TO: Jim Gambino
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Fax Phone 407 242 0625

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DATE:      4th September, 1996
          
No of Pages (including this one)    7

MESSAGE:

Through my connections with Oxford University I have managed to
get hold of this most excellent paper on Aloe Vera. As far as
I am aware it is the only proper double-blind placebo-controlled
trial to have ever been carried out and I am pleased to say with
tremendous results. Dusty was very excited when I showed it to
him and suggested that I fax it to you for your information.

With kind regards,


CC: Executive Committee

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Management of psoriasis with Aloe vera extract in a hydrophilic cream: a placebo-controlled, double-blind study

Taeewee A. Syed, S. Ashfaq Ahmad, Albert H. Holt, Seyed Ali Ahmad, Seyed Hassneh Ahmad and Mohamad Aatil

1. Department of Clinical Physiology, Malmo University Hospital, Malmo, Sweden.
2. Department of Chemistry, University of the Punjab, Lahore, Pakistan.
3. American Social Health Association, Research Triangle Park, North Carolina, U.S.A.
4. Medical Faculty, University of the Punjab, Lahore, Pakistan.
5. PR Hospital, University of the Punjab, Lahore, Pakistan.

Summary
The purpose of this double-blind, placebo-controlled study was to evaluate the clinical efficacy and tolerability of topical Aloe vera extract 0.5% in a hydrophilic cream to cure patients with psoriasis vulgaris. Sixty patients (36M/24F) aged 18-50 years (mean 25.6) with slight to moderate chronic plaque-type psoriasis and PASI (Psoriasis Area and Severity Index) scores between 4.8 and 16.7 (mean 9.3) were enrolled and randomized to two parallel groups. The mean duration of the disease prior to enrollment was 8.5 years (range 1-21). Patients were provided with a prescribed 100 g tube, placebo or active (with 0.5% Aloe vera extract), and they self-administered trial medication topically (without occlusion) at home 3 times daily for 5 consecutive days per week (maximum 4 weeks active treatment). Patients were examined on a weekly basis and those showing a progressive reduction of lesions, desquamation followed by decreased erythema, infiltration and lowering of PASI score were considered healed. The study was scheduled for 16 weeks with 12 months of follow-up on a monthly basis.

The treatment was well tolerated by all the patients, with no adverse drug-related symptoms and no dropouts. By the end of the study, the Aloe vera extract cream had cured 25/30 patients (83.3%) compared to the placebo cure rate of 2/30 (6.6%) (P<0.001) resulting in significant healing of the psoriatic plaques (32/35/6 (82.8%) vs placebo 2/30/6 (7.7%), P<0.001) and a decreased PASI score to a mean of 2.2. The findings of this study suggest that topically applied Aloe vera extract 0.5% in a hydrophilic cream is more effective than placebo, and has not shown toxic or any other objective side-effects. Therefore, the regimen can be considered a safe and alternative treatment to cure patients suffering from psoriasis.

Keywords: psoriasis, Aloe vera, herbal extracts, pharmaceutical creams

Correspondence: Dr. Taeewee A. Syed, The University of North Carolina at Chapel Hill, CB 7090, 547 Burnett-Womack Bldg., Chapel Hill, NC 27599-7098, U.S.A.

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Introduction
Psoriasis is a very common, non-infectious, inflammatory skin disease characterized by well defined, distinctive erythematous plaques yielding adherent silvery white scales, which may manifest bleeding points when removed (Auspitz's sign). Psoriasis may affect any cutaneous surface, but the commonest sites are the extensor surfaces of the elbows and knees, scalp (where scales may become extremely dense) and sacral areas. Precipitation of psoriasis may occur due to trauma (scratching, sunburn or surgical wounds), Koebner phenomenon, stress or genetic predisposition. The eruption of psoriasis may cause numerous symmetrical plaques affecting both sides of the body or may be limited to one or two patches. Men and women are equally affected, but it is more common in white people than in Asians and black people. In the majority of patients it appears for the first time between the ages of 5 and 25.

There is no satisfactory or effective cure for psoriasis. However, a variety of therapeutic modalities have yielded a limited efficacy with frequent side-effects. The available treatment, both local and systemic, which have to some extent proved effective include coal tar, Dithranol (anthralin), calcipotriol, corticosteroids, phototherapy (PUVA, psoralens with long-wave ultraviolet radiation), retinoids, methotrexate and other cytostatic drugs such as hydroxyurea and cyclosporin.

*Aloe vera* is a stemless, perennial, drought-resistant, succulent plant and has reportedly been used since ancient times for medicinal purposes (Klein & Penneys 1988; Shenton 1991; Kurt 1979). It belongs to the lily (Liliaceae) family, and has stiff grey to bright green lance-shaped leaves containing clear gel in a central unclavellateous pulp. Recent research has shown that the pharmacologically active agent is concentrated in both the gel and the rind of the *Aloe vera* leaf. The active agents have shown considerable analgesic, antiinflammatory, wound healing and anti-inflammatory properties (Duke 1985), thus justifying consideration of *Aloe vera* as an effective remedy for the treatment of psoriasis.

The purpose of this double-blind, placebo-controlled study was to evaluate the clinical efficacy and tolerance of *Aloe vera* extract (0.5%) in a hydrophilic cream to cure patients suffering from psoriasis vulgaris.

Patients and methods
Sixty presellected patients (36M/24F) aged 18-50 years (mean 25.6) with slight to moderate chronic plaque-type psoriasis were randomly allocated to two parallel groups. The diagnosis of psoriasis was established by both biopsy and the clinical manifestation of the characteristic silver-white erythematous psoriatic plaques. The mean duration of the disease was 8.5 years (range 1-21). The clinical course was measured using the PASI (psoriasis area and severity index) scoring method as described elsewhere (Froliksson & Petterson 1978). Prior to entry each patient underwent a general physical body examination including routine laboratory tests, such as haematology, complete blood cell count, urinalysis, pregnancy test and the demographic recording of the number of chronic plaques using Harpenden skin calipers. At the start and end of the study full-thickness 6-mm punch skin biopsies were taken under local anaesthesia with 1% lidocain from one lesion of each patient, and were stained with haematoxylin and eosin for the evaluation of acanthosis,
Parakeratosis, thinning, papillary vessel dilation and inflammatory infiltration. Subjects also reviewed oral and written information about the purpose of the study and, accordingly, an informed consent was obtained from all patients (Heinrich Declaration). The study was approved by the respective hospitals' ethical committees and also the district health authorities Lahore and Multan, and took place at official and private clinics and hospitals in Punjab, Pakistan, at the beginning of February 1991. Patients who had been treated with systemic steroids, cytotoxic drugs, beta-blockers, ultraviolet radiation therapy in the preceding 3 months, as well as patients with epilepsy, other types of psoriasis, and pregnant or lactating mothers were excluded.

Patients were allowed to use water-washable emollients during the course of study. Aloe vera extract was prepared as described elsewhere (Davis et al. 1991) and incorporated 0.5% by weight into a hydrophilic cream using a combination of mineral oil and castor oil (B.P.) as vehicle. Matching placebo cream contained no Aloe vera extract. Both active and placebo preparations (prepared at the Department of Chemistry, University of the Punjab, Lahore), were packed, 100g in tubes, were kept at ambient temperature. Patients were given a preceeded 100g tube (active/placebo) for one week's use and shown how to apply the trial preparation topically on their lesions 3 times daily (without occlusion and without exposure of lesions to sunlight) for 5 consecutive days, to a maximum of 15 applications per week. The study was restricted to 4 weeks of active treatment (protocol limitation). To assess the clinical efficacy and tolerance of the trial preparation, patients were examined once a week for up to 16 weeks and thereafter followed up on a monthly basis for 8 months. X-squared and Fisher's exact test with two-tailed values were used for significant test results.

Results
Patient compliance was excellent, the trial preparation was well tolerated and there were no drop-outs. All 60 patients were available for efficacy analysis. Every subject had 4 weeks active treatment, and during that period progressive reduction of desquamation, followed by decreased erythema, infiltration, resulting in moderate to excellent improvement or complete resolution of psoriatic lesions was noted. The mean duration of disease prior to entry was 8.5 years (range 1-21). By the end of the 4-week active treatment, 27/60 (45%) patients (18M/9F), and 46.7% (356/762) of psoriatic plaques were cured, resulting in a substantial lowering of the PASI score from a mean 9.3 to 2.2.

The Aloe vera cream cured a significantly larger number of patients than the placebo (23/30 (76.6%) vs 2/30 (6.6%), P<0.001). The active group also showed a higher number of healed chronic plaques (328/395 (82.8%) vs 28/366 (7.7%), P<0.001). Periodic laboratory tests, including complete blood cell count and urinalysis, were all within normal limits. Biopsy analysis revealed that cured lesions showed a decrease in the levels of epidermal acanthosis, parakeratosis, thinning, papillary vessel dilation, and inflammatory infiltration. Demographically, both treatment groups were comparable in age, race, marital status and duration of disease. The 60 subjects used a total of 245 tubes (100g) in 4 weeks. Patients experienced no drug-related adverse symptoms, either local or systemic, and there was no reporting of hypersensitivity or dermatitis.
parakeratosis, thinning, papillary vessel dilation and inflammatory infiltration. Subjects also received oral and written information about the purpose of the study and, accordingly, an informed consent was obtained from all patients (Helsinki Declaration).

The study was approved by the respective hospitals' ethics committees and also the district health authorities Lahore and Multan, and took place at official and private clinics and hospitals in Punjab, Pakistan, at the beginning of February 1991. Patients who had been treated with systemic steroids, cytotoxic drugs, beta-blockers, ultraviolet irradiation therapy in the preceding 3 months, as well as patients with epilepsy, other types of pustulosis, and pregnancy or lactating mothers were excluded.

Patients were allowed to use water-washable emollients during the course of study. Aloe vera extract was prepared as described elsewhere (Davis et al., 1991) and incorporated 0.5% by weight into a hydrophilic cream using a combination of mineral oil and castor oil (30% v/v) as vehicle. Matching placebo cream contained no Aloe vera extract. Both active and placebo preparations (prepared at the Department of Chemistry, University of the Punjab, Lahore), prescored, 100g in tubes, were kept at room temperature. Patients were given a prescored 100g tube (active/placebo) for one week's use and shown how to apply the trial preparation topically on their lesions 3 times daily (without occlusion and without exposure of lesions to sunlight) for 5 consecutive days, to a maximum of 15 applications per week. The study was restricted to 4 weeks of active treatment (protocol limitation). To assess the clinical efficacy and tolerance of the trial preparation, patients were examined once a week for up to 16 weeks and thereafter followed up on a monthly basis for 8 months.

X² and Fisher's exact test with two-tailed values were used for significant test results.

Results

Patient compliance was excellent, the trial preparation was well tolerated and there were no drop-outs. All 80 patients were available for efficacy analysis. Every subject had 4 weeks active treatment, and during that period progressive reduction of desquamation, followed by decreased erythema, infiltration, resulting in moderate to excellent improvement or complete resolution of pustular lesions was noted. The mean duration of disease prior to entry was 8.5 years (range 1-21). By the end of the 4-week active treatment, 27/60 (45%) patients (18.6/51%), and 45.7% (356/782) of pustular plaques were cured, resulting in a substantial lowering of the PASI score from a mean 9.3 to 2.2.

The Aloe vera cream cured a significantly larger number of patients from the placebo (25/30 (83.3%) vs 2/30 (6.6%), P=0.001). The active group also showed a higher number of healed chronic plaques (12/29/6 (42.8%) vs 2/24/6 (7.7%), P=0.001). Periodic laboratory tests, including complete blood cell count and urinalysis, were all within normal limits. Biopsy analysis revealed that cured lesions showed a decrease in the levels of epidermal acanthosis, parakeratosis, thinning, papillary vessel dilation, and inflammatory infiltration. Demographically, both treatment groups were comparable in age, race, marital status and duration of disease. The 60 subjects used a total of 243 tubes (100 g) in 4 weeks. Patients experienced no drug-related adverse symptoms, either local or systemic, and there was no reporting of hyperesthesia or dermatitis.
Table 1 Patients' characteristics

<table>
<thead>
<tr>
<th></th>
<th>Aloe vera group (n=30)</th>
<th>Placebo group (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>18M/12F</td>
<td>18M/12F</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>25.9</td>
<td>25.2</td>
</tr>
<tr>
<td>Plaques at baseline</td>
<td>396</td>
<td>376</td>
</tr>
<tr>
<td>Plaques cured after 4 weeks</td>
<td>322</td>
<td>28</td>
</tr>
<tr>
<td>Patients cured after 4 weeks</td>
<td>25(83.3%)</td>
<td>2</td>
</tr>
<tr>
<td>Sex.</td>
<td>16M/14F</td>
<td>M</td>
</tr>
<tr>
<td>Mean PASI at baseline</td>
<td>9.7</td>
<td>8.9</td>
</tr>
<tr>
<td>Mean PASI after 4 weeks</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Locations of plaques</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buttock</td>
<td>81</td>
<td>86</td>
</tr>
<tr>
<td>Knee</td>
<td>98</td>
<td>94</td>
</tr>
<tr>
<td>Elbow</td>
<td>96</td>
<td>89</td>
</tr>
<tr>
<td>Body surface</td>
<td>121</td>
<td>97</td>
</tr>
</tbody>
</table>

Table 1 summarizes the characteristics of the study population. The study was followed up on a monthly basis for 4 months and there were no relapses.

Discussion

One of the major findings of this study is that topical Aloe vera extract 0.5% cream significantly resolved psoriatic plaques and proved to be quite effective in healing patients suffering from psoriasis vulgaris. Patients complained of no adverse symptoms or other side-effects. They were pleased to be able to maintain their normal way of life while receiving treatment. Placebo recipients showed no change, indicating lack of efficacy.

A recent review (Labwobi et al. 1995) mentioned that 70% of patients preferred topical therapy for treating psoriasis. However, most of the current psoriatic treatments are suppressive and directed either at inducing a remission or relieving the patient's condition. At present, cyclosporine, calcitriol, calcipotriol, retinoids, dithranol and coal tar are among the usually accepted antipsoriatic compounds. Cyclosporine is a neutral cyclic-peptide that inhibits cell-mediated immune responses with its direct antiproliferation effect on epidermal cells. In a recent study, Ellis et al. (1995) reported 57% of their patients as completely resolved or cleared of psoriatic plaques with the use of 3 mg/kg per day cyclosporine (as maintenance agent) for a period of 4 months. Although cyclosporine has been shown to be very effective in the treatment of psoriasis, one cannot ignore its severe side-effects, namely gradual and progressive decline in renal function, hypertension and nephrotoxicity (Koo 1995).
Calcitriol (1,25-dihydroxyvitamin D₃) also inhibits proliferation and induces differentiation in epidermis. Both Smith et al. (1948), in a study of 7 subjects in a 6-week trial, and Percot et al. (1995) in a study of 4 children for a period of 8 weeks, reported favourable results with calciconal, but this compound is associated with the risk of hypercalcemia, hypercalciuria and induction of bone resorption.

Calcipotriol is a synthetic analogue of calcitriol but devoid of hypercalcemic and hypercalciuric side-effects. By using different concentrations of calcipotriol (topically) in an ointment on 50 patients, Kegh三维 (1989) reached a cure rate of 88%, accompanied by drug-related side-effects such as facial dermatitis on 5 patients during the course of treatment: 4 subjects dropped out. By using calcipotriol ointment for 6 weeks on 20 patients, Baxsta et al. (1994) achieved a cure rate of 85% (17/20), with 2 patients experiencing local adverse events.

Retinoids (retinate and acetate) are a group of compounds derived from vitamin A retinol acid, and more commonly prescribed for skin thick hyperkeratotic psoriatic lesions. Associated side-effects to retinoids include keratodermia, pruritus, general dryness of skin, lips and vagina and rise of blood lipids. Dithranol (Anthralin) inhibits granulocyte function and DNA replication. It is presumed that some of its beneficial effects may be due to the release of free-radical oxygen during therapy. Anthralin is an irritant, stains normal skin and requires medical supervision during its application, which has limited its use. Compared to these and other studies on topical treatment of psoriasis, this study demonstrates a statistically significant (P<0.001) healing in 4 weeks, without drug-related side-effects or dropouts.

Psoriasis is primarily a hyperproliferation of keratinocytes in the dermis. Aloe vera extract is a greasy-free penetrant which is readily absorbed into dermal and deeper tissues. It carries anesthetic, antiinflammatory, antiurticative, wound healing and anti-inflammatory components such as amino acids. The results of this study may suggest that the extract acted in an occlusive manner, keeping the skin moistened and at the same time directly inhibiting the psoriatic plaques by suppressing proliferation and stimulatory differentiation of the cells in the epidermis.

We have previously reported (Syed et al. 1995a,b) that many parameters must be observed in incorporating biologically active compounds into hydrophilic emulsions. In order to motivate and enhance the therapeutic efficacy of a drug in semi-solids (gel, cream and lotion, etc.), one has to consider the drug's preservation, antioxidation, bioavailability of the molecules, the type and status of the skin, the choice of a proper vehicle, and the actual interaction of the drug with the target cells (pharmacodynamics phase). These criteria are crucial in maximising the clinical response to the drug.

In conclusion, the results of this study indicate that Aloe vera extract 0.5% in a hydrophilic cream was well tolerated and appeared to be quite effective. It was beneficial in enhancing resolution and improvement in the majority of study patients compared to the placebo, which suggests its possible use as an alternative treatment of psoriasis vulgaris.
Acknowledgements
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References