EVALUATION OF THE EFFECTIVENESS OF TOPICAL ANTIBIOTICS IN TREATMENT OF MILD-MODERATE PLAQUE TYPE PSORIASIS

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ABSTRACT
A prospective study was done during the period from October 2005 to July 2006 at the Departments of Microbiology and dermatology, Basrah University Medical College, and aimed on the evaluation of the effectiveness of topical antimicrobial agents on the plaque type psoriasis clinically and bacteriologically, before and after drug therapy and to compare it with that of the non-involved skin of psoriatic patients and healthy controls. Bacteriological examination was carried out on 500 skin swabs taken from psoriatic plaques before and after treatment for 3 weeks with topical fusidic acid (2% concentration, IHP, Denmark) or tetracycline (3%, SDI) pre-and post-application and from uninvolved skin of psoriatic patients and from matched healthy controls. In addition to the responses to either fusidic acid or tetracycline, topical applications were assessed clinically by psoriasis severity index (PSI). Plaque psoriasis showed a significant clinical responses (P<0.001) to topical antimicrobial agents (changes in PSI score). Guttate psoriasis had no such responses. On the other hand, psoriasis plaques harboured a higher density (10⁴-10⁵ CFU/ml) of microbial population compared to the non-involved skin of psoriatic patients (Not exceeds 10² CFU/ml). Microbial density was reduced significantly (P<0.01) by 3 weeks after topical fusidic acid and tetracycline application (from >10⁵ to <10² CFU/ml). Staphylococcus epidermidis (a species of coagulase-negative staphylococci) was significantly the most prevalent bacteria (P<0.001) on the psoriatic plaques.

In conclusion, topical fusidic acid (2%) and tetracycline (3%) are effective in the treatment of mild to moderate plaque psoriasis but not in the treatment of guttate psoriasis. Staphylococcus epidermidis may play a role in the pathogenesis of plaque psoriasis. Further detailed study is suggested to clarify this role.

INTRODUCTION
Psoriasis is a chronic inflammatory skin disease of unknown causation[¹] Increasing evidence suggests an important role for bacteria in the initiation and/or propagation of psoriasis.[²] Although Staphylococcus aureus has been found in unusual heavy colonization on the skin of more than half of the patients with chronic plaque psoriasis,[³] yet, the most convincing clinical and experimental association between bacteria and psoriasis is in patients with acute guttate psoriasis.[⁴] Recent studies have demonstrated that certain products of bacteria can act as superantigens providing plausible mechanisms by which these bacteria could cause psoriasis.[⁵,⁶] It is reasonable to think about achieving clinical improvement in psoriasis through eradication of the implicated bacteria by topical antimicrobial agents. In the present study we performed two types of work. First, a clinical work for evaluation of responses of psoriatic lesions to topically applied antimicrobial agents. Second, a laboratory work for bacteriological examination of psoriatic plaques (before and after the application of topical fusidic acid) to assess its effect on the isolated bacteria and severity of psoriasis and to compare with that of the uninvolved skin of psoriatic patients and healthy controls.

MATERIALS AND METHOD
Part 1 A total of 200 individuals who completed the follow-up till the end those meeting the criteria of inclusion were enrolled in this study; 100 psoriatic patients (93 patients with plaque psoriasis and 7 patients with guttate psoriasis) and 100 controls (healthy individuals that were neither psoriatic nor having a family history of psoriasis). Only plaque and guttate psoriasis affecting less than 20% of the total body surface area were included in this study. None of the lesions were secondarily infected and none of the patients were on systemic or topical antimicrobial agents or steroids prior or during the study. Disease severity was assessed by an index named psoriasis severity index “PSI”. Scoring of this index is calculated in a way similar to that of psoriasis area and severity index “PASI” except in exclusion of the area involved. Three psoriatic plaques (sites) were selected from each patient for topical application of fusidic acid ointment (Fucin¹)}
IHP), tetracycline ointment (Samacyclin®, SDI) and clobetasol ointment as clobetasol propionate 0.05% (Dermodin®, SDI), one drug for each site. An additional fourth plaque was selected and left without treatment for comparison. All drugs applications for the first time were done under the observation of one of the investigators (as this work was part of MSc thesis and the follow-up done by the MSc student). The patients were carefully instructed to apply the drug twice daily for three weeks. Patients were seen after 1 week and 3 weeks post drug application and the drug was considered effective when the severity of the treated sites is reduced, according to PSI score to $\geq 20\%$ and $\geq 45\%$ from the base line after 1 and 3 weeks of treatment respectively.[7]

**PART 2:** Three hundred skin swabs were taken sequentially (by vigorous rubbing) from the sites treated with fusidic acid (100 swabs before drug application, 100 swabs after 1 week and 100 swabs after 3 weeks post drug application respectively). An additional 100 swabs were taken from uninvolved skin of psoriatic patients adjacent to the sites treated with fusidic acid. A 100 more swabs were taken from healthy controls. Bacterial suspension was made from each swab reaching a final dilution of 1:10000 ($10^4$) of the original sample.[8] Blood agar (HIMEDIA) and MacConkey (LAB-M) media were used for the primary cultivation. All plates were incubated aerobically at 37°C for 24-48 hours. Morphological criteria and biochemical tests (catalase test,[9] tube method coagulase test[10] and modified oxidase test[11]) were used to identify the primary isolates. API staph. system (BioMerieux),[12] was used for further identification of staphylococci. Slime test[13] was used to detect slime production. Bacterial growth density was assessed by the number of colonies of the primary cultivation. The following terms were suggested, as they were more convenient for the clinical use.[9] Mild growth for $\leq 4$ colonies ($\leq 4\times 10^4$ CFU./ml), moderate growth for 5-10 colonies ($= 5\times 10^5$- $1\times 10^5$ CFU/ml) and heavy growth for any figure above 10 colonies ($> 1\times 10^5$ CFU/ml). Sensitivity tests to fusidic acid (10 micrograms, oxoid), gentamicin (10 micrograms, bioanalyse) and tetracycline (30 micrograms, bioanalyse) were done by the disk agar diffusion (DAD) testing.[14,15]

**RESULTS**

**Part 1: Clinical work**

There were 93 (93%) patients with plaque psoriasis (47% males and 46% females) and 7(7%) patients with guttate psoriasis. Both sexes were affected in equal proportion for each type of psoriasis ($P>0.05$). Plaque psoriasis was reported more commonly (68.8%) at the age of 20-30 years (Table-1).

**Table 1. Age distribution of the study population**

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Type of psoriasis</th>
<th>Control No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plaque No. (%)</td>
<td>Guttate No. (%)</td>
</tr>
<tr>
<td>5-20</td>
<td>4 (4.3)</td>
<td>3(42.8)</td>
</tr>
<tr>
<td>21-35</td>
<td>64 (68.8)*</td>
<td>2(28.5)</td>
</tr>
<tr>
<td>36-50</td>
<td>13 (13.9)</td>
<td>2 (28.5)</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>12 (12.9)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>93 (93%)</td>
<td>7 (7%)</td>
</tr>
</tbody>
</table>

* $P<0.01$

The mean PSI at baseline for the studied sites was 7 for plaque psoriasis and 4 for guttate psoriasis. Changes in PSI are shown in Table-2. In plaque psoriasis 1 week after application of antimicrobials, the reduction of $\geq 20\%$ of PSI score was achieved in all of the 93(100%) sites treated with tetracycline and fusidic acid. This was not the case with clobetasol treated sites as there were only 20(21.5%) sites showed such responses. Three weeks post drug application, the sites that showed a reduction of $\geq 45\%$ of PSI score (i.e: marked clinical improvement) were 75(80.6%) for fusidic acid and 71 (76.3%) for tetracycline (Photo 1 and 2). These figures are highly significant ($P<0.01$) in comparison with the starting 93 untreated sites for each drug. In addition, none of the studied sites showed an increase in the score (relapse) during the following period other than the 25(26.8%) untreated sites. In guttate psoriasis, there was only a non significant ($P>0.05$) single site response to fusidic acid (Table-2) at the end of the study.
Table 2. The follow-up of responses to treatment at different intervals post-drug application

<table>
<thead>
<tr>
<th>Type of treatment</th>
<th>Plaque psoriasis</th>
<th>Guttate psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 week</td>
<td>3 weeks</td>
</tr>
<tr>
<td></td>
<td>X₁</td>
<td>R</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>93(100)</td>
<td>0</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>93(100)</td>
<td>0</td>
</tr>
<tr>
<td>Clobetasol</td>
<td>20(21.5)</td>
<td>0</td>
</tr>
<tr>
<td>No treatment</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data presented as the number of cases and their percentages.

X₁ = Reduction in PSI of ≥ 20%
X₂ = Reduction in PSI of ≥ 45%
R = Relapse = any increase in PSI
*P<0.01

Moreover, the present work showed that previous use (before the enrollment in the study) of different topical modalities of psoriatic therapy (regardless of the duration of application) had a lesser extent lower response to antimicrobials than those with no previous therapy (Table-3).

Table 3. Responses to antibiotic application in relation to previous use of psoriasis therapy

<table>
<thead>
<tr>
<th>Period or previous therapy</th>
<th>Applied antibiotics</th>
<th>Plaque psoriasis</th>
<th>Guttate psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>n (%) responding sites</td>
<td>No. of patients</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>T</td>
<td>F</td>
</tr>
<tr>
<td>2 – 3 months</td>
<td>52</td>
<td>39 (75)</td>
<td>35 (67.3)</td>
</tr>
<tr>
<td>4– 6 months</td>
<td>7</td>
<td>5 (71.4)</td>
<td>5 (71.4)</td>
</tr>
<tr>
<td>&gt; 6 months</td>
<td>1</td>
<td>1 (100)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>No treatment before</td>
<td>33</td>
<td>30 (90.9)</td>
<td>30 (90.9)</td>
</tr>
</tbody>
</table>

F= Fusidic acid, T= tetracycline.

Part 2: Bacteriological work

As shown in Table-4, *Staphylococcus aureus* isolates were encountered in only 1.2% of the isolates.

Table 4. The frequency of microbial isolation from plaque and guttate psoriasis cases.

<table>
<thead>
<tr>
<th>Bacterial isolates</th>
<th>Plaque psoriasis</th>
<th>Guttate psoriasis</th>
<th>Total</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>(%)</td>
<td>No. (%)</td>
<td>(%)</td>
</tr>
<tr>
<td>CONS</td>
<td>356 (94.6)*</td>
<td>20 (5.3)*</td>
<td>376 (94)*</td>
<td>92 (94.8)</td>
</tr>
<tr>
<td>Staph. aureus</td>
<td>5 (100)</td>
<td>0</td>
<td>5 (1.25)</td>
<td>5 (5.1)</td>
</tr>
<tr>
<td>Micrococci</td>
<td>59 (86.7)</td>
<td>9 (13.2)</td>
<td>68 (17)</td>
<td>25 (25.9)</td>
</tr>
<tr>
<td>Gram *ve bacilli</td>
<td>3 (75)</td>
<td>1 (25)</td>
<td>4 (1)</td>
<td>4 (4.1)</td>
</tr>
<tr>
<td>Negative cultures</td>
<td>11 (57.8)</td>
<td>8 (42.1)</td>
<td>19 (4.75)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>372 (93)</td>
<td>28 (7)</td>
<td>400 (100)</td>
<td>100</td>
</tr>
</tbody>
</table>

* P<0.01

= Coagulase-negative staphylococci

= strains presented only as mixed growths with CONS (figures represent an overlapping numbers).
Coagulase negative staphylococci (CONS) were significantly (P<0.01) the most prevalent bacteria forming 356 (94.6%) isolates in plaque psoriasis and 20(5.3%) isolates in guttate psoriasis with a percentage of 99.6% from the total. Gram negative bacteria were not encountered. Moreover, slime productions were not detected. All figures of microbial growth density are given in Table-5. Among the plaque psoriasis before treatment (group A1) moderate growth were significantly noticed in 55(59.8%) of these sites (P<0.01). Three weeks after treatment with fusidic acid (group A3) there were a reduction in the number of moderate growth to 10(11.2%) accompanied by a rise in the number of mild growth to 79(88.7%). In guttate psoriasis, mild growths were the only pattern encountered, unchanged pre- and post application of fusidic acid.

Table 5. Microbial growth density reduction during follow-up of Fucidic acid treatment

<table>
<thead>
<tr>
<th>Growth density</th>
<th>Mild</th>
<th>Moderate</th>
<th>Heavy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plaque Psoriasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>20</td>
<td>(21.7)</td>
<td>55</td>
<td>(59.8)</td>
</tr>
<tr>
<td>A2</td>
<td>53</td>
<td>(58.8)</td>
<td>30</td>
<td>(33.3)</td>
</tr>
<tr>
<td>A3</td>
<td>79</td>
<td>(88.7)</td>
<td>10</td>
<td>(11.2)</td>
</tr>
<tr>
<td>B</td>
<td>55</td>
<td>(61.1)</td>
<td>33</td>
<td>(36.8)</td>
</tr>
<tr>
<td>Total</td>
<td>207</td>
<td>(89.8)</td>
<td>128</td>
<td>(100)</td>
</tr>
<tr>
<td>Guttate Psoriasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>5</td>
<td>(100)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>A2</td>
<td>5</td>
<td>(100)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>A3</td>
<td>4</td>
<td>(100)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>6</td>
<td>(100)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>(8.8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>15</td>
<td>(15.4)</td>
<td>77</td>
<td>(79.3)</td>
</tr>
</tbody>
</table>

Mild: 10^1-3, Moderate: 10^4, heavy: 10^5-10^7 CFU/ml.
A1: before treatment, A2: 1 week, A3: 3 weeks, B: Uninvolved skin
Photo 1. Plaque psoriasis 1 day after application of topical antibiotics. Fusidic acid was applied to the right leg and tetracycline to the left one.

Photo 2. This photo belongs to the same patient above, showing the marked improvement in psoriatic lesions 3 weeks post antibiotic therapy.
DISCUSSION

The prevalence of psoriasis in relation to age and sex was similar to the usual epidemiology of psoriasis reported by other studies.\(^{[16]}\) The significant clinical responses of psoriasis to fusidic acid and tetracycline (P<0.01) can be attributed to their antibacterial effects since most of the bacterial isolates were sensitive to them and there were significant reduction in microbial growth densities. To our best of knowledge, there are no previous similar studies for comparison at least in our country. Two previous studies comparing topical antibiotic preparations for chronic plaque psoriasis\(^{[17,18]}\) are excluded as the active ingredients were being used for their local immunosuppressant properties, not as antimicrobial agents. The failure of topical steroid to show a similar marked clinical improvement can be explained by the loss of effectiveness after time from its use (tachyphylaxis) as it frequently prescribed by the dermatologists for psoriasis.\(^{[16]}\) Unremarkable responses to steroid can be used to exclude the emollient effect of the ointment base of the applied antimicrobials as a possible cause behind the clinical improvement.\(^{[16]}\) In a similar way we may exclude the steroidal effect of fusidic acid.\(^{[19]}\) Spontaneous remission as a probable cause of the clinical improvement\(^{[16]}\) is excluded by the none responses observed among the selected untreated sites. None of the sites treated with antimicrobials showed a relapse during the follow up of patients. This may be explained by the effective continuous action of these drugs as the clinical responses is proportionally related to the reduction in the density of the microbial agents that is thought to play a role in the pathogenesis of psoriasis. The relatively low responses of the previously treated plaque psoriasis inspite of the persistent reduction in microbial density may be attributed to other unknown factors involved in the pathogenesis of psoriasis. Although guttate psoriasis is closely associated with preceeding streptococcal pharyngitis or tonsillitis and systemic antibiotic may play a role in their management,\(^{[22]}\) the non-significant response to topical antimicrobial agents together with the unchanged microbial density make it possible to exclude the beneficial role of these drugs for the guttate psoriasis and the direct role of the isolated bacteria in the pathogenesis of this type of psoriasis where guttate psoriasis is possibly a cutaneous reaction to a distant focus of bacterial infection as tonsillitis, rather than to abundant colonization of psoriatic skin. However, there was no previous study for comparison. The pattern of the isolated bacteria was that of normal skin flora. Absence of gram negative bacteria may be because the subjects under study had not used systemic antibiotics, so the ecology of the skin had not changed.\(^{[23]}\) The lack of slime production can be explained by the non-infectious nature of these bacteria.\(^{[24]}\) Hence, a possible role of slime in the pathogenesis of psoriasis is excluded. The infrequent isolation of *Staphylococcus aureus* is in agreement with that of Noble et al.\(^{[25]}\) and can be explained by the usual small number of these bacteria among skin flora.\(^{[26]}\) On the other hand, this was in contrast to others who conducted their studies on a hospital admitted patients. This controversy may be related to the fact that our subjects were outpatients as it was found that outpatients with psoriasis seldom yielded *Staphylococcus aureus* on their skin.\(^{[25,28]}\) The constantly high prevalence of *Staphylococcus epidermidis* (a species of CONS) was also reported by other studies.\(^{[27,29]}\) This is expected since these bacteria form the majority of skin flora.\(^{[26]}\) Microbial growth density on the plaques was more than that of the uninvolved skin among patients with plaque psoriasis. Although this finding was compatible with other studies,\(^{[29,30]}\) no previous explanation was given to it, but the significant decrease in the growth density of these bacteria after the application of topical antibiotics accompanying the clinical improvement of the plaque psoriasis may assume a possible role for the isolated microorganisms, mainly *Staphylococcus epidermidis* species (as they were significantly the most prevalent one among the isolates) in the pathogenesis of psoriasis. This assumption can be strengthen by the previous induction of psoriasis by *Staphylococcus epidermidis*.\(^{[31]}\) Moreover, an auto vaccine made from the above bacteria yielded a clinical improvement in psoriasis.\(^{[32]}\) Furthermore, the ultraviolet radiation which has a killing effect to *Staphylococcus epidermidis* is a well known
therapy for psoriasis.[16] A possible mechanism for these bacteria to induce psoriasis is through the action of their superantigens[34] that elicit immunological changes with release of cytokines that cause skin changes similar to that of psoriasis. The predominant sensitivity to fusidic acid and tetracycline may be explained by the lack of mechanisms essential for developing drug resistance.[26] Since there was no significant resistance developed for the above drugs, their effective use for long period of time may be expected. Actually one of the patients was seen one year after his last follow up visit. He was doing very well with topical tetracycline. By the same way, un-effectiveness of time may be expected. Actually one of the above drugs, their effective use for long period of time may be expected. Actually one of the strains were resistant to it as most of the strains were resistant to it.

In conclusion, topical fusidic acid and tetracycline are of great value in the treatment of mild and moderate plaque psoriasis. No such benefit can be obtained for guttate psoriasis. Bacteria, mainly Staphylococcus epidermidis, may play a role in the pathogenesis of plaque psoriasis rather than the guttate psoriasis.

REFERENCES