Vulvar lichen sclerosus in postmenopausal women: a comparative study for treating advanced disease with clobetasol propionate 0.05%

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Summary

Background and objective: Clobetasol propionate 0.05% has been the mainstay in treating vulvar lichen sclerosus (VLS) for the past ten years. The usual length of therapy is two to 12 weeks. We conducted this study to evaluate the efficacy and safety of treating severe lesions of VLS in postmenopausal women for a longer time on a regular basis using clobetasol propionate.

Materials and methods: From 1997-2000, 137 women with VLS were examined in the Colposcopy and Laser Surgery Unit of "Alexandra" Hospital. Patients who were premenopausal, had previous therapy, exhibited mild or moderate disease or showed VIN or invasive cancer on vulvar biopsies were excluded from the study. The remaining women were divided into two groups. The first group applied clobetasol propionate 0.05% for three months and afterwards on an "as required" basis, whereas the second group used the ointment for six months on a regular basis. All patients were examined at two, three, six and 12 months following treatment. Signs and symptoms before and after therapy as well as side-effects caused by the ointment were recorded.

Results: The mean age of the women was 60.2 years. Fifty-four patients were divided into two categories. In the 6-month follow-up, 59% of the 1st group and 85% of the second had complete response regarding their symptoms whereas on the 12-month follow-up, the respective numbers were 48% and 74%. Concerning the signs, 30% of the first group and 55.5% of the second showed to have complete response after six months and 26% and 41% respectively after 12 months. All differences between the two groups, except the signs after 12 months, were statistically significant. There were no side-effects from the long-term use of clobetasol propionate 0.05%.

Conclusions: Conservative management of severe lesions of VLS in postmenopausal women using clobetasol propionate 0.05% for a long time (6 months) on a regular basis, seems to be a safe and effective therapy. Improvement is observed primarily on the symptoms and less on the signs.

Key words: Vulvar lichen sclerosus; Postmenopausal women; Clobetasol propionate.

Introduction

Vulvar lichen sclerosus (VLS) is a chronic dermatosis of unknown etiology, often posing a challenge regarding its management by the gynecologist or the dermatologist.

A variety of treatment options have been advocated in the past for the treatment of this dystrophy: topical applied ointments of testosterone, progesterone, retinoids, mild steroids and cyclosporine, representing the conservative approach, and alcohol injections, CO2 laser, cryosurgery, vulvar denervation and even vulvectomy as more aggressive and invasive methods of therapy [1, 2]. Today, surgery for VLS is reserved for cases that do not respond to conservative treatment and continue to exhibit the same symptoms and signs despite the variety of topically applied agents.

Although the use of potent topical steroids has been related to adverse side-effects, the amelioration of the symptoms in the vast majority of the patients has led several authors to believe that this should be the first-line therapy for VLS [3]. Clobetasol propionate 0.05% is the most commonly used potent topical steroid exhibiting both antipruritic and antiinflammatory characteristics. The length of standard treatment ranges between two weeks and three months with the majority of authors recommending afterwards either the usage of the cream whenever the patient presents symptoms or switching to a milder topical steroid [4].

We conducted this study to evaluate the efficacy and safety of treating severe lesions of VLS in postmenopausal women for a longer time on a regular basis using clobetasol propionate 0.05%.

Materials and methods

At the Colposcopy and Laser Surgery Unit of "Alexandra" Hospital, 137 consecutive patients with vulvar lichen sclerosus were examined over a 3-year period (1997-2000). Age, previous treatments, symptoms and the duration and appearance of the lesions were recorded for each patient. All women had previously undergone colposcopy. Multiple biopsies of the vulva were taken under 2% xylocaine injection of local anesthesia to confirm histologically VLS and exclude invasive carcinoma.

Only postmenopausal patients considered to present severe lesions of VLS not previously treated were included in this

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study. The two parameters assessed to categorize them as cases with advanced disease were the symptoms reported and the appearance of the lesions. A scoring system, similar to the one used by Bracco *et al.*, from 0-3 with three being the most severe symptom for the first parameter and appearance and extension of the lesion for the second, was applied [7]. Only patients that were scored with three on one or the other parameter were included in the study. Intractable itching and soreness with subsequent inflammation and possible bleeding of the genital area, burning that affected urination and defecation, and dyspareunia that led to complete abstinence from sexual intercourse were the main symptoms taken under consideration for a patient to be scored by three. Hyperkeratotic appearance of the lesions forming chalky white plaque affecting the clitoris and resulting in its phimosis, producing the disappearance of the labia minora and extending to the labia majora, perineal body, anus and thighs as well as severe erosions, fissures, sclerosis and scarring were signs of a score of three for the second parameter.

The treatment protocol consisted of topical application of clobetasol propionate ointment 0.05% in of both groups of women. All women used the ointment twice daily for two months, and daily for the third month. Women that defected from the first or second follow-up appointment and those that presented contact dermatitis were excluded from the study. Fifty-four patients remained and were then divided into two groups of 27 women each. Following this stage, subjects of the first group (Group A) were advised to apply the ointment on an "as required" basis, whereas subjects of the second group (Group B), continued to use the steroid on a daily basis for the fourth month, three times weekly for the fifth month and two times weekly for the last month.

All women were examined before the initiation of therapy and at 2,3,6 and 12 months after treatment. The symptoms and clinical appearance of the lesions were recorded on a score-based form that resulted in a classification of complete or partial response to therapy or no change.

Statistical analysis was performed using ordinal logistic regression. A p value of less than 0.05 was considered statistically significant.

Results

From the 137 patients, 42 exhibited mild or moderate disease according to the scoring system, eight were premenopausal, in three the vulvar biopsies obtained showed invasive carcinoma of the vulva, in two vulvar intraepithelial neoplasia (VIN), and 11 had had previous therapy. Five women (45%) had been treated in the past with topical steroids, two (18%) with androgens, two with alcohol injections, one (9%) with progesterone and one by skinning vulvectomy. From the remaining 71 patients that entered the study, four presented contact dermatitis in the first week of application and were withdrawn from the study, and 13 were lost to follow-up (Table 1).

The mean and median age of the patients was 60.2 and 60 years, respectively and the range 43-81 years (95.0% CI). The mean duration of symptoms was 6.2 years with a range from one to 17 years.

All 54 patients (100%) presented with vulvar pruritus with soreness (78%) being the second most frequent symptom. The majority of the subjects (94%) exhibited hyperkeratotic white plaque, and a significant percentage (71%) was found to have extension of the disease to the labia majora, perineal body and anus, while phimosis of the clitoris was the third leading sign found in 61% of the women. Symptoms and signs prior to therapy are shown in detail in Table 2.

Table 1. — *Patients with VLS examined over a 3-year period.*

Category	No of patients	Percentage	Comments
Invasive Ca of the vulva	3	2	Excluded
VIN	2	1	Excluded
Premenopausal VLS	8	6	Excluded
Previously under treatment	11	8	5 with topical steroids 2 with androgens 2 with alcohol injections 1 with progesterone 1 skinning vulvectomy All excluded
Mild/Moderate postmenopausal VLS	42	31	Excluded
Severe postmenopausal VLS	71	52	4 developed contact dermatitis 13 lost in follow-up 17 excluded
Total	137	100	83 patients excluded 54 patients participated in the study

VLS: Vulvar Lichen Sclerosus

Sixteen patients (59%) of the first group versus 23 (85%) of the second had complete remission of their symptoms after six months, whereas 48% versus 74% were the respective numbers after 12 months. Three subjects (11%) from the first group showed no change of symptoms after six months and this number was raised to four (15%) after 12 months. Comparatively, one patient (4%) of the second group showed no change at the 6- and 12-month follow-up. The five patients whose symptoms did not respond to therapy after six or 12 months were treated surgically. Eight (30%) and seven women (26%) from the first group and 15 (55.5%) and 11 (41%) from the second, exhibited complete remission of their signs six and 12 months, respectively, from the beginning of treatment. The same nine patients (33%) from the first group and four (14.5%) and seven (26%) from the

Table 2. — *Symptoms and signs prior to the initiation of therapy.*

Symptoms	Percentage	Signs	Percentage
Pruritus	100%	Whiteness	94%
Soreness	78%	Extensive disease (labia majora, perineal body, perianal area, thighs)	68%
Symptoms affecting urination and defecation	55%	Phimosis of the clitoris	61%
Severe dyspareunia	53%	Fissures	35%
Tearing	17%	Erosions	22%
Bleeding	12%	Sclerosis	22%

Table 3. — *Symptoms and signs following 6 and 12 months of therapy in groups 1 and 2.*

SYMPTOMS AFTER 6 MONTHS				
	Group 1		Group 2	
	No of patients	Percentage	No of patients	Percentage
Complete response	16	59	23	85
Partial response	8	30	3	11
No change	3	11	1	4
Total	27	100	27	100
Ordinal Logistic Regression p=0.040				

SYMPTOMS AFTER 12 MONTHS				
	Group 1		Group 2	
	No of patients	Percentage	No of patients	Percentage
Complete response	13	48	20	74
Partial response	10	37	6	22
No change	4	15	1	4
Total	27	100	27	100
Ordinal Logistic Regression p=0.043				

SIGNS AFTER 6 MONTHS				
	Group 1		Group 2	
	No of patients	Percentage	No of patients	Percentage
Complete response	8	30	15	55
Partial response	10	37	8	30
No change	9	33	4	15
Total	27	100	27	100
Ordinal Logistic Regression p=0.040				

SIGNS AFTER 12 MONTHS				
	Group 1		Group 2	
	No of patients	Percentage	No of patients	Percentage
Complete response	7	26	11	41
Partial response	11	41	9	33
No change	9	33	7	26
Total	27	100	27	100
Ordinal Logistic Regression p=0.299				

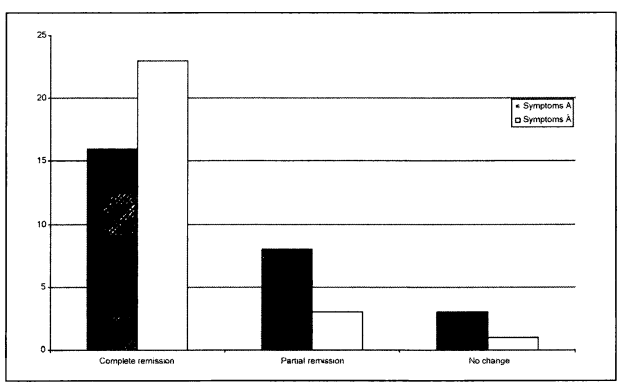
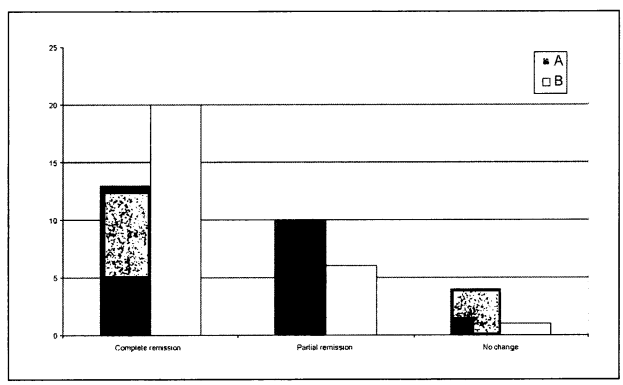


Figure 1.



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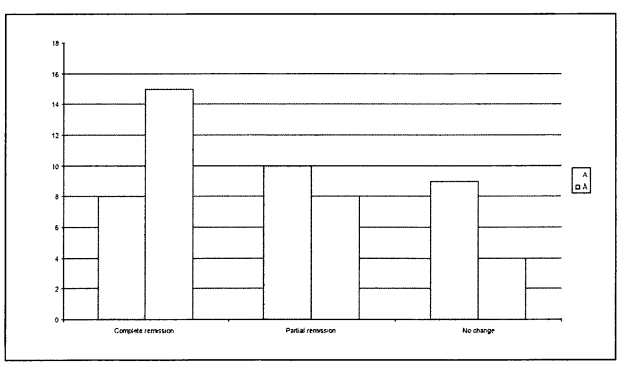

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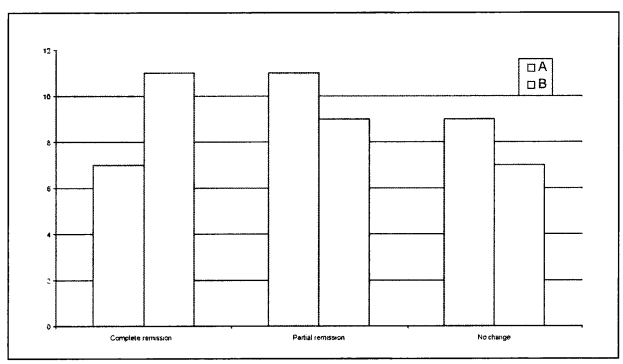

Figure 4.

second, exhibited no change in the appearance of the lesions following six and 12 months, respectively. From the 16 patients that did not respond after 12 months, five had no change in either their symptoms or signs and were treated surgically and the remaining 11 showed no change in their signs and were managed conservatively. From the five women that underwent surgery, four were treated by laser CO2, and one by skinning vulvectomy.

The results in detail are shown in Table 3. When the two groups were compared for both symptoms and signs, we found statistically significant differences: **p**: 0.040 and **p**: 0.043 for the symptoms on the 6- and 12-month follow-up visits respectively and **p**: 0.040 for the signs after six months. The difference between the two groups for the signs following 12 months from the beginning of therapy was not significant (**p**: 0.299).

Discussion

Despite the conjectures that genetic, autoimmune and local factors as well as several infective agents are responsible for vulvar lichen sclerosus, its etiology remains unknown [4]. Thus, treatment has been symptomatic and currently ultra-potent topical applied steroids seem to provide the best solution for this disease.

Clobetasol propionate, a potent fluorinated steroid is thought to be the treatment of choice for VLS. However, contact dermatitis, atrophy and infection of the genital area where this steroid is applied, are some of the side-effects that prevent physicians from using it for a long time [5]. In a study conducted in the UK, 78.5% of the genitourinary physicians used a topical steroidal agent for treating VLS with the majority of them (50%) prescribing a potent corticosteroid for up to six weeks, while 27% were administering it only for two weeks and only 19% for 8-12 weeks [6]. These figures outline the reluctance with which superpotent local steroids like clobetasol propionate are faced.

In the present study, we found that clobetasol propionate 0.05% can be used safely on a regular basis for six months in postmenopausal women with severe disease without adverse side-effects. Our results show a significant increase in the percentage of women (85%) who received therapy on a regular basis for a 6-month period and obtained complete remission of symptoms, in comparison with the group of women that stopped clobetasol after three months and used the ointment only on an "as required" basis (59%). These numbers dropped on the 12-month follow-up defining thus the relapse rate but still the difference between the two groups was statistically significant (74% vs 48%). The percentages of women whose symptoms were completely alleviated following the 3-month therapy were lower than those reported by other authors, but this might be possibly due to selection bias (e.g., the severity of the disease of the subjects that participated in the present study). Concerning the appearance of the lesions, the results of the first group are consistent with those of other authors, but there was a marked improvement in the percentage of complete remission in patients in the second group only at six months, the difference being statistically significant [7, 8]. Contact dermatitis to clobetasol has been reported and indeed we experienced four cases of women that failed to continue the use of the ointment due to this side-effect [9]. Dalziel *et al.* reported no secondary infection or atrophy in nine women examined 24-39 months following the use of clobetasol although they applied the ointment only for three months [10]. We also did not observe any such complications in any of our groups, a fact particularly significant for the arm that used the drug for six months on a regular basis and despite the fact that the follow-up time was not as long. Furthermore, Carli *et al.* histologically examined seven patients who used clobetasol for six months on a regular basis and showed that there was a marked improvement not only in the clinical but also in the histological profile of the vulvar skin of the patients, increasing their epidermal Langerhans cells in levels close to normal [11]. It would also seem of importance to mention that treatment of childhood VLS with superpotent topical corticosteroids over a period of 1-6 months yielded excellent results with minimal complications [12, 13].

Overall, three of our VLS patients (2.1%) were found to have invasive cancer of the vulva and two (1.4%) vulvar intraepithelial neoplasia, the percentages being similar to these of large studies that indicate the potential risk of invasive cancer in VLS to be from 3-5% [14]. However, after 12 months of follow-up among the women that were treated either for three or six months, we did not identify any invasive cancer cases. Despite this fact, the issue of altered histological features of the vulvar epithelium that might cover vulvar intraepithelial neoplasia or invasive carcinoma following treatment with a super-potent steroid remains open to elucidation.

Taking into consideration that the Colposcopy Unit of our hospital is a referral center for vulvar disease in this country, the number of our patients in the present study reflects the difficulties in conducting a prospective randomized trial. However, the above-mentioned results led these authors to suggest that selected women presenting with advanced VLS lesions might have a lot to benefit from long-term use of clobetasol, as it appears to be a safe and effective method of treatment. Nevertheless, these patients should be under close surveillance, preferably with vulvoscopy and colposcopically directed biopsies whenever needed, at the follow-up visits.

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