European Review for Medical and Pharmacological Sciences 2013; 17: 2668-2674

Efficacy of a Dermoxen® lenitiva for pruritus genitalis in a randomized, double blind trial

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Abstract. – BACKGROUND: Pruritus can be defined as an unpleasant cutaneous sensation associated with the immediate desire to scratch. In particular external intimate zone could be hit by pruritus genitalis because of several reasons (bacterial infection, fungal infection, stress, bad intimate behavior, synthetic intimate clothes).

AIM: The aim of the study was to compare the efficacy of Dermoxen® Lenitiva cream versus a methylprednisolone aceponate 0.1% based cream in treating pruritus of the external genitalia.

PATIENTS AND METHODS: Independent, randomized, double-blind, controlled trial in two University affiliated Italian Hospitals. 80 women, affected by aspecific pruritus genitalis with negative vaginal swab for bacterial or fungal infections or other pathogenic causes of itching, were selected and blindly treated by Dermoxen® Lenitiva cream or methylprednisolone aceponate 0.1% based cream. The main outcome measures were: the reduction of sensation of pruritus, evaluated by a visual analog scale (VAS) pain score, and improvement of intimate wellness sensation, and comfort during sexual intercourse, frequency and severity of adverse reactions.

RESULTS: Significant reduction of itching sensation was verified for each treatment.

CONCLUSIONS: Based on our results, DermoXen® Lenitiva vaginal cream showed efficacy so as methylprednisolone aceponate 0.1% based cream for itching treatment on external female genitalia and improved intimate comfort and comfort in sexual intercourse.

Key Words:
External intimate zone, Vaginal itching, Vaginal cream, Methylprednisolone aceponate, DermoXen, Lenitiva.

Introduction

Pruritus is a common and complex process that involves the stimulation of free nerve endings found superficially in the skin and has multifactorial etiologies[1].

It is an unpleasant sensation of the skin or skin-to-mucosa transitional surfaces leading to the desire to scratch[2].

Itch is induced by a variety of stimuli, including mechanical, chemical, thermal, and electrical stimulation of the skin. Cutaneous sensitivity to pruritic stimuli is discontinuous and has a spot-like distribution (itch points), whose density equals that of pain points[3-5]. Chronic and severe itching reduces greatly the quality of life in patients, and may cause damages of the skin barrier and the release of inflammatory mediators that potentially induce or aggravate itching, resulting in reinforcement of scratching[6].

The visual analogue scale (VAS) is the most reliable and valid itch assessment scale and is closely followed by the numerical rating scale (NRS)[7-8].

However, treatment strategy to reduce itch is rather limited, and the effect of the various treatments is highly variable[9]. Oral antihistamines and topical corticosteroids, frequently used to suppress itching in atopic dermatitis, have limited effect in most types of chronic pruritus and often have caused a variety of adverse effects[10-13]. Although anti-inflammatory therapies such as topical glucocorticoids, and more recently, topical immunosuppressive agents (tacrolimus, ascomycin, mycophenolate mofetil), are considered mainstays of itch therapy, prevention of cutaneous xerosis and rehydration of dry skin represent critical components for successful management of patients affected by itching. Use of effective emollients combined with hydration therapy, helps restore and preserve the stratum corneum barrier, and may decrease the need for topical corticosteroids[14].

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Itching in genital area has multiple causes (bacterial infection, fungal infection, stress, bad intimate behavior, synthetic intimate clothes) and, if there are no obvious causes, is defined non-specific[15-17].

The most common vulvo-vaginal symptoms include irritation, burning, erythema, and sometimes dysuria and dyspareunia[18-19].

Methylprednisolone aceponate (MPA) is a corticosteroid with strong vasoconstrictive and potent glucocorticoid receptor-binding properties and rapid metabolic clearance. Topical MPA demonstrates a low rate of percutaneous penetration and an associated low prevalence of local and systemic side-effects[20].

Applied once-a-day to affected skin, topical MPA is rapidly effective and safe in the treatment of moderate to severe atopic dermatitis[21]. A new cosmetic cream, based on 0.1% of *Zanthoxylum alatum* fruit extract [CAS number 91770-90-0] and 0.05% of 2-3-(4-hydroxyphenyl)-1-oxopropyl-amino-benzoic acid, better known as Dihydroavenanthramide [CAS number 697235-49-7] is currently available to treat pruritus genitalis.

The aim of this study was to evaluate the antipruritic effect of DermoXen® Lenitiva (DMX) versus MPA based cream [CAS number 86401-95-8] and their effects on intimate comfort and comfort during sexual intercourse.

Patients and Methods

The study was conducted in two University-affiliated Hospitals in Italy, during 2011, as an independent, randomized, double blind controlled trial.

80 women, affected by aspecific pruritus genitalis with negative vaginal swab for bacterial or fungal infections or other pathogenic causes of itching, were selected. Inclusion criteria were: patients in good health status and in compliance with study protocol age > 18 years. Exclusion criteria were: use of analgesics during the last 24 hours; dermatological pathology on the treated zone (eczema, etc.); use of topical or systemic treatment during the previous weeks, that could have interfered with the assessment of acceptability of the product test; subjects enrolled in another clinical trial during the period of study; use of anti-inflammatory drugs, antihistamines, antidepressants, anxiolytics or tranquilizers in previous month; and excessive use of tobacco (>3-5 cigarettes/die) or alcohol (>2 glasses of wine or 2 glasses of beer).

The study was approved by the local Ethics Committee and conducted in compliance with the Helsinki Declaration**.** An informed consent was obtained by each subject enrolled before topic administration.

Women were divided by computerized random selection into two groups, each one of 40: Group I was treated with DMX group, Group II with MPA based cream [CAS number 86401-95-8]. DMX cream is based on natural extracts: a vegetal active ingredient, extracted from *Zanthoxylum bungeanum* fruit and Diidroavenanthramide, a biotechnological active derived from the structure of avenantramide. The test formulation was Dermoxen® Lenitiva, a cosmetic cream formulation at pH 5.5, supplied by Ekuberg Pharma Industry, in 50 ml packaging, batch number SAEXP270314. The creams were provided by Ekuberg Pharma Industry (Martano, Lecce, Italy) and both creams were used once a day for 30 days.

Clinicians delivered two tubes of cream to all patients: each tube was totally white and marked with a number and a code, unknown to clinicians, but registered by the manufacturer, to respect the randomized blind investigation form.

All patients were randomized for single blind treatment, with a randomization of 1:1 by generated sequential number. So, each patient was recommended to blindly use the tube as the only treatment, by an application on the external genitalia once a day for one month. Patients were allowed to use neutral cleansing daily.

Severity of external intimate pruritus was evaluated by the subjects according to a semi-quantitative score between 0 and 4, where 0 = none; 1 = slight; 2 = moderate; 3 = severe; 4 = very severe.

This parameter was evaluated at t0 (before the use of the creams) at t1 (after 15 days) and t2 (after 30 days of treatment).

A tailored questionnaire was administered as Visual Analogue Scale (VAS) during monitoring visits, to evaluate the level of comfort at the genital region and during sexual intercourse (dyspareunia).

A semi-quantitative score between 0 and 4, (0 = bad; 1 = slight; 2 = moderate; 3 = good; 4 = optimum) was used to evaluate these parameters

Skin status of every subject involved in the study, was described: A = normal skin, B = combination skin, C = greasy skin and D = dry skin).

The antipruritic effect was determined on the base of variations in VAS score, between different times of product application. Each woman received a diary sheet in order to daily record signs and symptoms.

Measurement and Main Results

A visual analog scale (VAS) pain score was generated and subsequently obtained from each patient immediately after the end of treatment. So we observed reduction of sensation of pruritus in both treatment. In addiction, improvement of intimate wellness sensation, and comfort during sexual intercourse, frequency and severity of adverse reaction, have also been observed.

Statistical Analysis

Continuous variables were reported as the mean ± standard deviation (SD) or standard error of the mean (SEM) and categorical factors were reported as percentages. Two-way analysis of variance (ANOVA) test was used to examine differences between and within groups on different examination days. Within groups, changes from baseline were evaluated by means of the two-tailed paired Student's *t*-test. The comparisons between groups on different examination times were also analyzed with student's *t* test. The chi-square test was used to analyze categorical variables, while comparisons between 2 groups were performed. In all cases, the Kolmogorov-Smirnov test was applied to test for a normal distribution. Statistical analyses were performed with MedCalc software, version 11.4.1.0, and *p*-values < 0.05 were considered significant.

Results

A total of 68 subjects were enrolled and divided into two groups of 32 and 36 women treated with DMX and MPA respectively (8 subjects in Group I and 4 subjects in Group II dropped out).

Mean age was similar in the two study groups with values of 34.4±6.6 years and 34.1±8.1 respectively (Table I).

In terms of skin characteristics, no significant differences were detected between groups (Table I).

A significant reduction ($p < 0.0001$) of the itch severity was observed for each group, 15 and 30 days after initiation of treatment.

No significant difference was instead observed between the two treatments (Figure 1).

A significant improvement was observed in levels of comfort at genital region in both Group I (15 days: $p < 0.0001$; 30 days: $p < 0.0001$) and Group II (15 days: $p < 0.001$, 30 days: $p < 0.0001$) for different treatment time.

The subjects treated with DMX (Group I) show a level of comfort higher ($p < 0.0180$) than those treated with MPA (Group II) (Figure 2).

Better comfort in sexual intercourse as a result of the treatments were observed in both groups.

In particular, in Group I perceived initial comfort level was increased from a value of 0.5 to 1.9 ($p < 0.0001$) after 15 days up to a score of 2.9 ($p < 0.0001$) at the end of treatment.

In subjects treated with MPA (Group II) we observed an improvement in symptoms with a score of 1.1 ($p < 0.0016$) and 1.4 ($p < 0.0057$) at 15 and 30 days of treatment respectively.

Group I showed level of comfort significantly higher ($p < 0.0001$) than that of group treated with MPA (Group II) (Figure 3).

No overall adverse reaction to treatments was reported.

Discussion

Pruritus is one of the major complaints in dermatological and internal diseases. Although it can be extremely distressing and as disabling as severe pain; its pathophysiology is still not completely understood. Itch and pain seem to be transmitted by the same nerve fibers, the slow-conducting unmyelinated C fibers. The existence of specialized itch fibers remains to be documented. Itch can appear either after direct me-

Table I. Baseline characteristics of the two groups.

	Group I (DMX)(n = 32)	Group II (MPA)(n = 36)	p
Age (mean ± SD)	34.4 ± 6.6	34.1 ± 8.1	0.2540
Parity (mean ± SD	1.1 ± 1.0	1.2 ± 1.0	0.6430
Normal skin	15 (46.9%)	15 (41.7%)	0.8516
Combination skin	6 (18.8%)	6 (16.7%)	0.9253
Greasy skin	7 (21.9%)	8 (22.2%)	0.7960
Dry skin	4 (12.5%)	7 (19.4%)	0.6554

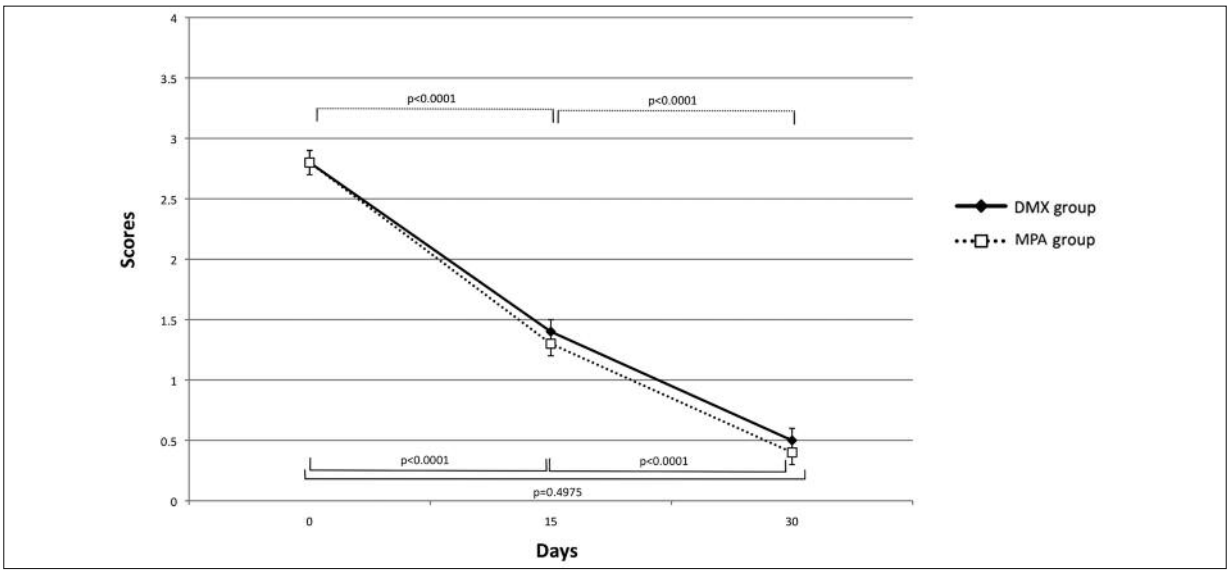

Figure 1. Level of itching in Groups I (DMX) and II (MPA), after 15 and 30 days of treatment. (Data are expressed as mean score ± SEM).

chanical stimulation of the itch receptors or through activation or release of mediators which would stimulate the itch receptors[22].

Itch is often defined as a sensation that induces the urge to scratch. Scratching, in turn, gives instant relief from itch, presumably through activation of mechanical nociceptors in the skin but unfortunately, and especially around external intimate zone, scratching will exacerbate the underlying skin condition by inducing additional inflammation in the skin[23].

Several topical drugs are currently used in the itching treatment. Among them, capsaicin, isolated from pepper plants of the genus *Capsicum*, has been demonstrated to deplete substance P from C-fibers when applied repeatedly and to reduce both pain and itch.

Polidocanol is a non-ionic surfactant with local anesthetic properties.

Creams containing 3% polidocanol have been successfully used in the treatment of atopic dermatitis.

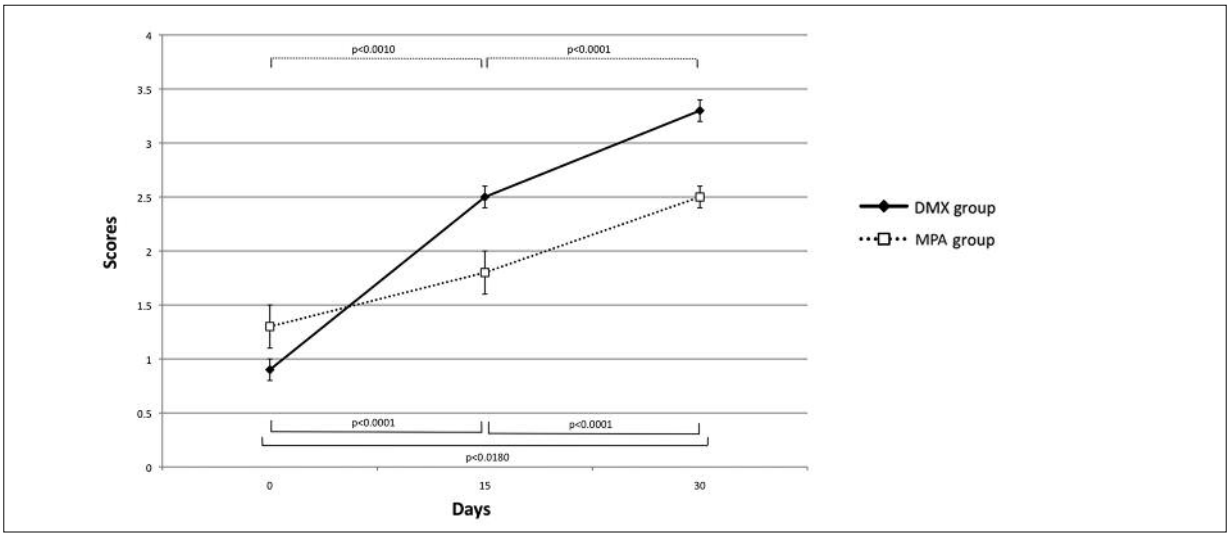

Figure 2. Level of comfort at the genital region in Groups I (DMX) and II (MPA), after 15 and after 30 days of treatment. (Data are expressed as mean score ± SEM).

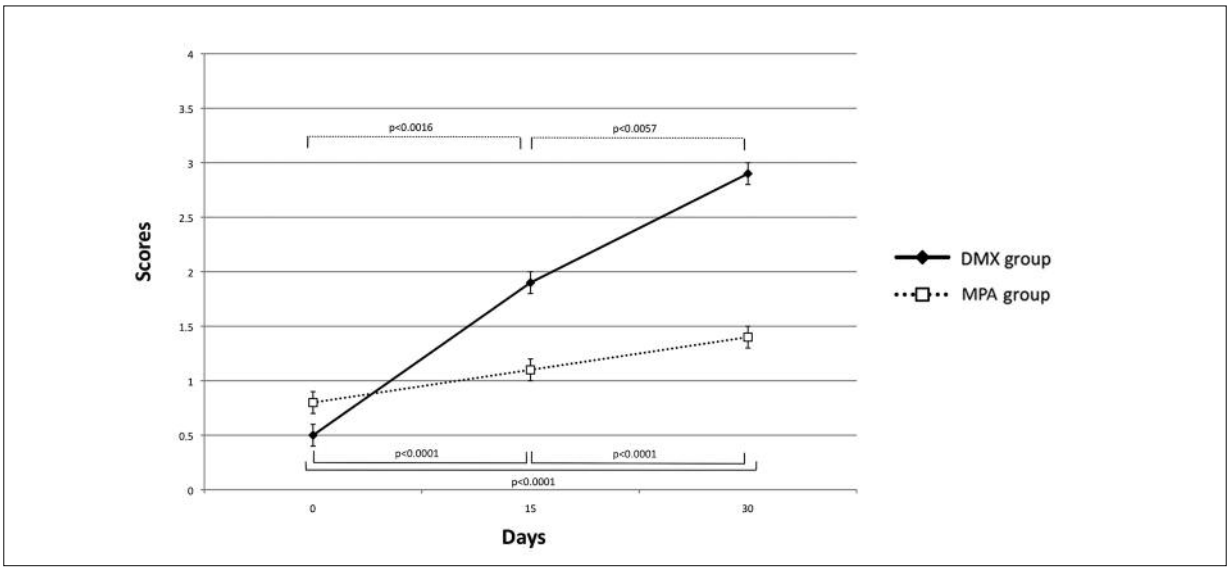

Figure 3. Level of comfort in sexual intercourse in Groups I (DMX) and II (MPA), after 15 and after 30 days of treatment. (Data are expressed as mean score ± SEM).

Recent studies have demonstrated that, even though oral administration of aspirin seems to have little or no effect on clinical itch, topical aspirin has an antipruritic effect in experimentally induced itch[24,25]. Red ginseng has been used as a traditional medicine, especially in Asian countries.

The major components of RG are ginsenosides[26], which have been reported to exhibit various biological activities, including anti-inflammatory and antitumor effects[27,28].

In our clinical trial we tested the efficacy of a lotion, containing natural extract derived from *Zanthoxylum bungeanum* fruit and Diidroavenantramide, a biotechnological active derived from the structure of avenantramide and Jojoba oil, in reducing non specific itch regarding external intimate zone.

Zanthoxylum alatum Roxb. (Rutaceae) is a perennial plant of Chinese origin, usually growing in Sichuan region. The scientific name more commonly used in literature is *Zanthoxylum bungeanum Maxim*[29,30]. Its fruits are widely used as a spice to reduce irritating properties of some foods. In traditional medicine, the oily extract of this plant is used to soothe and alleviate itching and toothache[31].

Recently, Japanese papers report analgesic activity of some isolated amides from *Zanthoxylum alatum Roxb*[32,33]. Moreover, the physiological mechanism underlying the tingling sensation induced by the amide hydroxyl- -sanshool is described[34].

Dihydroavenathramide is a synthetic molecule derived from the structure of natural avenanthramide. Avenanthramides (anthranilic acid amides), a class of compounds found in oat at very low concentrations, have been reported to have antiitching activity. Anti-itch and anti-redness efficacy of three naturally occurring avenanthramides (avenanthramides A, B and C) have been previously demonstrated. It has been studied also the efficacy of four synthesized avenanthramides: avenanthramides D and E and dihydroavenanthramides D and E. These various avenanthramides differ in the substituents on the cinnamic acid and anthranilic acid rings. Avenanthramides D and E have the same substitution pattern in the cinnamic acid moiety as A and B, and only differ in the anthranilic acid part[35].

The present study showed that an intimate cream based on natural active principles such as *Zanthoxylum alatum Roxb* and with dihydroavenanthramide, both with anti itching and soothing activity, could be as effective as registered drug in treating aspecific itching.

Such a cosmetic cream could be used to reduce the repeated exposure to corticosteroids, antihistaminics or antibiotics in recurrent itching of external intimate zone. However, the activity of *Zanthoxylum bungeanum* and Dihydroavenanthramide is well documented and can explain the efficacy of the product. This kind of combination led to a synergistic effect, potentiating antiitching effects. In conclusion, a vaginal cream

was reliably documented with regard to its efficacy and safety in treating itching, giving patients a better intimate comfort, improving sexual intercourse thanks to reduction of itching and state of irritation of external intimate zone, and resulting absolutely well appreciated by the majority of patients undergone the study. Furthermore, this cream didn't show to have the bad collateral effects of corticosteroids and antihistaminics molecules, and it is a valid alternative to approved drugs.

It gives a good satisfaction in intimate hygiene, helping to have better sexual intercourse, based on the strong action on itching. Other studies have been planned to test the efficacy of Dermoxen Lenitiva with higher percentages of *Zanthoxylum bungeanum* and dihydroavenanthramide than those used in this trial.

Conclusions

This preliminary and indipendent trial confirms that DermoXen® Lenitiva vaginal cream had efficacy so as methylprednisolone aceponate 0.1% based cream for itching treatment on external female genitalis in women and improves intimate wellbeing. The trial results needs to be extended to a larger number of subject, with more physical conditions and few exclusion criteria.

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