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Efficacy of chlortetracycline treatment on vulvar non-neoplastic epithelial disorders

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Summary

Objective: To observe the effectiveness of chlortetracycline (aureomycin) treatment on vulval white lesions and to explore its possible pathogenesis. *Materials and Methods:* From January 2001 to April 2011, 194 patients with vulvar non-neoplastic epithelial disorders were divided into three groups according to therapy regimens received, ie, chlortetracycline treatment group (72 cases), chlortetracycline + beclomethasone treatment group (66 cases), and beclomethasone treatment group (56 cases); their local changes of vulvar lesions were observed and efficacy of these treatment profiles was evaluated after one year. *Results:* Effective rates of chlortetracycline group, chlortetracycline + clobetasol group and clobetasol groups were 86.1% (62/72), 87.9% (58/66), and 62.5% (35/56), respectively. There was a significant difference among these three groups (Hc = 10.7766, $p = 0.0046$), the curative rate of clobetasol group was markedly lower than that of the former two groups ($p = 0.0072$ and $p = 0.0019$), but was not statistical significant ($p = 0.6077$) when compared between the former groups. *Conclusion:* The occurrence of vulvar non-neoplastic epithelial disorders may be associated with chlamydia and mycoplasma infection, the chlortetracycline is an effective drug for this illness, the mechanism of which might be related to killing pathogens directly and inhibiting inflammatory mediators.

Key words: Vulvar white lesions; Squamous cell hyperplasia; Lichen sclerosis; Chlortetracycline.

Introduction

Vulvar white lesions, also known as vulvar non-neoplastic epithelial disorder, is a group of chronic diseases of degeneration and pigment change in female genital skin and mucosal tissue, which features local skin's intractable itching, hypopigmentation, atrophy, even adhesions, and cicatrice with the disease progression, that seriously affect the patient's quality of life. Because the exact cause of the disease is currently unknown, there is no ideal method of treatment to cure this disease [1-3]. In 2001, the authors began applying the chlortetracycline (aureomycin) to treat it and had achieved good results.

Materials and Methods

General Information

From January 2001 to April 2011, the authors observed 194 cases of vulvar non-neoplastic epithelial disorders, including 30 cases in adolescent girls, 58 in reproductive-age women, and 106 in postmenopausal women. All patients had to undergo a vulvar lesions biopsy to get a conformed pathological diagnosis. Histological types included squamous cell hyperplasia, lichen sclerosis, and mixed type (Table 1). Median age of the patients was 42.2 years (17 to 73 years). Patients were randomly divided into the chlortetracycline treatment group (72 cases), chlortetracycline + clobetasol (propionate clobetasol) group (66 cases) and clobetasol group (56 cases). There were no significant differences ($p > 0.05$) among the three groups in age, pathological type, severity of symptoms, and duration of disease. This therapeutic programme was approved by the hospital ethics committee and all patients signed a medical informed consent form before the start of this treatment.

Therapeutic schedule

Chlortetracycline eye ointment was smeared on the affected area twice daily for three months, with another course of treatment started after two months if necessary—two courses in all. Propionate clobetasol cream was painted on the surface of lesions twice a day in the first month, once daily in the second to third months, and twice weekly for another trimester—altogether six months. The chlortetracycline + clobetasol group was applied these treatments alternately according to the above programmes.

Determine the efficacy

All patients were followed up once monthly for one year. Efficacy after treatment was assessed by rank of cure: 1) resolved: the symptoms disappeared, the elasticity and pigmentation of the genital skin and mucosa were basically recovered to normal, the chapped ulcers and atrophy were healing; 2) obviously improved: the symptoms disappeared and lesions restored as described above by more than 80%; 3) slightly improved: itching relieved and lesions restored as described above by more than 50%; 4) no change: no change between before and after treatment.

Statistical Analysis

The statistic method adopted was the rank sum test (Kruskal and Wallis test) of enumeration data to analyse by using DPS7.5 statistic software. *P* values < 0.05 were considered statistically significant.

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Table 1. — *Histological types of vulvar non-neoplastic epithelial disorders in three groups.*

	Chlortetracycline	Chlortetracycline + clobetasol	Clobetasol	Total
Squamous epithelial hyperplasia	22	18	14	54
Lichen sclerosus	20	26	24	70
Mixed type	30	22	18	70
Total	72	66	56	p= 0.4550

Results

The three groups were comparable in effective rate (Table 2). The number of both cured and obviously improved cases were 62 in the chlortetracycline treatment group (86.1%), 58 in chlortetracycline + clobetasol group (87.8%), and 35 in clobetasol group (62.5%) respectively. The difference was statistically significant between the former two groups and the clobetasol group (p = 0.0072 and p = 0.0019), but no significant difference was showed when comparing the chlortetracycline group with the chlortetracycline + clobetasol group (p = 0.6077).

In the chlortetracycline group, two patients appeared with obvious vulvar itching and lesions relapse within six months after treatment, of which one case was squamous cell hyperplasia and the other lichen sclerosis. In the chlortetracycline + clobetasol group, one patient's squamous epithelial hyperplasia recurred in six months after treatment. The clobetasol group also showed good mitigation by treatment, but one year later ten cases recrudesced, including five cases with squamous cell hyperplasia, two with lichen sclerosis type, and three with mixed type.

Discussion

Vulvar non-neoplastic epithelial disorder is a gynecological disease that is difficult to treat and often recurs, causing great physical or mental pain to the patient. One of reasons difficult to treat is uncertain in etiology. It is supposed that genetics, autoimmune, local irritation, hormone metabolism, and local chronic injury might be the cause of this disease [2,3]. Therefore, its treatment methods are diverse, such as hormones (triamcinolone acetonide, fluocinolone acetonide, testosterone propionate, progesterone, etc.), vitamins, lasers, high-intensity focused ultrasound, traditional Chinese medicine, and others. Propionate clobetasol ointment treatment achieved good results. It is a potent topical corticosteroid preparations, which can effectively penetrate into skin corneum, and works well as anti-inflammation, anti-allergy, anti-proliferation, anti-itch immune-suppression, and vasoconstriction. However, it's long-term side effects, such as the topical vulvar skin's telangiectasia, hirsutism, atrophy, infection, and prolonged unhealed chaps, as well as a higher recurrence rate, have repeatedly been brought to attention [2-5].

Over nearly three decades, the authors observed chlortetracycline treatment had positive effects treating vulvar non-neoplastic epithelial disorders. In this study, the authors compare the curative effect among three treatment groups, chlortetracycline, clobetasol, and chlortetracycline + clobetasol, attempting to find a more efficacious regimen. The results revealed the improvement rate of the chlortetracycline treatment group (86.1%) was a little lower than that of chlortetracycline + clobetasol group (87.8%), but no statistical difference was found between these two groups. Nevertheless, the efficiency rates of these two groups to treat vulvar non-neoplastic epithelial disorders were higher than that of clobetasol group (62.5%, p = 0.0072 and p = 0.0019). In addition, the relapse cases in the clobetasol group were also higher when compared with the former two groups. In view of the above the authors conclude that chlortetracycline preparation is an effective drug to treat white lesions of vulva.

The chlortetracycline belongs to the class of tetracycline antibiotics, a broad-spectrum antibacterial agent family, the antibacterial mechanism of which is that they can specifically combine with the bacterial position A of 30S ribosomal subunit, to prevent the linking of the aminoacyl-tRNA in this position, consequently inhibiting bacterial protein synthesis. In addition to inhibiting gram-positive, gram-negative, and anaerobes, they can effectively kill most Rickett genera, the genus Mycoplasma, Chlamydia, atypical Mycobacterium genus, spirochetes, and some protozoa. The tetracycline has a higher concentration in the organization of human body, especially in stomach, lung, bladder, oral mucosa, and other parts. Cancer tissue has a strong affinity to it and can quickly take it into cells [6, 7].

The mechanism of chlortetracycline treating vulvar non-neoplastic epithelial disorders effectively may be related to killing chlamydia and mycoplasma. The present authors speculate that occurrence of vulvar non-neoplastic epithelial disorders is most likely due to infection of chlamydia mycoplasma. Chlamydia and mycoplasma often exist in specific organs, such as eyes, nostrils, anus, mouth, vagina, etc. When mycoplasma or chlamydia infects humans, the first invasion place is epithelial cells, in which they begin to grow and reproduce quickly then enter the monocyte-macrophage

Table 2 — *Clinical efficacy of three treatment groups.*

Groups	n	Resolved	Obviously improved	Slightly improved	No change	P value
Chlortetracycline	72	32	30	6	4	Hc=10.7766,
Chlortetracycline + clobetasol	66	32	26	6	2	df=2
Clobetasol	56	17	18	11	10	p=0.0046

1<–>2 p = 0.6077 1<–>3 p = 0.0072 2<–>3 0=0.0019

system to proliferate, resulting in the death of infected cells. Meanwhile, they are also capable of evading the host immune defense function and get intermittent protection. The pathogenic mechanism of mycoplasma and chlamydia is to inhibit the metabolism of the infected cells, leading to the release of dissolved enzymes and the cytotoxicity of metabolites, causing local or systemic allergy, and autoimmunity [8-12]. Chlamydia species can produce a similar endotoxin to the that of gram-negative bacteria. The lipopolysaccharide and protein in the exterior of the endotoxin can induce chlamydia to adsorb in susceptible cells, promoting the susceptible cell endocytosis to chlamydia, and preventing the fusion of phagosomes and lysosomes, so that chlamydia can multiply inside the phagocytic vesicle and suppress cell metabolism until it is eventually destroyed [8-10]. Toxic substances of mycoplasma metabolism, such as dissolved nerve mycoplasma producing neurotoxins, cause nerve cell membrane damage. Mycoplasma urealyticum producing urea can bring large amounts of ammonia to damage cells [11, 12]. The present authors speculated that genital epithelial cell destruction, allergy, and autoimmunity, for the pathogenic mechanism of chlamydia and mycoplasma in vulvar nonneoplastic epithelial disorders, may be the important reasons for local itching, depigmentation, atrophy, scarring, and adhesion.

Chlortetracycline, in addition to killing chlamydia and mycoplasma, also play an important role in suspension of further damage to the epithelial cells, especially blocking or repairing local inflammation and clearing inflammatory mediators. Existing data found that the tetracycline could restrain activity of matrix metalloproteinase (MMP) and phospholipase A2 (PLA2), as well as strongly clean out oxygen free radicals [13-18]. These inflammatory cytokines, such as oxygen-free radicals, have been found to have a concerning relationship with the white lesions of the vulva [19].

In summary, the authors believe that chlortetracycline eye ointment for external use is an effective drug to treat vulvar non-neoplastic epithelial disorders, whose possible main mechanism may be its resistance to chlamydia and mycoplasma. The latter two are perhaps the prime suspect of vulvar nonneoplastic epithelial disorders. The present study group is carrying out an experiment on local histological pathogens of vulvar non-neoplastic epithelial disorders in order to obtain a clear conclusion.

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