Management of Plaque Type Psoriasis with Aloe Vera (*Aloe Barbadensis*) Extract in Hydrophilic Ointment versus Clobetasol Propionate Ointment: A Prospective Randomized Double Blind Controlled Trial

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ABSTRACT

BACKGROUND: Psoriasis is considered as a genetically programmed disease of dysregulated inflammation, which is driven and maintained by multiple components of the immune system. Topical medications both evidenced-based medical and herbal, are widely utilized as treatment for psoriasis affecting less than 20% of the total body surface area of involvement.

OBJECTIVE: To compare the efficacy and safety of aloe vera (AV) extract in hydrophilic ointment versus clobetasol propionate in hydrophilic petrolatum in the resolution of lesions of plaque type psoriasis.

METHODS: A randomized, double blind, controlled 4-week study was designed. Forty-six patients randomly received AV ointment and 0.05% clobetasol propionate and their clinical responses were evaluated using Psoriasis Area Severity Index (PASI). The Psoriasis Disability Index (PDI) was also used to evaluate treatment satisfaction from the topical medications.

RESULTS: Intent to treat analysis done at the end of four weeks showed statistical significance in the mean difference between the treatment groups that is 3.4 (CI:0.6-6.1; P:0.0174). Similarly, per protocol analysis elucidated a significant difference of 3.69 (CI:0.89,6.49 P:0.0115) in the means of both the Aloe vera and the clobetasol group.

CONCLUSION: This study showed the efficacy of AV extract in hydrophilic ointment is not inferior to that of Clobetasol propionate ointment in hydrophilic petrolatum for the treatment of plaque type psoriasis. In both groups there were no recorded adverse events and the patients showed marked improvement in the quality of life after treatment.

I. INTRODUCTION

Psoriasis is a clinically well characterized, inflammatory and hyperproliferative skin disorder that results partly from chronic dysregulation of the immune response.[1] Its prevalence varies largely from 0.1 percent to 11.8 percent with the highest reported incidences in Europe specifically in Denmark and Faeroe island (2.9 and 2.8 percent respectively). This incidence is close to 2.2 to 2.6 percent as measured in the United States in contrast to 0.4 percent recorded from Asia.[2]

Efforts on genetic isolation of the multiple genome-wide linkage studies on psoriasis, the Psoriasis susceptibility 1 (PSORS1) locus has been consistently confirmed. This is located on the major histocompatibility complex chromosome 6p21.3. Furthermore, multiple HLA alelles have been associated with psoriasis HLA-B13, HLAB37, HLA-B57, HLA-Cw1, HLA-Cw6, HLA-DR7 and HLA-DQ9.[2] This genetic perturbation can be triggered by environmental stimuli, systemic illness, medication (infections, medications, antigenic stimuli, physical and or emotional stress).[3] Histopathology has provided a useful framework for cause-and-effect relationship between the cellular assault and the development of psoriatic lesion.[2] Initial pinhead sized with marked edema may show spongiosis with focal hypogranulosis confined to one or two papillae with dermal infiltrates are predominantly mononuclear cells. Developing lesions may show suprapapillary thinning, hypogranulosis, psoriasiform dermatitis, in addition to the munro microabscess and Kogoj abscess.[2,4]

Topical therapy is still the fundamental and remains to be the cornerstone of treatment in the management of psoriasis patients with 20% or less body surface area involvement.5 Various treatment techniques such as combination, rotational and sequential therapy using topical agents are in place for psoriasis. 3 Combination therapy is utilized to benefit from the multiple mechanisms of action of the drugs combined at lower individual doses to provide synergistic or additive efficacy with reduced toxicity. Rotational therapy on the other hand aims to minimize the risk of cumulative toxicity by switching from one therapy to another before the initial agent has a chance to build to potential toxic levels. Lastly, a better-studied technique of treatment is the sequential therapy for psoriasis developed to maximize the short term efficacy of topical agent while minimizing the side effects. This entails three phases: (1) Clearance phase usually utilizes rapidly acting topical agents which often has greater side effects (2) Transitional phase, which when once a patient shows improvement, introduction to a maintenance therapy is undertaken; and (3) Maintenance phase, use of maintenance treatment for as long as needed.[5] All of these techniques aim to maximize the short-term efficacy of topical agent while minimizing toxicity.[6]

Topical corticosteroid, one of the most favored topical treatment for psoriasis has proven its versatility and efficacy in resolving lesions of psoriasis. The mechanisms of action include anti inflammatory, immunosuppressive, anti-proliferative and vasoconstrictive properties. Disease severity, areas of affectation, patients preference, age of the patient, choice of the appropriate potency and its vehicle should all be considered in utilizing topical corticosteroids. Recommendation of dosing regimen is from once to twice daily application; and the duration of use and short term efficacy vary greatly on the steroid potency. Possible toxicities of steroid use can be expected to occur either locally or systemically.[7]

Discussion of other frequently used topical therapy for psoriasis such as vitamin D analogues such as Calcipotriene or calcitriol, retinoids like tazarotene, topical calcineurin inhibitors (tacrolimus and pimecrolimus), coal tar, anthralin, salicylic acid and skin moisturizers are all beyond the scope of this study.[8,9,10,11]

Notwithstanding the advances and researches about psoriasis and its treatment, absolute cure remains to be very challenging. As psoriasis is a chronic condition, it is valuable to note that the safety of treatment for long-term use is relevant. Often the duration of the treatment is restricted by the cumulative toxicity of medications. Furthermore, treatment can be complicated by various adverse events and on the patient's end, treatment exhaustion. The increasing popularity of herbal therapy among patients and physicians flood the medical literature due to the numerous claims of its efficacy.

The natural herbal alternatives, aloe vera (AV) is proven to be a well-researched plant with quite a number of proposed health benefits. More than 300 species of Aloe plants are studied up to this date. It is a cactus-like plant that grows readily in hot, dry climates and The peripheral bundle sheath cells of AV produce an intensely bitter, yellow latex, commonly termed aloe juice, or sap, or aloes. AV sap and AV gel are often confused. Unlike aloes, AV gel contains no anthraquinones, which are responsible for its strong laxative effects.[13] The content of polysaccharides in Aloe plants may vary due to differing climatic conditions, different varieties or perhaps most crucially, different gel preparation techniques. For the gel preparation this also encompass the incorporation of other natural polysaccharides which preserve the integrity of AV polysaccharide during storage. At any rate, Aloe products have been shown to contain widely varying levels of polysaccharides.

Several published trials done by Syed et al in 1996 and Paulsen et al in 2005 compared aloe vera and placebo for resolution of psoriatic plaques. These studies illustrated equivocal and unfavorable efficacy respectively.[14,15] In 2009, a published report by Choonhakarn et. al compared the superiority of AV cream versus triamcinolone cream for treatment of psoriasis.[16] Despite varying results in previously conducted researches, this study was undertaken to verify clinical efficacy of aloe vera in terms of resolving plaques of psoriasis without the adverse events expected from using topical agents such as corticosteroids.

II. MATERIALS AND METHODS

Study design and patient selection

This is a randomized, double blind controlled clinical trial consisting of safety and efficacy testing conducted at East Avenue Medical Center (Quezon City, Philippines) conducted between October 2012 to August 2013. A non-inferiority framework was used to evaluate the comparability of the therapeutic modalities in terms of efficacy.

Inclusion criteria included male or female patients with plaque type psoriasis with less than 25% body surface area of involvement or Psoriasis Area Severity Index (PASI) less than 32, aged 18-65 years old without any systemic disease, no intake of any oral maintenance medication and did not undergo phototherapy. A washout period of one week is necessary for patients applying other topical medications.

This study was approved by the ethics committee under the supervision of the Chair of the Institutional Ethics and Review Board of the East Avenue Medical Center and was conducted in accordance with the ethical standards set by the Helsinki

Materials

The standard drug clobetasol propionate 0.05% ointment was obtained from licensed pharmaceutical company. Authenticated leaves of Aloe barbadensis was soaked in 70% ethyl alcohol, distilled to extract varying concentrations (15%, 20%, 25% and 50%) and were finally incorporated in the final ointment base. The aloe vera extract and standard drug were compounded to attain the same odor, color, texture and consistency. and was packaged into uniform 50-gram white plastic tubes.

Study Procedure

Part I: Safety Evaluation

Subjects ages 18-65 years of age, male or female, with an essentially normal physical and cutaneous findings were recruited for irritancy patch testing. Those with history of atopy and other dermatologic diseases, with previous use of oral and topical steroids, oral antihistamines or immunosuppressive drugs for the past 2 weeks were excluded. Written informed consent from all volunteers was obtained

The varying concentrations of aloe vera extract were placed onto individual IQ Ultra Square chambers and were placed at the upper back of volunteers, secured and left on for 2 days. The patients were assessed on the 48th and the 72nd hour. The reactions were recorded in accordance to the International Contact Dermatitis Research Group Scoring. Homogenous erythema on the 48th hour, which did not persist on the 72nd hour was read as Irritant Contact Dermatitis (ICD).

Part II: Clinical Trial

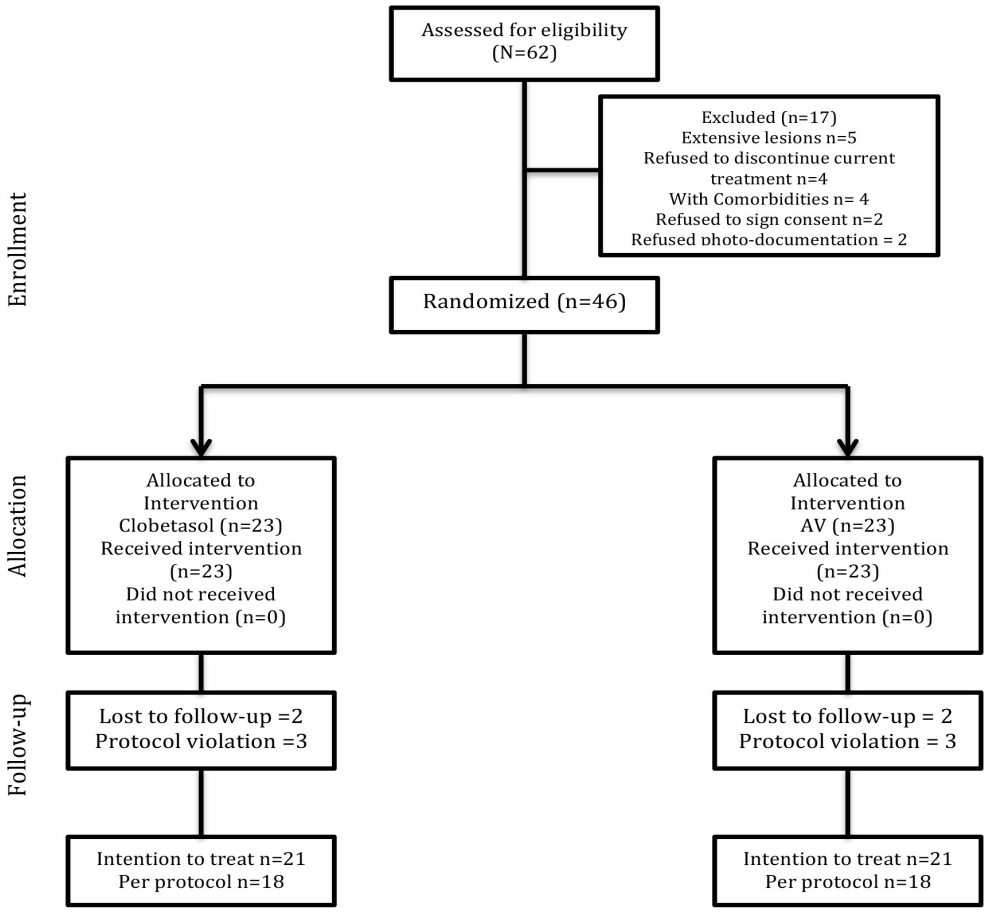
On initial consult, patient underwent extensive history taking of baseline characteristics, detailed physical examination including PASI score determination, photo-documentation and patients were instructed to answer the Psoriasis Disability Index (PDI) at the beginning and end of treatment. Another party guaranteed randomization of clinical trial materials using simple table of random numbers. Patients were instructed to apply the medication over affected areas, twice daily after bathing for 4 consecutive weeks with bimonthly follow-up with strict avoidance of normal skin. On every follow-up PASI determination and photo-documentation were performed.

Outcome Measures

The primary outcome measure was the mean change in PASI score from baseline, week 2 and week 4 of treatment and the change in the Psoriasis disability (PDI) score of patients from baseline to the week 4 of treatment. The secondary outcome was the presence or absence of adverse events.

Statistical analysis

Descriptive analysis was done to illustrate the results of the safety evaluation as well as the reporting of adverse events. For the clinical trial, the improvement differences in PASI and PDI score assessments between groups were analyzed using an independent T-test both for the intent-to-treat (ITT) and per protocol (PP) analysis. The difference between treatment groups were estimated at 95% confidence interval. Furthermore, an intent-to-treat analysis was performed to account for protocol violations and carried forward the recorded data accordingly.



III. RESULTS

Safety Evaluation

Ten healthy volunteers (5 male, 5 female) ages 25-60 years old, were included in the safety evaluation. Results showed that there were three volunteers, one male and two females, who showed doubtful reaction on the 48th hour with the 50% AV extract which when further monitored on the 72nd hour returned negative; this is labeled as ICD. The rest of the other concentrations returned negative results. The concentration utilized for the clinical trial was the next lower dose that is 25% AV extract.

Clinical Trial

Study Patients

Sixty-two patients were assessed for eligibility to join the trial of which only 43 qualified for enrollment (See Figure 2). Twenty-three patients enrollment (See Figure 2). Twenty-three patients (19 males, 17 females) were randomized between the two treatment groups. Four patients were lost to follow-up (50% from AV group, 50% from Clobetasol group), 6 had protocol violations (50% from AV group, 50% from Clobetasol group) see figure 1. Protocol violations consisted of undergoing elective surgery, taking systemic medication, application of other concomitant topical medication, abrupt cessation of topical application.

Intent to treat population showed 21 patients per treatment arm (n=42) while the per protocol population analysis showed 18 patients per treatment arm (n=36). Baseline demographics and disease parameters are presented in Table 1. Both groups had similar baseline characteristics with the exception of a higher PASI and PDI scores in the AV group. In addition, patients from both groups utilized mainly topical treatment, while some utilized combination of all three regimen.

Table 1. Baseline demographics and disease parameters

	AV n=21	**Clobetasol n=21**
Age (years)		
Mean±SD	40.8 ± 14.6	37.9 ± 11.0
Range	18-63	18-60
Gender, n (%)		
Male	9 (43%)	11 (52%)
Female	12 (57%)	10 (48%)
Previous		
Topical only	21	21
Phototherapy	2	1
Systemic	4	5
Baseline Scores		
PASI	15.6 ± 6.8	10.8 ± 5.2
PDI	16.0 ± 8.3	11.8 ± 10.4

Per protocol analysis of the psoriasis disability index showed that the AV group had a mean PDI score of 16.0 + 8.3 at baseline that decreased to 8.9 + 6.38 at week 4. On the other hand, the clobetasol group showed a mean of 11.8 + 10.44 at baseline, which showed an absolute mean decrease to 6.6 + 5.73 at the end of treatment. The between group difference in adjusted means was 6.18 + 8.84 (CI: 3.25-9.10, P:0.5136) showing no statistical difference at the end of treatment. See table 2.

The results further showed that marked (PASI 75) and moderate responses (PASI 50) were attained by both treatment groups, while the slight response (PASI<50) was dominated by the clobetasol group. It is noteworthy to mention that one patient

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