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Topical Application of *Curcumin Longa* 5% Rhizome Ethyl Acetate Extract in Ointment Form versus Mupirocin 2% Ointment in the Treatment of Impetigo and Folliculitis: A Double Blind, Randomized Controlled Trial

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Abstract

Introduction: Impetigo is a common dermatosis of childhood commonly caused by *Staphylococcus aureus* and Group A *Streptococcus*. Antibiotics, topical or systemic, are the backbones of current treatment of impetigo. The spread of multi-drug resistant pathogens is one of the most serious threats to successful treatment of bacterial diseases. According to the World Health Organization, the use of medicinal plants is the most common form of traditional medication worldwide. Curcumin longa, commonly known as yellow ginger or turmeric or luyangdilaw, is a sterile plant from the Zingiberaceae family. *Curcumin longa* has been shown to possess significant anti-inflammatory and anti-microbial effects.

Objectives: The general objective of this study is to determine the efficacy and safety of *Curcumin longa* 5% rhizome ethyl acetate extract in ointment versus mupirocin 2% ointment in the clinical improvement or resolution of localized impetigo and/or folliculitis among patients seen in the JRRMMC, Department of Dermatology, and outpatient department.

Methods: Patients with localized impetigo and/or folliculitis that met the inclusion criteria were recruited. Informed consent obtained, photographs taken at baseline (week 0). Similar subjects were used to compare both medications Group A (mupirocin 2% ointment) and Group B (*Curcumin longa* 5% rhizome ethyl acetate extract in ointment) to assure that we are dealing with the same microorganism. All patients were instructed to clean the lesions using normal saline solution using a gauze or cotton and to apply the afore mentioned medications using a cotton swab thrice daily for two weeks, or until resolution of lesions are noted. The patients were examined every week for 2 weeks and the primary investigator assessed if there is a reduction in the number of lesions and evidence of local adverse reaction (erythema, pain, itch, crusting, etc.). Photographs were taken every visit to assess improvement. Another resident physician in the same department was blinded and was assigned to distribute the ointments, in identical containers, to the recruited and qualified patients. Safety evaluation consisting of monitoring and recording all spontaneous adverse events were also noted.

Results: Thirty eight patients were included in the study. 135 lesions were treated with Mupirocin, 133 with *Curcumin longa*. Of the 38 participants, three (7%) were considered to be dropouts owing to lost to follow up. After two weeks of treatment, 71.05% (27/38) of the mupirocin group and 52.63% (20/38) of the *Curcumin longa* group had resolution of the lesions; however, these differences are not statistically significant (p-value = 0.08). Female patients with age groups of 2 to 5 and 6 to 10 were noted to have the highest improvement both at 13%. Male patients ages 2 to 5 were noted to have the highest improvement at 10%. The mean Skin Infection Rating Scale (SIRS) after first week for the mupirocin group was 0.93 and 1.46 for the *Curcumin longa* group, and after second week for the mupirocin group was 0.37 and 0.83 for the Curcumin longa group which in both cases reflects large improvements relative to baseline (p-values < 0.001), but insignificant differences from each other (p-value = 0.063 and 0.074 respectively). Mupirocin-treated lesions recover significantly quicker than Curcumin longa-treated ones (first week, 72% and 31 %, respectively) with these proportions being significantly different at a p-value of < 0.032. There were no significant differences in the incidence of adverse effects/withdrawal rates between groups (p-values of 0.06, 0.28, and 0.09, respectively).

Conclusion: Our results showed that topical application of *Curcumin longa* 5% rhizome ethyl acetate extract in ointment is of comparable efficacy and safety profile to mupirocin 2% in ointment in the treatment of localized impetigo and folliculitis. However, mupirocin-treated lesions recover significantly quicker than Curcumin longa-treated ones. Those in the *Curcumin longa* group also experienced adverse reactions such as pain, erythema, blister formation, exudates, crusting and itch. Generally, the results implied that at the end of 2 weeks, both treatments had produced similar improvements on lesion counts.

Introduction

Impetigo is a common dermatosis of childhood commonly caused by *Staphylococcus aureus* and Group A *Streptococcus* [1-3]. Impetigo typically presents a transient vesicle or pustule that quickly evolves into a honey-colored crusted plaque that can enlarge to greater than 2 cm in diameter with surrounding erythema usually on the face and extremities [1,2]. Antibiotics, topical or systemic, are the backbones of current treatment of impetigo. Recently, estimates of the global burden of impetigo are 111 to 140 million people especially from developing countries are affected at any given time [1]. In the department of dermatology of the Jose R. Reyes Memorial Medical

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Center (JRRMMC), there are 175 cases of impetigo in 2014 and 173 in 2015.

The spread of multi-drug resistant pathogens is one of the most serious threats to successful treatment of bacterial diseases [1,3-6]. According to the World Health Organization (WHO), the use of medicinal plants is the most common form of traditional medication worldwide. Regulation of herbal medicines is a key means of ensuring safety, efficacy and quality of herbal medicinal products. WHO has been receiving an increasing number of requests from governments for guidance on how to regulate herbal medicines [5]. In 2003, the Department of Health (DOH) of the Philippines released a list of the top ten herbal medicinal products that can be safely used [7].

Curcumin longa, commonly known as yellow ginger or turmeric or luyangdilaw, is a sterile plant from the Zingiberaceae family which originated from India and is now cultivated in other tropical countries like the Philippines [8-10]. This plant does not produce any seeds and grows up to 3 to 5 feet tall with dull yellow flowers [8]. *Curcumin longa* has been shown to possess significant anti-inflammatory, anti-oxidant, anti-carcinogenic, anti-mutagenic, anti-coagulant and anti-microbial effects [9-18]. *Curcumin longa* has also been shown to have significant wound healing properties as it acts on various stages of wound healing to hasten the process. It also has the ability to enhance granulation tissue formation, collagen deposition, tissue remodeling and wound contraction [8,14].

Application of herbal medicinal plants as alternatives to chemical agents for the treatment of infections has been reported by many authors, but few researchers focus on these. Therefore, this study aims to determine the efficacy and safety of the use of topical ointment of *Curcumin longa* on impetigo.

We report herein a randomized double blind controlled study on the efficacy and safety of topical application of *Curcumin longa* 5% rhizome ethyl acetate extract in ointment form versus mupirocin 2% ointment in the treatment of impetigo and folliculitis in patients seen at the Department of Dermatology of Jose R. Reyes Memorial Medical Center.

Methodology

An Institutional Review Board / Institutional Ethics Committee of the Jose R. Reyes Memorial Medical Center approved the study prior to its initiation following the guidelines of good clinical practice.

Study design: This study is a double blind, randomized, controlled trial.

Study setting and duration: The study was conducted at the Dermatology Outpatient Department (OPD) of Jose R. Reyes Memorial Medical Center from July 2016 to September 2016.

Inclusion criteria

1. Patients clinically diagnosed with impetigo and/or folliculitis at the out-patient department clinically

2. Male or Female patient

3. 1 to 30 years old

4. No other constitutional symptoms such as fever, lymphadenopathy

5. Willing to follow-up once a week for 2 weeks

Exclusion criteria

1. Patients with known hypersensitivity to any of the test medications

2. Patients with constitutional or systemic symptoms such as fever, lymphadenopathy that will need systemic antibiotic treatment

3. Immunocompromised patients

4. Active infected lesions in obvious need of systemic therapy

5. Patients who have been given oral/topical antibiotics within 2 weeks

6. Patients with comorbidities such as diabetes mellitus, hypertension that in the judgment of the investigator might interfere with the study.

7. Not willing to follow-up once a week for 2 weeks

Thirty eight patients were recruited in this study. Patients were recruited during clinic hours in the outpatient department of the JRRMMC Dermatology and asked to sign a written informed consent. The patients were interviewed to get a detailed history. They were also examined by the primary investigator. Information regarding age, sex, number of lesions and site of involvement were obtained. No bacteriological examination was done prior to starting the treatment. The same subject were used to compare both medications Group A (mupirocin 2% ointment) and Group B (*Curcumin longa* 5% rhizome ethyl acetate extract in ointment) to assure that we are dealing with the same microorganism. They were instructed by a study associate on which lesions will they apply medications A and B. Areas of application of medications A and B were randomly selected. The patients were instructed to clean the wound with normal saline solution, using gauze or cotton. Then the *Curcumin longa* 5% rhizome ethyl acetate extract in ointment or mupirocin 2% in ointment was applied with cotton swab at the center of the lesion thrice a day [2]. All patients were asked to apply the aforementioned medications for two weeks, or until resolution of lesions are noted. Parents or guardians were asked to report local side effects (erythema, pruritus, burning sensation) for this time period.

The patients were examined every week for 2 weeks and the primary investigator assessed if there is a reduction in the number of lesions and evidence of local adverse reactions.

The photographs of the lesions were taken at the start of the study (week 0), every week for 2 weeks (week 1 and 2) to assess effectiveness and monitor adverse reactions. A digital camera was used and the photos were taken at the physical examination room of the JRRMMC, Department of Dermatology, OPD. The primary investigator assessed the improvement of the lesions of the study participants. Another resident physician in the same department was blinded and was assigned to distribute the ointments to the recruited and qualified patients.

The trial was stopped on patient who experienced irritation (burning sensation, diffuse erythema, itchiness, pain) or hypersensitity

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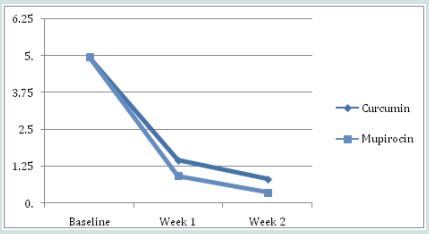

Figure 1: Mean SIRS throughout treatment in both groups.

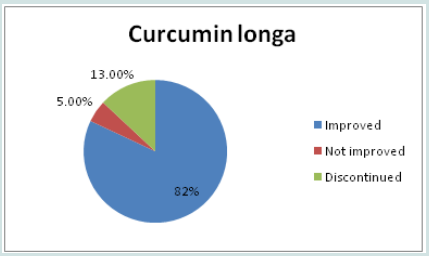

Figure 2: Patient Improvement on Curcumin longa.

with the topical ointment being used. The patients were considered as a withdrawal from the study. Any patient who failed to follow up every week within two weeks and those who failed to comply with the treatment, or those who used other topical medications other than the one provided were also included as withdrawals. The results of those who withdraw from the study were included in the analysis with an intention to treat principle.

Curcumin longa or yellow ginger were obtained from University of the Philippines, Los Banos, Laguna that is identified by a botanist. The *Curcumin longa* 5% rhizome ethyl acetate extract in ointment form was prepared by the University of the Philippines-Manila, College of Pharmacy, Industrial Pharmacy Unit. The mupirocin 2% ointment purchased from GlaxoSmithkline, a company producing this medication in the market. Both *Curcumin longa* 5% rhizome ethyl acetate and mupirocin 2% in ointment were prepared identically into a yellow, greasy ointment without any smell and placed in identical containers.

Outcome measures

The initial SIRS baseline scores were recorded as a patient-level average and as such are identical across treatment and control; subsequent SIRS scores were taken at 1 week and 2 weeks after treatment onset and recorded as averages of lesions treated with either mupirocin or Curcumin longa, respectively.

Statistical analysis

Descriptive analysis and summary statistics were performed using and two-sample t-tests using the Stat Plus. Both per protocol analysis and intention to treat analysis (primary analysis) were done. P-values <0.05 were regarded as statistically significant.

Results

Patient characteristics

Thirty eight patients were included in the study. 135 lesions were treated with mupirocin and 133 with Curcumin longa. (Kindly refer to Table 1 for the baseline characteristics of the participants) The biggest components of baseline SIRS were erythema (1.8) and pain/itch (1.23).

Of the 38 participants, three (7%) were considered to be dropouts owing to lost to follow up. The dropout rate was in line with the 5-20% expected range in clinical trials. Because patients were each treated with both mupirocin and Curcumin longa, the dropout rate is identical between treatment and control.

Clinical effects

4.2.1. Proportions of patients with complete healing: After two weeks of treatment, 71.05% (27/38) of the mupirocin group and 52.63% (20/38) of the *Curcumin longa* group had resolution of the lesions; however, these differences are not statistically significant (p-value = 0.08).

Improvement based on age group and gender distribution. Female patients with age groups of 2 to 5 and 6 to 10 were noted to have the highest improvement both at 13%. Male patients ages 2 to 5 were noted to have the highest improvement at 10%.

Table 1: Baseline characteristics of patients.

Age Distribution (in years)	
0 to 1	Female, 10% (4/38)
	Male, 7% (3/38)
2 to 5	Female, 15% (6/38)
	Male, 15% (6/38)
6 to 10	Female, 13% (5/38)
	Male, 13% (5/38)
11 to 15	Female, 7% (3/38)
	Male, 10% (4/38)
>16	Female, 1% (1/38)
	Male, 1% (1/38)
Baseline SIRS, mean ± SD	4.97 ± 0.58
Curcumin longa	2.75 ± 1.74
Mupirocin	3.26 ± 2.18
Sex %	Female, 50% (19/38)
	Male, 50% (19/38)
Diagnosis	
Folliculitis	23.6% (9/38)
Impetigo	76.13% (29/38)

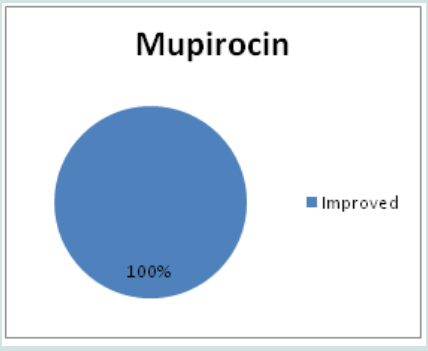

Figure 3: Patient Improvement on Mupirocin.

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Table 2: Proportions of patients with complete healing.

Age Distribution (in years)	
0 to 1	Female, 7% (7/38)
	Male, 5% (2/38)
2 to 5	Female, 13% (5/38)
	Male, 10% (4/38)
6 to 10	Female, 13% (5/38)
	Male, 7% (3/38)
11 to 15	Female, 5% (2/38)
	Male, 5% (2/38)
>16	Female, 1% (1/38)
	Male, 1% (1/38)

Mean SIRS post-treatment

The mean Skin Infection Rating Scale (SIRS) after first week for the mupirocin group was 0.93 and 1.46 for the *Curcumin longa* group, and after second week for the mupirocin group was 0.37 and 0.83 for the *Curcumin longa* group which in both cases reflects large improvements relative to baseline (p-values < 0.001), but insignificant differences from each other (p-value = 0.063 and 0.074 respectively) (Figure 1).

Time to healing

While the two-week recovery proportions between mupirocin and *Curcumin longa* are statistically indistinguishable from each other, we do see that mupirocin-treated lesions recover significantly quicker than Curcumin longa-treated ones. After the first week, 72% of the Mupirocin-treated lesions had recovered as compared to only 31% for Curcumin longa-treated ones, with these proportions being significantly different at a p-value of < 0.032.

Adverse effects/withdrawal rates

During treatment of Curcumin longa, four patients (10%) experienced erythema and pain, two (5%) had blister formation, four (10%) had exudates, thirteen (34%) had crusting and itch. For the mupirocin ointment group, five (13%) had crusting, eleven (28%) had erythema and eight (21%) had experienced itch. Five (13%) patients in the *Curcumin longa* group prompted to discontinue the treatment due to adverse effects while two (5%) did not see any improvement. All the patients improved in the mupirocin group.

There were no significant differences in the incidence of adverse effects/withdrawal rates between groups (p-values of 0.06, 0.28, and 0.09, respectively).

Discussion

Impetigo is a highly contagious skin infection that mainly affects infants and children [1,19]. It is estimated that the global burden for impetigo is 111 to 140 million people especially from developing countries at any given time [1]. In the department of dermatology of the Jose R. Reyes Memorial Medical Center (JRRMMC), there are 175 cases of impetigo in 2014 and 173 in 2015.

Impetigo typically presents a transient vesicle or pustule that quickly evolves into a honey-colored crusted plaque that can enlarge to greater than 2 cm in diameter with surrounding erythema usually on the face and extremities [1-4]. Constitutional symptoms are usually absent but regional lymphadenopathy may be present in up to 90% of patients with prolonged, untreated infection. If untreated, the lesions may slowly enlarge and involve new sites over several weeks. In some individuals, impetigo may clear on its own in two to three weeks, but antibiotics can shorten the course of the disease and help prevent the spread to others. Treatment of localized, mild to moderate impetigo with mupirocin ointment or cream, removal of crusts, and good hygiene is sufficient for resolution [1,20]. Other topical antibiotic agents are: Retapamulin 1% ointment which is also effective for localized impetigo and secondarily impetiginized dermatitis as well, although decreased efficacy against MRSA was noted in some trials [21]; Fusidic acid is an equally effective topical agent for localized impetigo and has very few adverse effects topically. Systemic antibiotics may be required in extensive cases [1].

According to the WHO global report on surveillance on antimicrobial resistance in 2014, it is important to take note that over the last 30 years, no major new types of antibiotics have been developed and currently high levels of antibiotic resistance is found in all regions of the world. Few, if any, of the available treatments options remain effective for common infections. In South-East Asia, more than one quarter of Staphylococcus aureus infections are reported to be Methicillin-Resistant (MRSA), meaning that treatment with standard antibiotics does not work [5]. The spread of multi-drug resistant pathogens is one of the most serious threats to successful treatment of bacterial diseases [1,3,4,6].

According to the World Health Organization, the use of medicinal plants is the most common form of traditional medication worldwide. Regulation of herbal medicines is a key means of ensuring safety, efficacy and quality of herbal medicinal products. WHO has been receiving an increasing number of requests from governments for guidance on how to regulate herbal medicine. (WHO Strategy on Traditional Medicine) [5].

One of the herbal medicines used since the ancient time is the *Curcumin longa* commonly known as yellow ginger or luyangdilaw. Curcumin longa, from the Zingiberaceae family [8]. It is originally from South India, China and Indonesia but is now currently grown in most of the tropical countries especially in the South East Asia including the Philippines [8-10].

The anti-bacterial property of *Curcumin longa* against a wide range of gram positive, including *Streptococcus* and Staphylococcus, and some gram negative microorganisms has been attributed to the presence of alkaloid and veleric acid, a byproduct from curcumin manufacture [9]. *Curcumin longa* has also been shown to have significant wound healing properties as it acts on various stages of wound healing to hasten the process. It also has the ability to enhance granulation tissue formation, collagen deposition, tissue remodeling and wound contraction. Most notably, Curcumin was shown to inhibit the production of tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1), two main cytokines released from monocytes and macrophages that play important roles in the regulation of inflammatory responses. Of equal importance is Curcumin's ability to inhibit the activity of NF-(κ)B (nuclear factor kappa-light-chain-enhancer of activated B cells), a transcription factor that regulates many genes implicated in the initiation of inflammatory responses. For a while, NF-(κ)B has been considered oxidant responsive, highlighting the correlation between oxidation and inflammation in

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wound healing. Oxidative stress is a significant factor in the wound healing process and generally inhibits tissue remodeling [14].

In a study done in JRRMMC Department of Dermatology in 2014 by Bernales-Mendoza et al. *Streptococcus* pyogenes is the most common microorganism isolated to cause impetigo [22].

In another study done in the same department in 2011 by Gorkhali et al. an *in vitro* study using the *Curcumin longa* extract showed the following zones of inhibition: 3 to 5 mg/mL concentration for *Staphylococcus aureus* and MRSA; 5 mg/mL concentration for Group A beta hemolytic *Streptococcus* [23]. An *in vivo* study was also done by Gorhkhali et al. using only 4mg/mL of ethyl acetate extract of *Curcumin longa* ointment there was only a clinical cure rate in 50% of the patient and they concluded that the use of 4 mg/mL of ethyl acetate extract of *Curcumin longa* ointment is not as effective as mupirocin ointment in the treatment of impetigo.

Based on the given data on that the most commonly isolated microorganism is *Streptococcus* pyogenes and that the zone of inhibition is seen in 5mg/mL, we used 5mg/mL extract of *Curcumin longa* in the treatment of impetigo and folliculitis [24-26].

In this study, it was assessed that there is no significant difference in the resolution of lesions after 2 weeks of application of *Curcumin longa* 5% rhizome ethyl acetate extract in ointment as compated to mupirocin 2% ointment. Twenty eight out of the thirty eight subjects noted complete resolution of the lesions in the *Curcumin longa* group. There was one hundred percent resolution of the lesions in the mupirocin group. While the two-week recovery proportions between mupirocin and *Curcumin longa* are statistically indistinguishable from each other, we do see that mupirocin-treated lesions recover significantly quicker than Curcumin longa-treated ones [27-30]. After the first week, 72% of the mupirocin-treated lesions had recovered as compared to only 31% for Curcumin longa-treated ones, with these proportions being significantly different.

Conclusion

Our results showed that topical application of *Curcumin longa* 5% rhizome ethyl acetate extract in ointment is of comparable efficacy and safety profile to mupirocin 2% in ointment in the treatment of localized impetigo and folliculitis. However, mupirocin-treated lesions recover significantly quicker than Curcumin longa-treated ones. Generally, the results implied that at the end of 2 weeks, both treatments had produced similar improvements on lesion counts.

The researcher recommends that on future studies on *Curcumin longa* by increasing the sample size population, specifying the body parts included, determining its efficacy against other microorganisms (gram negative) and its use in other preparation (such as in cream) and concentration.The author also recommends that there should be a bacteriological examination of each patient diagnosed with impetigo prior to application of the treatment to know specifically if the *Curcumin longa* is more effective or equally effective for specific species (*Staphylococcus aureus* or *Streptococcus*).

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