation of the disease. Therefore, clinicians need to find a drug that is effective and can be used safely for a longer period of time.

This study showed that there was a meaningful improvement in the histopathological changes of vulvar leukoplakia with crisaborole therapy compared with vitamin E treatment, indicating that crisaborole is an effective therapy for vulvar leukoplakia. In contrast to the aforementioned drugs used to treat vulvar leukoplakia, our administration is safer and more effective. Clenbuterol ointment is a small-molecule topical PDE-4 inhibitor approved in the United States for the treatment of patients aged 2 years and older with mild to moderate atopic dermatitis[16]. We decided to use crisaborole ointment for topical treatment due to its mechanism of action:

1. intramolecularly targets and selectively acts on the PDE-4 enzyme in the degradation of cyclic adenosine monophosphate (CAMP);
2. inhibits the release of inflammatory cytokines by inhibiting PDE-4 enzyme, which in turn increases CAMP-dependent protein kinase A activity and inhibits NFAT and NFKB signaling pathways downstream;
3. inhibits the release of various cytokines, including tumor necrosis factor-α, interferon-γ, and interleukin-2.

In addition, due to its small molecular weight, crisaborole facilitates transdermal penetration[17].

In addition, data from pivotal studies and long-term safety studies suggest that patients can well tolerate long-term treatment (>48 weeks) with crisaborole ointment[18]. Therefore, crisaborole ointment meets the safety needs of patients with vulvar leukoplakia who require long-term maintenance therapy.

The weakness of this study was its relatively small sample size. However, an a priori sample size calculation determined that the selected sample was large enough to demonstrate a

clinically meaningful difference in the histopathological changes of vulvar leukoplakia.

Vulvar leukoplakia includes a range of disorders that compromise the quality of life of patients. Standard forms of traditional treatment have their limitations, side effects, and complications. Hence, alternative methods are needed to influence them, such as the use of crisaborole ointment, which can effectively treat vulvar leukoplakia and improve the symptoms and pathological changes of the vulvar skin. Moreover, the adverse reactions of crisaborole were less, so it is well prescribed by clinicians. Continuous monitoring these patients will be helpful to better understand the role crisaborole could play in the treatment of vulvar leukoplakia.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted in accordance with the Declaration of Helsinki and approved by the Jiangxi maternal and Child Health Hospital. All participants signed an informed consent form for inclusion in the study.

AUTHOR'S CONTRIBUTIONS

LL: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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