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Efficacy of a detergent combined with a moisturiser for the treatment of pruritus associated with xerosis in an elderly population affected by Kaposi's sarcoma.

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Abstract

BACKGROUND: Xerosis is common among patients with Kaposi's sarcoma (KS). The aim of our study was to evaluate the efficacy of a detergent containing dihydroavenanthramide D 5% combined with a moisturiser containing 1% of menthol for the treatment of chronic pruritus associated with xerosis in elderly KS patients.

METHODS: We conducted a prospective, open-label, intra-individual, right/left comparative study. During the 4-week treatment study, patients used the test products on the right lower limb, and a basic skin cleanser plus basic cream on their left lower limb, in a predefined protocol. A 10 cm Visual Analogue Scale (VAS), the hydration index (HI) of the stratum corneum and the Overall Dry Skin Score (ODSS) were used to assess pruritus and xerosis severity on admission, at 2 and 4 weeks.

RESULTS: Thirty patients (24 males, 6 females, mean age: 76.6 ± 6.8 years) were enrolled. At the end of 4 weeks, the mean pruritus VAS score declined from 4.2±2.2 to 1.7±1.4 on the right side, and from 4.2±2.2 to 2.3±1.5 on the left side. The HI score increased from 25.6±15.0 to 46.1±12.3 on the right side, and from 26.0±15.2 to 35.4±12.6 on the left side. Differences between the right and left limbs were significant for VAS score ($p=0.0064$), HI ($p<0.0001$) and ODSS values ($p=0.0049$). There was no adverse reaction to the test products.

CONCLUSIONS: Daily use of a detergent containing dihydroavenanthramide D 5% combined with a moisturiser containing 1% of menthol improves chronic pruritus associated with xerosis in elderly adults with KS.

Introduction

Xerosis is one of the most common senile dermatoses.[1] However, little is known about its exact prevalence in the community, which ranges from 30% to 75%.[2-7] Clinical manifestations of xerosis are erythema, scaling and fissuring, and the lower limbs are the most common anatomical areas involved. These lesions may often be associated with itching, and consequent scratching may cause excoriations, which increase the risk of super-infections, particularly in the setting of an atrophic, senile skin.[8]

On the other hand, chronic pruritus is also frequent in the elderly, and itch has been reported to affect 12% of geriatric population.[5] Interestingly, in a study by Valdes-Rodriguez *et al*. chronic itch was reported by 25% of elderly subjects, and 69% of them also suffered from xerosis.[9]

Skin ageing is a process leading to a skin barrier function impairment. The stratum corneum regulates skin hydration by modulating trans-epidermal water loss (TEWL). In the elderly, the decrease in the amount of ceramides of the stratum corneum favours TEWL. Moreover, diminished cutaneous blood flow and sebaceous glands activity, epidermal thinning and destruction of dermal collagen fibrils contribute to xerosis.[1,10] In addition to these physiological metabolic changes, the use of certain treatments, history of atopy, external irritant agents, climate, endocrine disorders and renal failure represent factors associated with an increased risk of dry skin in the elderly.[8,11]

Our centre at Ospedale Policlinico in Milan is nationally-renowned for the diagnosis and treatment of non-HIV-associated Kaposi's sarcoma (KS), an endothelial neoplasm which usually presents on the skin of the lower limbs of elderly people. Among the 1400 patients with KS followed up at our centre, we have noticed that more than three quarters of subjects had extremely dry skin, especially on the legs, and in a considerable number of these patients this condition was associated with persistent pruritus (personal observations).

Emollients and soap substitutes are the cornerstone of the management of xerosis, as they are able to restore the skin barrier function. However, there are no data in the literature reporting an improvement in pruritus associated with xerosis in patients with KS after the use of detergents and/or emollients.

The aim of the present study was to evaluate the efficacy and tolerability of a detergent containing dihydroavenanthramide D 5% combined with a moisturiser containing 1% of menthol for the treatment of dry itchy skin in an elderly population affected by KS.

Materials and methods

Study design

This was a prospective, single centre, open-label, intraindividual, right/left comparative study, to assess the efficacy of a detergent containing dihydroavenanthramide D 5% and an emollient cream containing 1% of menthol in the treatment of pruritus associated with xerosis in elderly patients with classic KS.

Ethics

The study was carried out in accordance with the Declaration of Helsinki, after approval by the local NHS Research Ethics. Patients provided written informed consent before the beginning of the study.

Patients

Thirty patients with classic KS suffering from pruritus of the lower limbs associated with xerosis were enrolled between April 2016 and June 2016 at the Department of Dermatology, University of Milan, Italy. Patients of both sexes, aged ≥ 65 years were allowed to participate in this trial. Additional inclusion criteria for each participant were as follows: (i) dry skin

localized on the lower legs, without clinically apparent differences in xerosis or itch severity between the two limbs; (ii) pruritus on the lower legs persisting for more than 6 weeks. Exclusion criteria were: (i) skin lesions within the target areas interfering with clinical evaluations; (ii) topical treatments on the target areas within the past 2 weeks; (iii) systemic immunosuppressive treatments or antihistamine medications within the past 4 weeks; (iv) history or symptoms of psoriasis or atopy; (v) diseases which may induce pruritus, such as thyroid disorders, psychiatric illness, polycythaemia, diabetes, biliary cirrhosis, hepatic cholestasis, renal failure, multiple sclerosis, parasitosis or viral infection.

Assessments

The severity of pruritus was assessed by patients using an established 10-cm Visual Analogue Scale (VAS)[12] measured before and after each phase of the study, identifying 4 severity levels (mild: ≥ 1-< 4 points; moderate: ≥ 4-< 7 points; severe ≥ 7-< 9 points; very severe: ≥ 9 points).[12]

The hydration index (HI) of the stratum corneum was measured by corneometry (Corneometer®, Courage-Khazaka electronic GmbH, Cologne, Germany) on the external face of the lower legs, making three measurements on adjacent areas and considering the average value. The greater the degree of skin hydration, the higher the corneometry value recorded.[13]

The Overall Dry Skin Score (ODSS) was adopted to assess the clinical severity of xerosis, ranging from 1 (faint scaling, faint roughness, and dull appearance) to 4 (large scales, advanced roughness, eczematous changes, and cracks).[14]

All clinical evaluations at baseline and during the follow-up were assessed by the same investigator (A.T.).

Therapeutic protocol

At baseline (T0) demographic, clinical data and pruritus VAS score were registered for each participant. A target area affected by xerosis on the external face of a lower leg was identified, hence, ODSS and HI values were registered. The same procedure was repeated for the contralateral lower extremity.

All participants were informed about the aims of the study and treatment modalities. More specifically, they were asked to use exclusively the skin cleanser and moisturiser formulated for itchy skin on their right lower limb, and to use exclusively a basic skin cleanser and a basic cream on their left lower limb. They had to use the skin cleansers once a day and the moisturisers twice a day for 4 weeks. All the products were provided by our centre and no other topical agents were admitted for the whole duration of the study. Details of the composition of the products tested are indicated in Table 1.

Participants underwent follow-up visits at weeks 2 (T1) and 4 (T2). At each follow-up visit, clinical examination, pruritus VAS score and assessment of ODSS and HI levels were performed for both target areas.

Statistical Analysis

Data were analyzed using GraphPad Prism 5 (GraphPad Software, San Diego California USA, www.graphpad.com). The Wilcoxon matched-pairs signed rank test, which is a non parametric test, was used to compare values (left vs. right limb) on the same patient; p values < 0.05 were considered as statistically significant.

Results

Patient characteristics at baseline are described in Table 2. The study population (mean age: 76.6 ± 6.8 years) presented considerably more males (M:F=4:1). The mean duration of KS was 12.6 ± 8.2 years, and all patients complained of chronic itch on the lower limbs, of 3-18

years' duration (average of 10.8 years). The degree of pruritus was mostly mild or moderate (25 out of 30 patients).

The results of our study are described in Table 3. At baseline, the severity of pruritus and xerosis assessed respectively by means of VAS and ODSS, were identical between the lower limbs in each of the 30 patients, while the differences of HI values between the two limbs were not statistically significant.

After 4 weeks (T2), patients' assessments of pruritus (by VAS) showed significantly greater improvement for the limbs treated with the test cleanser plus emollient (1.8 ± 1.4) than for the limbs treated with basic cleanser and emollient (2.3 ± 1.5; $p = 0.0064$) (Figure 1). The mean ODSS values were 0.8 ± 0.8 for the limbs treated with the test products and 1.3 ± 1.0 for the limbs treated with basic products ($p = 0.0049$). Finally, the mean HI values (arbitrary Corneometer® units) were 46.1 ± 12.3 for the limbs treated with test products and 35.4 ± 12.6 for the limbs treated with basic products ($p = < 0.0001$) (Figure 1). Consequently, all differences were statistically significant at T2 (Table 3). Moreover, the three parameters assessed showed a statistically significant improvement for the limbs treated with the test products compared with the limbs treated with basic products also at T1 (Table 3).

There was no adverse reaction to the test products. Two patients presented an important reduction of erythema of the treated right limb compared to the left limb treated with basic products only (Figure 2).

Discussion

Xerosis has been proposed to be the most common underlying cause of chronic pruritus in the elderly and itch is present in a high percentage of the population aged 65 and over. [9] Efficacy of emollients in reducing xerosis in the elderly has been previously shown.[15]

Our study examined the effectiveness of a cleanser containing dihydroavenanthramide D 5% combined with an emollient containing 1% of menthol for the treatment of chronic pruritus associated with xerosis in elderly patients suffering from KS. We showed that the regular use of a cleanser and an emollient specific for dry, itchy skin, significantly reduces the intensity of the pruritus after only two weeks, as detected by the improvement in pruritus VAS score observed in most patients with KS. At the same time, the limbs treated with the detergent containing dihydroavenanthramide D 5% combined with the moisturiser containing 1% of menthol showed a better improvement in xerosis than the limbs treated with basic topical products.

The efficacy of the two test products regarding pruritus is reasonably related, besides the emollient effect, also to the presence of menthol and dihydroavenanthramide D. In fact, menthol inhibits itch signal transmission by activating the cold-sensitive transient receptor potential cation channel subfamily M member 8 (TRPM8).[16] On the other hand, dihydroavenanthramide D is a synthetic compound of the avenanthramides (active components of oat), which shows anti-inflammatory and anti-itch properties.[17]

Our study population was entirely represented by elderly people and presented considerably more males (M:F=4:1) than females, in line with the epidemiology of classic KS which mainly affects elderly men. Despite this imbalance of study participants, we believe that the results may be reliably extrapolated to both sexes and all age groups because the products work by physical action only.

All patients tolerated the 1% menthol emollient and no adverse reaction was noticed. However, this component has been considered irritant by some authors and new TRPM8 have been proposed for the topical treatment of chronic pruritus.[18] Interestingly, in two of our patients, tolerability was better on the leg treated with the test products compared to the legs treated with the basic products. Whether this finding was related to the concomitant use of

dihydroavenanthramide D, which has known anti-irritant properties, or it was an accidental phenomenon, is unclear.

In our study, not only pruritus, but also HI and ODSS improved significantly in target areas treated with moisturiser containing menthol, and this is logically linked to the composition of the emollient. The lack of an emollient vehicle group is a limit of our study, but since basic cleansers and emollients are the most frequently prescribed products by dermatologists and other physicians, we think that our intra-patient comparison of the two treatment options is also valuable.

It is well known that pruritus negatively impacts on quality of life.[19] In patients affected by classic KS, which is a chronic neoplastic disorder often associated with lymphoedema and pain of the lower limbs,[20] xerosis and pruritus may lead to further worsening of the quality of life. Due to the scarcity in the literature of randomized controlled studies on senile xerosis treatments in oncologic patients, no standardized guidelines are available.

This study showed that the daily use of a detergent containing dihydroavenanthramide D combined with a 1% menthol moisturiser is a safe treatment and can relieve pruritus associated with xerosis in elderly patients suffering from KS. Additional studies with a larger sample size and longer follow-up would be useful to further support our data.

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Figure legends

Figure 1. Graphs showing variation in pruritus overall visual analogue scale (VAS) scores (A, B) and in hydration index values (C, D) at baseline (T0) and after 4 weeks (T2) of treatment with the test products (see paragraph Study Design) on the right leg and a basic skin cleanser plus basic cream on the left leg of KS patients. The statistical significance was calculated with the Wilcoxon matched-pairs signed rank test (** = $p \leq 0.01$; *** = $p \leq 0.001$; ns = not significant).

Figure 2. Patient with classic KS suffering from pruritus and xerotic eczema of the lower limbs after 4 weeks of treatment with the test products (see paragraph Study Design) on the right leg and basic products on the left leg. An important reduction of erythema of the treated right limb (asterisk) compared to the left limb was noticed.

Table 1. Composition of the products tested.

Product tested	Composition
Test cleanser	Aqua, glycerin, decyl glucoside, disodium cocoyl glutamate, citric acid, panthenol, propylene glycol, sodium levulinate, butylene glycol, pentylene glycol, sodium anisate, hydroxyphenyl propamidobenzoic acid, ascorbyl palmitate.
Basic skin cleanser	Aqua, polysorbate 20, PEG-120 methyl glucose dioleate, disodium cocoamphodiacetate, sodium cocoamphoacetate, sodium laureth sulfate, sodium chloride, methyl gluceth-20, citric acid, tocopherol.
Test emollient	Aqua, caprylic/capric triglyceride, glycerin, dicaprylyl carbonate, dimethicone, sucrose stearate, glyceryl stearate citrate, menthol, cetearyl alcohol, xanthan gum, ethylparaben, methylparaben, benzoic acid, sodium citrate, citric acid, sodium hydroxide.
Basic emollient	Aqua, hydrogeneted polydecene, butyrospermum parkii butter, glycerin, ammonium acryloyldimethyltaurate/VP copolymer, ceramide 3, cholesterol, stearic acid, palmitamide MEA, squalane, caprylyl glycol, hydroxyethyl acrylate/sodium acryloyldimethyl taurate copolymer, o-cymen-5-ol, polysorbate 60.

Table 2. Patient characteristics at baseline.

Characteristic	Value
Gender, n (%)	
Male	24 (80%)
Female	6 (20%)
Age (years) ± standard deviation	76.6 ± 6.8
History of KS (years) ± standard deviation	12.6 ± 8.2
History of pruritus (years) ± standard deviation	10.8 ± 7.6
Degree of pruritus, n (%)	
Mild	13 (43.3%)
Moderate	12 (40%)
Severe	3 (10%)
Very severe	2 (6.7%)

Table 3. Observed values between right lower limb treated with the test products and left lower limb treated with basic products at baseline (T0), after 2 weeks (T1) and after 4 weeks (T2).

	Test products	Basic products	P-value
At baseline: mean (± SD)			
VAS pruritus	4.2 (± 2.2)	4.2 (± 2.2)	NS
ODSS	3.0 (± 0.9)	3.0 (± 0.9)	NS
HI	25.6 (± 15.0)	26.0 (± 15.2)	0.5619
At T1: mean (± SD)			
VAS pruritus	2.3 (± 1.6)	3.0 (± 1.9)	0.0009
ODSS	1.4 (± 1.1)	1.7 (± 1.0)	0.0087
HI	41.0 (± 12.4)	33.1 (± 28.7)	0.0003
At T2: mean (± SD)			
VAS pruritus	1.7 (± 1.4)	2.3 (± 1.5)	0.0064
ODSS	0.8 (± 0.8)	1.3 (± 1.0)	0.0049
HI	46.1 (± 12.3)	35.4 (± 12.6)	< 0.0001

HI, hydration index; NS, not significant (identical values); ODSS, overall dry skin score; SD, standard deviation; VAS, overall visual analogue scale.