A Randomized, Double-Blind, Controlled Study on the Safety and Efficacy of 10% Bee Propolis Ointment versus 2% Mupirocin Ointment on Superficial Pyodermas caused by *Staphylococcus Aureus*

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BACKGROUND: Superficial pyoderma is a skin condition commonly seen in a dermatology primary care setting. This infection is caused by invasion of the skin with pathogenic bacteria, most commonly *Staphylococcus aureus*. The current drug of choice for this condition is 2% mupirocin ointment. Unfortunately, the high cost of this drug may significantly affect compliance and overall cure. There is also the risk of developing drug resistance to mupirocin with prolonged treatment. Hence, there is a need to explore alternative treatments for superficial pyodermas caused by *S. aureus* that are low-cost, safe and effective. Bee propolis, a resinous substance from beehive, is a potential alternative treatment for *S. aureus* superficial pyodermas considering its anti-inflammatory effects and strong antibacterial properties against staphylococci. Its safety and efficacy in the treatment of such dermatoses however, need to be investigated.

OBJECTIVES

The general objective is to determine the safety and efficacy of 10% bee propolis ointment versus 2% mupirocin ointment in the treatment of superficial pyodermas caused by *S. aureus*. The specific objectives are: 1) to compare the bactericidal activity of 10% bee propolis ointment and 2% mupirocin ointment based on the percentage of patients bacteriologically cured (negative for *S. aureus*) at Day 14 of treatment; 2) to compare the efficacy of 10% bee propolis ointment and 2% mupirocin ointment in treating superficial pyodermas caused by *S. aureus* based on the clinical efficacy grading of erythema, edema, induration and size of lesions at baseline, Day 3, Day 7 and Day 14 of treatment; 3) to compare the Participant's Global Assessment score in the 10% bee propolis and 2% mupirocin treatment groups at Day 3, Day 7 and Day 14 of treatment; and, 4) to compare the occurrence and severity of adverse cutaneous reactions in the 10% bee propolis and 2% mupirocin treatment groups at Day 3, Day 7 and Day 14 of treatment.

METHOD

The study involved two phases. Phase I was a 72-hour I.Q. Chamber Irritancy patch test of the test medication, 10% bee propolis ointment on thirty (30) healthy volunteers. Reading and interpretation of results were done after 48- and 72 hours. The irritancy potential was computed and from this, the test medication was classified as non-irritant, mild irritant or too irritant. Classification of 10% bee propolis as non-irritant and safe (non-allergenic) prompted continuation of the study to the next phase.

The second phase was a clinical trial involving 60 patients aged 18 to 60 years old, clinically diagnosed to have superficial pyoderma defined as a lesion that measures less than 5 cm with absence of co-morbid diseases and constitutional signs and symptoms, according to Eron et al. and confirmed to have lesions infected by *S. aureus* as detected by Gram stain and culture of wound discharge. These patients were randomly assigned into one of two treatment groups: 10% bee propolis ointment or 2% mupirocin ointment. There were 30 patients in each treatment arm. Patients were instructed to apply the assigned ointment twice daily for two weeks. Bactericidal activity of the assigned ointment was determined based on the percentage of patients cured at the end of the treatment period (Day 14). The efficacy of the assigned ointment was also evaluated based on clinical efficacy grading of erythema, edema, induration and size of lesions at baseline, Day 3, Day 7 and Day 14 of treatment. Erythema, edema and induration of lesions were scored or graded based on a 5-point scale while lesion size was determined by measuring the widest diameter of the lesion in centimeters. Patients were also asked to rate the improvement of their condition using a Participant's Global Assessment scale. The presence of adverse cutaneous reactions (if any) was also noted on each visit. All data were subjected to statistical analyses to compare the effects of the medications in the two treatment groups.

RESULT

In Phase I of the study, all 30 healthy adult volunteers who were subjected to patch testing did not exhibit a positive reaction to 10% bee propolis ointment after 48- and 72 hours. The computed primary irritancy index score for this test product was zero. Hence, 10% bee propolis ointment was classified as non-irritant and safe, prompting continuation of the study into the next phase: the clinical trial. In Phase II, data were recorded for 53 subjects (88.33%) who completed the trial. Twenty-two out of thirty patients (73.33%) in the bee propolis group were bacteriologically cured (negative for *S. aureus*) while 24 out of 30 patients (80%) in the mupirocin group were bacteriologically cured after two weeks of treatment. Nevertheless, results of the chi-square test showed that the proportion of patients with positive bacterial activity (*S. aureus* still present in wound discharge) did not vary significantly between the two treatment groups ($p=0.542$). Figure a.1 shows the percentage of patients cured and not cured in each treatment group.

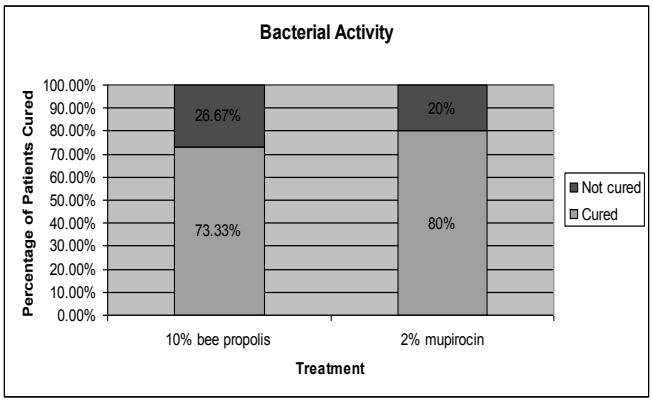

Figure a.1. *Percentage of patients bacteriologically cured and not cured in the 10% bee propolis and 2% mupirocin group after two weeks of treatment*

Erythema of patients was also reduced in both treatment groups from moderate to severe at baseline to less than mild at Day 14 of treatment. Results of the Mann-Whitney test showed that the mean severity score of erythema did not vary significantly between the two treatment groups at baseline (p=0.5351), Day 3 (p=0.4804), Day 7 (p=0.6975), and Day 14 (p=0.2385) of treatment. Figure a.2 shows the mean severity score of erythema in each treatment group over time.

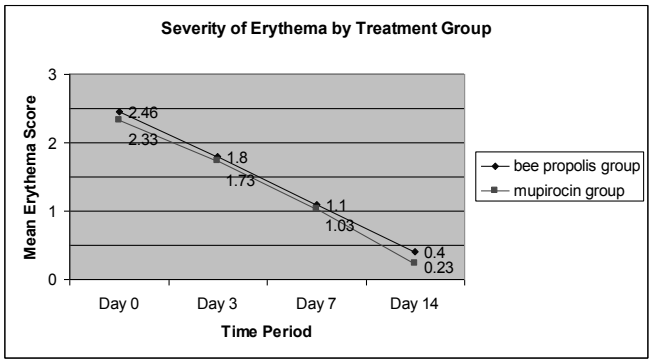

Figure a.2. *Mean severity score of erythema in the 10% bee propolis and 2% mupirocin group over time*

Edema of patients was also reduced in both treatment groups from moderate to severe at baseline to less than mild at Day 14 of treatment. Results of the Mann-Whitney test showed that the mean severity score of edema did not vary significantly between the two treatment groups at baseline (p=0.8427), Day 3 (p=0.5903), Day 7 (p=0.4759), and Day 14 (p=0.3751) of treatment. Figure a.3 shows the mean severity score of edema in each treatment group over time.

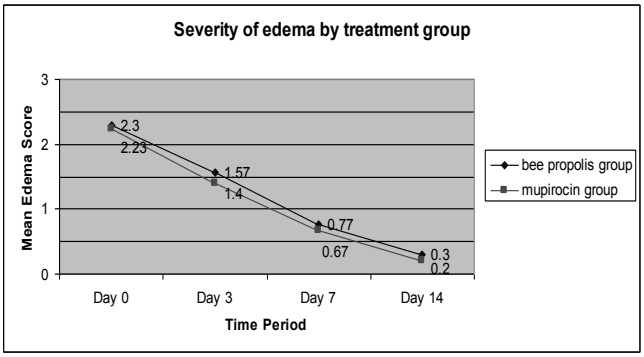

Figure a.3. *Mean severity score of edema in the 10% bee propolis and 2% mupirocin group over time*

Induration of patients was also reduced in both treatment groups from moderate to severe at baseline to less than mild at Day 14 of treatment. Results of the Mann-Whitney test showed that the mean severity score of induration did not vary significantly between the two treatment groups at baseline (p=0.8101), Day 3 (p=0.8830), Day 7 (p=0.5259), and Day 14 (p=0.2638) of treatment. Figure a.4 shows the mean severity score of induration in each treatment group over time.

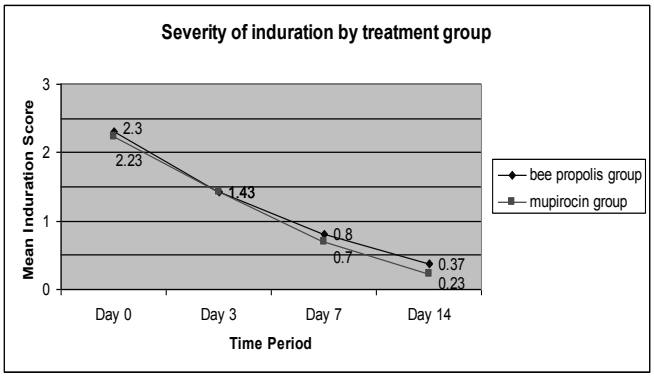

Figure a.4. *Mean severity score of induration in the 10% bee propolis and 2% mupirocin group over time*

The size of lesions also decreased in both treatment groups. Results of the Mann-Whitney test showed that the mean lesion size did not vary significantly between the two treatment groups at baseline (p=0.7211), Day 3 (p=0.5638), Day 7 (p=0.3489), and Day 14 (p=0.3606) of treatment. Figure a.5 shows the lesion size in each treatment group over time.

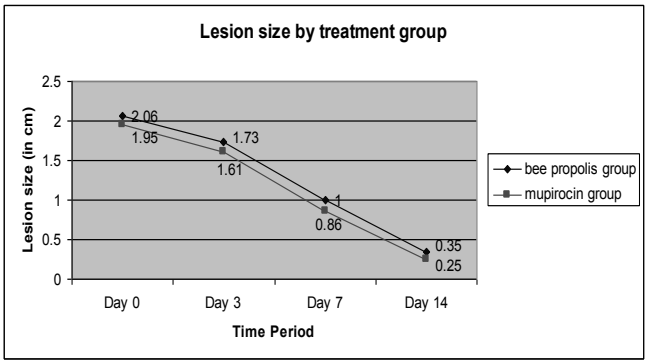

Figure a.5. *Lesion size in the 10% bee propolis and 2% mupirocin group over time*

The Participant's Global Assessment (PGA) score given by patients at Day 3, Day 7 and Day 14 of treatment was also reduced from slight to moderate response at baseline to almost cleared at Day 14 of treatment in both the 10% bee propolis and 2% mupirocin treatment groups. Results of the Mann-Whitney test showed that the PGA score did not vary significantly between the two treatment groups at Day 3 (p=0.5706) and Day 14 (p=0.6536) but it did vary significantly at Day 7. The PGA score in the bee propolis group was significantly higher than that of the mupirocin group at Day 7 (p=0.0175). This is attributed to the subjectivity of the test and the fact that patient perception of improvement can vary significantly. Figure a.6 shows the PGA score given by patients in both treatment groups at Day 3, Day 7 and Day 14 of treatment.

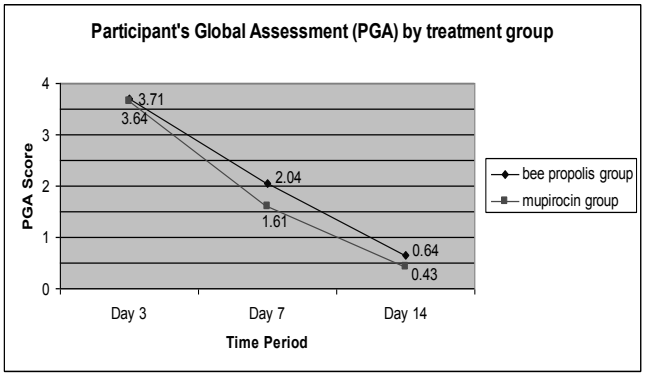

Figure a.6. *Participant's Global Assessment (PGA) scores in the 10% bee propolis and 2% mupirocin group over time*

There was only one adverse event of mild stinging sensation and pruritus noted for 10% bee propolis ointment after 3 days of treatment. There were no adverse events reported in the mupirocin group. Nevertheless, results of the Fisher's exact test showed that the proportion of patients with AE did not vary significantly (p=0.50) in the two treatment groups.

In summary, there were no statistically significant differences in bactericidal activity (p=0.542), efficacy based on clinical efficacy grading of erythema (p=0.4513), edema (p=0.4324), induration (p=0.4324) and size of lesions (p=0.5775), PGA score (p=0.0627), and adverse events (p=0.509) between the two treatment groups after holding the effects of time constant.

CONCLUSION

1) Ten percent bee propolis ointment is comparable in bactericidal activity to 2% mupirocin ointment against *S. aureus* in superficial pyodermas; 2) ten percent bee propolis ointment is comparable in efficacy to 2% mupirocin ointment based on clinical efficacy grading of erythema, edema, induration and size of lesions; 3) ten percent bee propolis ointment is comparable to 2% mupirocin ointment in terms of Participant's Global Assessment (PGA) score at Day 3 and Day 14 except on Day 7, where a significant difference was noted between the two treatments but nevertheless attributed to the subjectivity of the test and how patient perception of improvement can vary signficantly; and 4) both 10% bee propolis ointment and 2% mupirocin ointment were well-tolerated, producing no significant adverse reactions in *S. aureus* superficial pyoderma patients within two weeks of treatment.

Therefore, 10% bee propolis ointment is equally safe and effective as 2% mupirocin ointment in the treatment of superficial pyodermas caused by *Staphylococcus aureus*. Ten percent bee propolis ointment can therefore be considered a good cost-effective alternative to 2% mupirocin ointment in the treatment of *S. aureus* superficial pyoderma.

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APPENDIX A

DOCUMENTATION

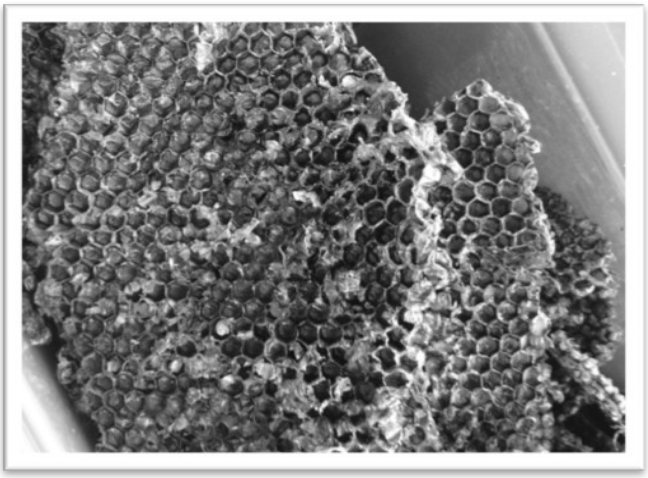

Figure A.1. *Source of bee propolis*

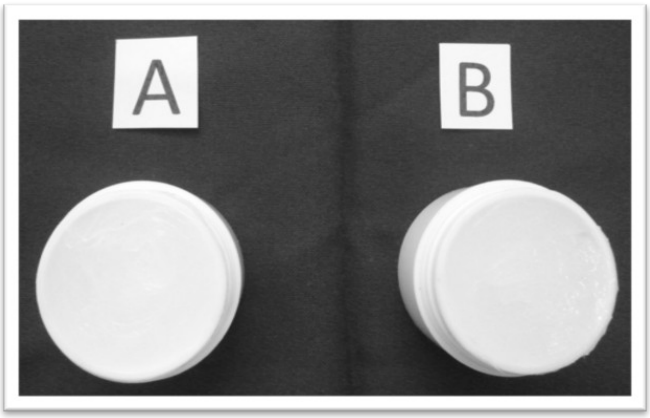

Figure A.2. *Test materials in 10-gram jars*

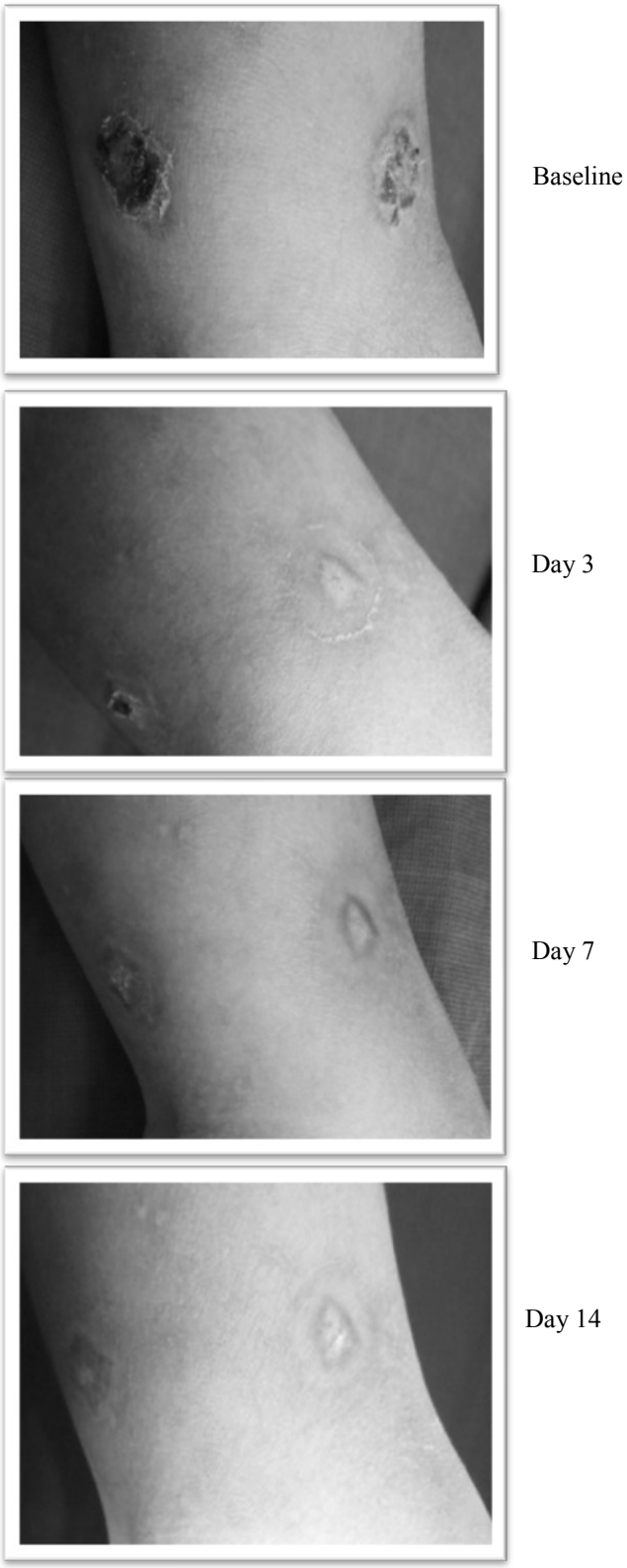

Figure A.4. *Superficial pyoderma lesions of representative subject no. 1 in the 10% bee propolis group at baseline, Day 3, Day 7 and Day 14 of treatment*

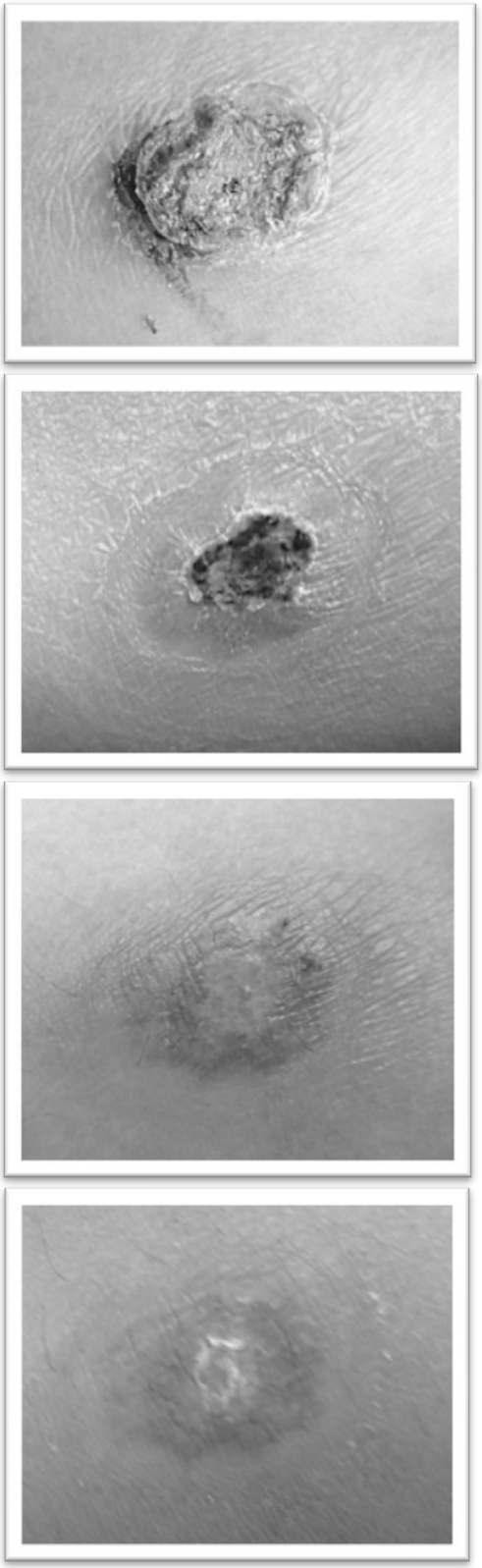

Figure A.5. *Superficial pyoderma lesion of representative subject no. 2 in the 10% bee propolis group at baseline, Day 3, Day 7 and Day 14 of treatment*

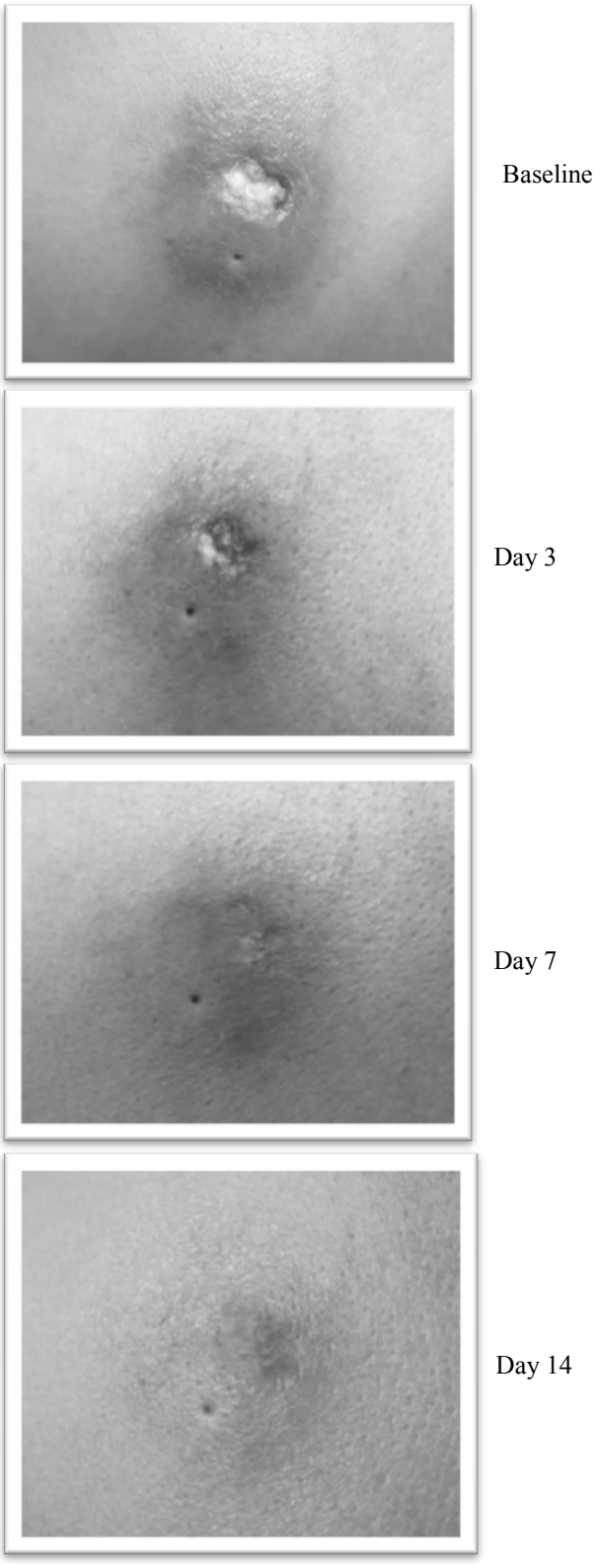

Figure A.6. *Superficial pyoderma lesion of representative subject no. 1 in the 2% mupirocin group at baseline, Day 3, Day 7 and Day 14 of treatment*

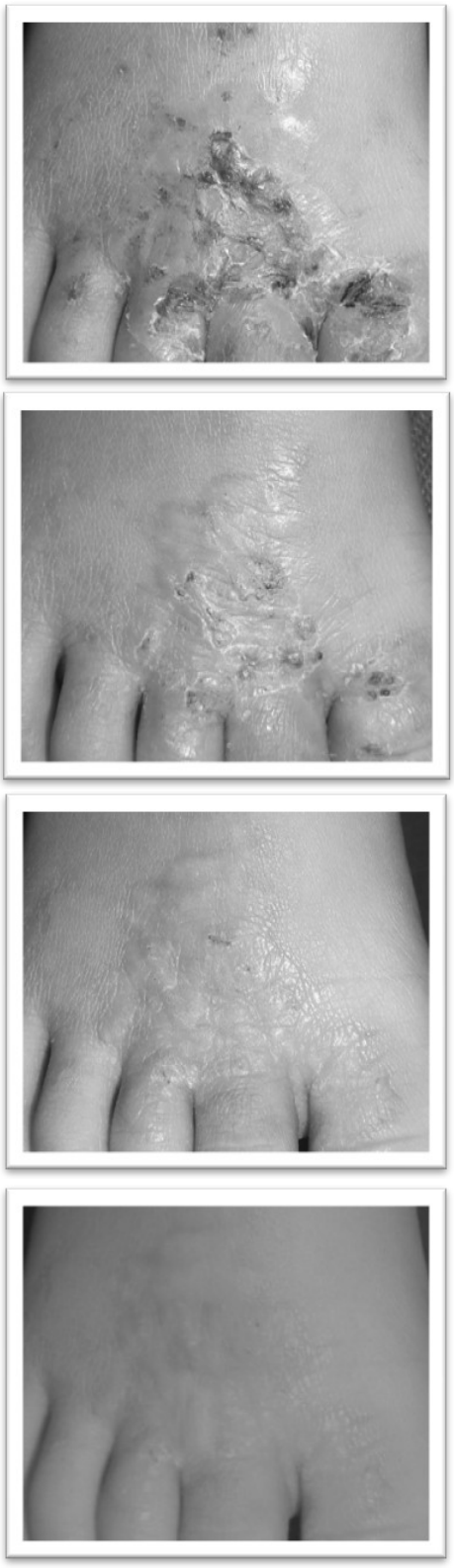

Figure A.7. *Superficial pyoderma lesion of representative subject no. 2 in the 2% mupirocin group at baseline, Day 3, Day 7 and Day 14 of treatment*