SPMC JHCS

RESEARCH

Randomized, double-blind, controlled trial on the efficacy of 12.5% pomelo peel ointment versus 2% mupirocin ointment in the management of localized impetigo contagiosa

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Article editor
Joanne Kate Milana-Martinez

Received
13 February 2018

Accepted
2 October 2019

Published online
26 December 2019

Cite as
Chiu AL, Visitacion L. Randomized, double-blind, controlled trial on the efficacy of 12.5% pomelo peel ointment versus 2% mupirocin ointment in the management of localized impetigo contagiosa. *SPMC J Health Care Serv*. 2019;5(2):1. http://n2t.net/ark:/76951/jhcs9b96wn

ABSTRACT

Background. Extracts from several citrus plants have antimicrobial properties and have been used for certain infectious skin conditions.

Objective. To compare the efficacy of 12.5% pomelo peel ointment and 2% mupirocin ointment in the management of localized impetigo contagiosa.

Design. Randomized, double-blind, controlled trial.

Setting. Dermatology Outpatient Clinic in Southern Philippines Medical Center, Davao City, from September 2012 to November 2012.

Participants. 46 male and female patients, aged 2-15 years old, and clinically diagnosed with localized impetigo contagiosa.

Interventions. Participants were randomized to receive either 12.5% pomelo peel ointment (PPO) or 2% mupirocin ointment (MO), thinly applied on impetigo lesions twice daily for 7 days.

Main outcome measures. Clinical success defined as either 'complete resolution of lesions' or 'dryness of the lesions without crusts, with intact skin, and with no to minimal local erythema' at any time within 7 days from the start of intervention.

Main results. The 23 patients in 12.5% PPO group had similar baseline demographic and clinical characteristics as the 23 patients in the 2% MO group. Within 7 days from the start of intervention, 15 of the 23 patients (65.22%) in the PPO group and 19 of the 23 patients (82.61%) in the MO group had clinical success (p=0.1792).

Conclusion. Pomelo peel ointment is as efficacious as mupirocin ointment in the management of localized impetigo contagiosa.

Keywords. antimicrobial, antiseptic, citrus, staphylococcus aureus

INTRODUCTION

Mupirocin is one of the most effective topical antibiotics used in the management of localized impetigo contagiosa, an infectious dermatologic condition commonly affecting children and caused by *Staphylococcus aureus or Streptococcus pyogenes*.[1-4] Until recently, mupirocin, retapamulin, and fusidic acid have been the mainstays in the management of localized impetigo contagiosa.[3 4] Several studies have demonstrated the usefulness of hydrogen peroxide cream—an antiseptic and bacteriostatic agent—in the management of localized impetigo contagiosa in patients who are neither systemically unwell nor at high risk of developing complications.[5 6] Hydrogen peroxide use has been considered to be just as effective as topical antibiotics in reducing the spread of infection in localized impetigo, without the risk of contributing to the antimicrobial resistance of causative organisms.[4 6]

Localized impetigo contagiosa usually heals spontaneously within 2-3 weeks, but topical antibiotics are commonly given to patients to reduce the spread of infection to other body parts or to other people. Topical antibiotics also relieve discomfort, improve cosmetic appearance by preventing scarring, and prevent the occurrence of complications such as

IN ESSENCE

Citrus plant extracts have been known to possess antimicrobial properties.

Localized impetigo contagiosa usually resolves spontaneously, but patients are typically given topical antibiotics to control the spread of infection.

In this randomized controlled trial among 46 patients with localized impetigo contagiosa, the group that received 12.5% pomelo peel ointment and the group that received 2% mupirocin ointment had similar proportions of patients with resolved impetigo lesions within 7 days of treatment.

acute poststreptococcal glomerulonephritis.[3,4]

Mupirocin is relatively expensive.[7] There is also the problem of microorganisms developing resistance to mupirocin.[8] Thus, there is a need to develop alternative products, such as plant extracts and other active compounds, that will produce cheaper medications, and help vary the current armamentarium for bacterial skin infections. Additionally, the use of natural products as antimicrobials may afford fewer adverse effects and better patient tolerance.

Although *in vitro* studies have demonstrated the antimicrobial properties of citrus plant extracts,[9-11] *in vivo* studies in humans about their antimicrobial properties are lacking. The closest study among humans involved the use of gel formulations of orange (*Citrus sinensis*) peel essential oils in the treatment of patients with acne.[12]

Pomelo (*Citrus maxima* or *Citrus grandis*), the world's largest citrus fruit, has been investigated for its antimicrobial and anti-inflammatory effects.[13] *In vivo* studies of *C. grandis* extracts and phytochemicals demonstrated the anti-inflammatory activities of pomelo peel through the inhibition of xylene- and carrageenan-induced edema in mice.[14] Pomelo peel extract contains vitamin C and flavonoids—naringenin and hesperidin—which are responsible for wound healing in experimentally-induced wounds in diabetic rats.[15]

We did this study to compare clinical success between those who were given 12.5% pomelo peel ointment (PPO) and those given 2% mupirocin ointment (MO) as treatment for localized impetigo contagiosa.

METHODOLOGY

Study design and setting

We did a randomized double-blind, controlled trial from September 2012 to November 2012 among patients clinically diagnosed with impetigo contagiosa at the Dermatology Outpatient Clinic in Southern Philippines Medical Center (SPMC), and barangay health centers in Agdao, Sasa, and Buhangin, Davao City. The specialty clinic at SPMC receives about 7,500 patient visits yearly, while each of the barangay health centers has an average of 175 dermatologic visits yearly.

Participants

Patients 2 to 15 years old, clinically diagnosed with localized impetigo contagiosa, with individual lesion diameter of not more than 2 cm, and with total skin surface involvement of less than 5% were recruited into the study. Excluded were patients who had known sensitivity to any ingredients in the treatment drugs, infections of deeper skin structures, temperature of more than 37.5° C and cervical lymphadenopathies, as well as those who used systemic antibiotics or topical therapeutic agents 48 hours prior to entry into the study.

To determine the minimum sample size for this study, we assumed that patients prescribed with mupirocin ointment for impetigo contagiosa will have 96.67% clinical cure.[16] Calculation was done in order for the study to detect a 30% difference in clinical cure rates between the two treatment groups as statistically significant. In a test for difference of two proportions carried out at 95% level of confidence, a total sample size of at least 46 will have 80% power of rejecting the null hypothesis if the alternative holds.

Interventions and randomization

Pomelo peel ointment 12.5%. The PPO was prepared using the USP29-NF24 formulation as described in the US Pharmacopeia, 2006 Edition.[17] Pomelo peel extract was prepared by mixing 125 grams of air-dried pomelo peel with 125 mL ethyl alcohol and storing the mixture in a tightly closed container for two weeks. Extraction was then done through rotary evaporation of the mixture. PPO was prepared by an industrial pharmacist by mixing 62.38 mL propylene glycol with water, 130.95 g cetyl alcohol, 0.119 g methylparaben, 0.083 grams propylparaben, 547.62 grams white petrolatum, 0.15 gram sodium lauryl sulfate dissolved in water, and 93 grams pomelo peel ethanolic extract. The 12.5% concentration used to create the PPO was chosen based on the results of a study on the minimum inhibitory concentration (MIC) of *Citrus paradisi* (grapefruit), *Citrus grandis* (pomelo), and *Citrofortunella microcarpa* (calamansi).[18]

To initially test the allergenicity of the product, the ointment was tested on 10 healthy volunteers through patch testing. A thin layer, approximately 0.25 g, of the ointment was applied on a 1cm x 1cm skin area on the nape of each subject and allowed to stay for 72 hours with transparent occlusive dressing. Only one subject reported mild pruritis, which spontaneously resolved, on the test area 48 hours after application. For the rest of the subjects, readings on the test

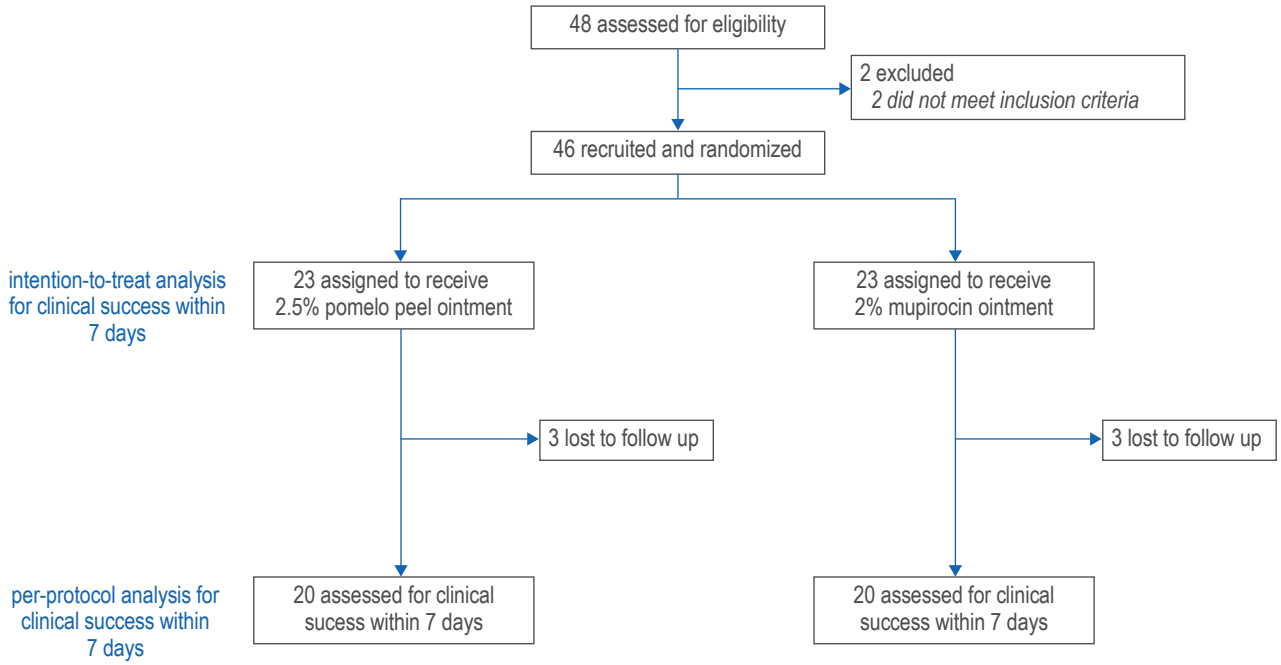

Figure 1 Screening, randomization, follow-up and analysis of patients in the study.

area after 48 and 72 hours showed the absence of pruritis, eythema, macules, papules, vesicles, or other skin lesions.

Mupirocin. Commercial 2% MO was procured for use in this study.

Both ointments were similar in appearance and odor, and were packaged in identical 10-mL-capacity cosmetic jars.

Randomization

We randomly assigned patients to one of two treatment arms. Each of the patients in the first group received a 10-mL jar of 12.5% PPO, while each of those in the second group received a 10-mL jar of 2% MO. Each patient also received a bar of hypoallergenic soap. A research assistant was in charge of dispensing the randomly assigned medications to patients. The allocation of treatment intervention was known only to the research assistant, and was unknown to the physicians, and the patients and/or their adult caregivers.

The patients and/or their caregivers were instructed to wash the skin lesions twice a day for seven days using the hypoallergenic soap provided and to apply a small amount of the ointment on the skin lesions right after washing. They were also instructed to return for follow-up three and/or seven days after the start of ointment application.

RESULTS

A total of 46 patients with localized impetigo contagiosa were recruited into and included in the primary analysis of this study, 23 of whom were randomized to receive PPO, and the remaining 23 were randomized to receive MO. Figure 1 shows the flow of patients from recruitment, randomization, and follow-up.

The baseline characteristics of patients in both intervention groups are shown in Table 1. The two groups were comparable in terms of mean age, sex distribution, mean duration of illness, and comorbidities.

Table 2 shows the proportion of patients who had clinical success within 7 days from treatment. Both intention-to-treat and per protocol analyses showed that the proportions of patients with clinical success within 7 days in the two treatment groups were comparable.

No patient from any treatment group experienced pruritus, erythema, burning, or pain during the follow-up.

Sensitivity analyses

Sensitivity analyses using best and worst case scenarios for the outcome results of patients who did not have clinical success before they were lost to follow-up are shown in Table 3. The results on comparison of proportions of clinical success were inconsistent across the

Table 1 Baseline characteristics of patients

Clinical factors	12.5% pomelo peel ointment n=23	2% mupirocin ointment n=23	p-value
Mean age ± SD, *years*	4.35 ± 2.99	4.65 ± 2.19	0.6957
Sex, *frequency (%)*			0.7646
Male	14 (60.87)	13 (56.52)	
Female	9 (39.13)	10 (43.48)	
Duration of illness ± SD, *days*	3.5 ± 2.04	2.87 ± 1.22	0.1674
Comorbidities, *frequency (%)*			
Cough	1 (4.35)	2 (8.70)	1.0000*
Colds	1 (4.35)	1 (4.35)	1.0000*
Myalgia	0 (0.00)	1 (4.35)	1.0000*

* Using Fisher's exact test.

Table 2 Proportion of patients with treatment success

Outcome and analyses	12.5% pomelo peel ointment	2% mupirocin ointment	p-value
Clinical success within 7 days, *frequency (%)*			
Intention-to-treat analysis	15/23 (62.22)	19/23 (82.61)	0.1880
Per-protocol analysis	15/20 (75.00)	19/21 (90.48)	0.1880

Table 3 Sensitivity analyses

Characteristics	12.5% pomelo peel ointment	2% mupirocin ointment	p-value
Scenario 1*	18 (78.26)	21 (91.30)	0.2182
Scenario 2†	18 (78.26)	19 (82.61)	0.7101
Scenario 3‡	15 (62.22)	21 (91.30)	0.0320§

* Scenario 1 - All patients who did not have the outcome before they were lost to follow-up were assumed to have the outcome.
† Scenario 2 - All patients in PPO group who did not have the outcome before they were lost to follow up were assumed to have the outcome. All patients in MO group who did not have the outcome before they were lost to follow up were assumed not to have the outcome.
‡ Scenario 3 - All patients in PPO group who did not have the outcome before they were lost to follow up were assumed not to have the outcome. All patients in MO group who did not have the outcome before they were lost to follow up were assumed to have the outcome.
§ Significant at $p<0.05$.

scenarios, suggesting non-robustness of difference in proportions of clinical success between the two groups.

DISCUSSION

Key results

In this study, we found out that 12.5% PPO and 2% MO had comparable results in terms of clinical success—i.e., proportion of patients with complete resolution or dryness of the lesions of impetigo contagiosa—within 7 days from the start of intervention.

Strengths and limitations

We were able to demonstrate that 12.5% PPO can be used as an alternative to 2% mupirocin ointment in the management of localized lesions of impetigo contagiosa. Further, we have also found out that the application of 12.5% PPO on the skin did not cause pruritus, erythema, burning, or pain among the patients in our study. We believe that this is the first study in literature that uses pomelo extract on humans to assess its effectiveness against impetigo contagiosa.

There were some limitations in this study. We did not perform formal studies to determine the physicochemical characteristics of the PPO we developed. These studies can generate useful information (i.e., pH, viscosity, stability, etc.) that can facilitate replication and mass production of the new formulation

in the future.[19] Also, the observation period in our study, within which we measured clinical success in the management of localized impetigo lesions, was rather short. While 7 days may be enough to determine local changes in lesions, the same duration may not reasonably be adequate for the observation of common and equally important sequelae of localized impetigo contagiosa such as recurrence of lesions, spread of lesions to other parts of the body, and transmission of infection to other people.[2 4]

Interpretation

A recent meta-analysis showed the effectiveness of mupirocin ointment in the cure of localized impetigo contagiosa.[20] Mupirocin is bactericidal at high concentrations and bacteriostatic at lower concentrations.[21-24] More recently, the UK National Institute for Health and Care Excellence issued a draft on the guidelines on antimicrobial prescribing strategy for impetigo, recommending the use of topical hydrogen peroxide 1% cream or another topical antiseptic as first-line agent in the management of localized impetigo contagiosa.[5] Since localized impetigo contagiosa may spontaneously heal without treatment,[3 4] hydrogen peroxide cream may be a more practical choice for the management of the condition. The use of antiseptics rather than antimicrobials in this case would help prevent the development of antibiotic resistance in bacteria.[25]

Several in vitro studies have demonstrated the bacteriostatic and bactericidal effects of pomelo peel and other citrus peel extracts and essential oils.[9-11] Beta-sitosterol, oleic acid, and limonene—phytochemical components found in great quantities in pomelo peel extract—all exhibit antimicrobial activity.[26-28] Hence, citrus fruit peel essential oils are commonly incorporated into some topical medications that are widely used for the management of skin infections.[29] Clearance of lesions among our patients was probably due to the antimicrobial property of the pomelo peel extract and its components.

Generalizability

The patients in our study represent those who are typically seen in outpatient clinics and subsequently diagnosed as having impetigo contagiosa. Our participants were mainly male and female children who consulted for the management of impetigo within the first few days of the appearance of lesions. As what is typical in this group, some of our patients had non-dermatologic symptoms—cough, colds, and/or myalgia—that accompany the skin lesions. The results of this study, specifically the role of PPO in the management of localized impetigo contagiosa, may therefore be applied to most patients diagnosed to have the localized form of infection.

CONCLUSION

In this randomized controlled trial among patients with localized impetigo contagiosa, proportions of patients with resolved impetigo lesions within 7 days of intervention were comparable between the group that received 12.5% PPO and the group that received 2% MO.

Contributors

ALC and LV both had substantial contributions to the study design, and to the acquisition, analysis and interpretation of data. ALC and LV wrote the original draft and subsequent revisions, and both authors reviewed, edited, and approved the final version of the manuscript. ALC and LV both agreed to be accountable for all aspects of the work.

Acknowledgments

We would like to thank Dr Nicolo A Paderna, Research Coordinator of the Department of Ophthalmology in Southern Philippines Medical Center, for his help in the implementation of this research report.

Ethics approval

This study was reviewed and approved by the Department of Health XI Cluster Ethics Review Committee (DOH XI CERC reference P12042701).

Reporting guideline used

CONSORT Checklist (http://www.consort-statement.org/Media/Default/Downloads/CONSORT%202010%20Checklist.doc)

Article source

Submitted

Peer review

External

Funding

Supported by personal funds of the authors

Competing interests

None declared

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