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Original Research Article

A Comparative Study of Topical 1% Ozenoxacin Cream and 2% Mupirocin Cream for the Treatment of Impetigo in Children

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Abstract:

Background: Ozenoxacin, a novel topical antibiotic with potent bactericidal activity against gram-positive bacteria, has recently received food and drug administration approval for the appropriate therapeutic management of impetigo which a extremely contagious bacterial skin infection.

Objectives: To evaluate the safety, bacteriological efficacy, and clinical outcomes of 1% ozenoxacin cream against 2% mupirocin cream following a 7-day, twice-daily topical treatment period for paediatric impetigo patients.

Methods: This single-centre, open-label, random allocation study included 33 subjects with impetigo who attended the dermatology outpatient facility of a tertiary care hospital in central India. Subjects were randomized into two groups; group A received topical ozenoxacin whereas group B received mupirocin. Clinical and bacteriological efficacy was assessed using the skin infection rating scale and microbiological culture. Safety and tolerability were also evaluated.

Results: The clinical efficacy of ozenoxacin was shown to be superior to that of mupirocin, as evidenced by a more rapid achievement of positive treatment outcomes after a 4-day period. (8 of 16 vs 2 of 17; p-value = 0.038). Ozenoxacin also demonstrated superior clinical (14 of 16 vs 13 of 17) and microbiological (15 of 16 vs 14 of 17) success as compared with mupirocin, after 7 days of therapy. Both the drugs were well tolerated, with only one subject on topical mupirocin experiencing adverse effect which was not serious.

Conclusion: Both ozenoxacin and mupirocin have demonstrated efficacy and excellent tolerability as topical treatments for impetigo in paediatric patients aged 2 to 10 years. The study revealed that Ozenoxacin had a notable benefit in terms of its prompt onset of response.

Keywords: Ozenoxacin, Mupirocin, Impetigo.

Introduction

Impetigo is a highly contagious infection of the superficial epidermis that most commonly affects children 2 to 5 years of age, although it can occur in any age group. Among the paediatric population, impetigo is the most frequent bacterial skin infection and the third most frequent skin disease overall.[1] Treatment of impetigo typically involves local wound care along with topical antibiotic therapy. For individuals with uncomplicated localized impetigo, topical antibiotic therapy is considered the treatment of choice. For topical therapy, the chosen antibiotic must provide coverage against both Staphylococcus aureus and Streptococcus pyogenes. Topical therapy eliminates isolated diseases and restricts their spread in the community. It is now generally accepted that impetigo can be treated effectively with topical mupirocin, a well-established antibacterial agent which is proven effective and may be equivalent to oral antibiotics.[2] Mupirocin obtained Food and Drug Administration (FDA) approval for use in impetigo in April 2002. Another potent topical antibiotic, ozenoxacin has been introduced recently which obtained FDA approval for use in the management of impetigo in patients aged 2 months and older in December 2017.[3] Most commonly used topical antibiotics in cases of impetigo are mupirocin, retapamulin, and fusidic

acid. However, because of issues of antibiotic resistance and potential side effects, there is always demand for better acting topical formulations.

Aim & Objectives: The present study is an attempt to compare the clinical and bacteriological effectiveness as well as safety of ozenoxacin versus mupirocin in the treatment of impetigo in children.

Methodology

Study design: The clinical and bacteriological efficacy of topical application of ozenoxacin cream 1% (w/w) and mupirocin cream 2% (w/w) were compared in a single-centre, open-label, random allocation study in 33 subjects with impetigo, amenable to therapy with a topical antibiotic. This study was carried out in the outpatient facility of the Department of Dermatology, Venereology and Leprosy, Maharaja Yeshwantrao Hospital, Indore, Madhya Pradesh, India. The study was performed over one year. The study was approved by the Institutional Ethical Committee and because all the subjects were below 12 years of age, a written informed consent was obtained from the subject's legal guardians after properly explaining to them about the study procedure in their language.

Participants were considered eligible for the study if they were between the age range of 2 months to 12 years, possessed a medical diagnosis of impetigo, and obtained a minimum total score of 3 on the Skin Infection Rating Scale (SIRS), which included a minimum exudate and/or pus score of 1 out of a potential 3. The initial measured afflicted area ranged from 2-100 cm2 and didn't surpass 2% of the total body surface area.

Subjects who had signs and symptoms of systemic spread of the infection or other types of pyodermas were excluded. Immunosuppressed, diabetic, and subjects with other systemic disorders were also not recruited in the study. Before recruitment, a history of allergic manifestation to previously applied topical formulations was obtained, subjects with a positive history of such allergy were excluded. Similarly, subjects giving a history of concurrent topical or systemic antibacterial therapy during the past four weeks were also excluded.

After fulfilling all the inclusion and exclusion criteria, the subjects were randomly allotted to treatment groups. A total of 16 subjects and a total of 17 subjects were randomly allocated to the treatment group A (ozenoxacin therapy) and group B (mupirocin therapy), respectively. During our study Zimba® Cream, Sun Pharmaceuticals Industries Ltd, Mumbai, India was used as a brand of ozenoxacin and T-bact® Cream, GlaxoSmithKline Pharmaceuticals Ltd, Mumbai, India was used as a brand of mupirocin. The caretakers of the participants were given instructions to provide a thin coating of the given cream, twice daily for duration of seven days, after the removal of diseased crusts and debris using soap and water.

Baseline characteristics and relevant medical history of the subjects were recorded during their visits in a case proforma. The clinical assessments of the subjects were performed at the baseline (visit 1), after four days (visit 2), and after seven days (visit 3) of treatment. The bacteriological assessments were performed before initiating the therapy and after the completion of seven days of treatment by swab culturing from the affected site. Clinical photographs of the recruited subjects were also obtained.

Assessments: Evaluation of clinical and bacteriologic efficacy was determined by a blinded observer, a consultant from our department, not involved in this study. The clinical efficacy of the treatment was determined by assessing whether there was a complete resolution of the treated lesions. This was measured by evaluating the absence of blistering, exudate and/or pus, crusting, along with itching and/or pain (with a SIRS score of 0), as well as minimal erythema and/or inflammation (with a SIRS score of ≤1). If these criteria were met, no further antibiotic therapy was deemed necessary for the affected area. An improvement was defined as a reduction of more than 10% in the overall Systemic Inflammatory Response Syndrome (SIRS) score when compared to the baseline. This definition does not meet the requirements for individual SIRS scores indicating a cure. Conversely, a failure was characterised by a lack of a clinical improvement or a worsening of the patient's condition.

In the assessment of bacteriological effectiveness, a cure was defined as either the eradication of the pathogen responsible for persistent lesions at the conclusion of therapy or the absence of culture material if no lesion remained. The failure was determined when the initial pathogen remained detectable following the treatment.

Participants who did not show a response to the prescribed therapeutic intervention at the conclusion of the trial period, or participants who experienced negative responses, were transitioned to suitable systemic antibiotics. The assessment of safety was conducted by considering adverse occurrences, vital signs, and a physical examination.

Data were analysed using a 2-group $\chi 2$ test with $P < 0.05$ indicating statistical significance.

Observation and Results

During the study period, a total of 33 subjects with impetigo were recruited. The age of the subjects ranged from 2 to 10 years. The mean age of the study population was 5.48 years with a standard

deviation of 2.17. There was an increased male preponderance with a male to female ratio of 1.36:1. The socioeconomic status of patients was assessed using a modified Kuppuswamy scale. The majority of the subjects belonged to the lower-middle class and upper-middle class. The average duration of disease before the presentation was 2.85 days. The bulk (82%) of the subjects presented with non-bullous impetigo.

The two treatment groups were comparable with respect to baseline characteristics [Table-1].

Table 1: Baseline characteristics of patients in both treatment groups

Variable	Category	Ozenoxacin treated [group A] n=16	Mupirocin-treated [group B] n=17	Total (N=33)	p-value
Age (in years)	Mean	5.6	5.4		
	Range	2 to 10	2 to 10		0.986
Gender	Male	10	9	19	
	Female	6	8	14	0.728
Socioeconomic status	Upper class	1	1	2	
	Upper-middle class	2	3	5	
	Lower middle class	6	7	13	
	Upper-lower class	7	6	13	
	Lower class	0	0	0	1.000
Duration of disease before presentation	Mean	2.8	2.9		
	Range	1 to 5	1 to 5		1.000
Clinical presentation	Bullous impetigo	3	3	6	
	Non-bullous impetigo	13	14	27	1.000
Symptoms	Only pain	4	5	9	
	Only itching	2	1	3	1.000
	Both	10	11	21	
Severity	Mild	5	6	11	
	Moderate	10	10	20	1.000
	Severe	1	1	2	

The clinical and bacteriological outcome of therapy in the two groups is shown in Table-2. Overall, both antibiotics were equally effective. After seven days of therapy, ozenoxacin affected a clinical cure in 87.5% of subjects as compared to 76.5% of subjects in the mupirocin-treated group. However, clinical assessment on day 4 of therapy revealed that 50% of subjects treated with ozenoxacin showed complete cure as compared to 12% of subjects treated with mupirocin. This difference was statistically significant (p-value = 0.038). Clinical assessment was not done in 1 subject in group B because treatment was stopped due to adverse reaction.

Table 2: Clinical and bacteriological outcomes of topical therapy

Variable	Category	Ozenoxacin-treated [group A] n=16	Mupirocin-treated [group B] n=17	Total (N=33)	p-value
Clinical assessment on day 4	Cure	8	2	10	
	Improvement	8	14	22	
	Failure	0	0	0	
	Not done	0	1	1	**0.038***
Clinical assessment on day 7	Cure	14	13	27	
	Improvement	2	3	5	
	Failure	0	0	0	1.000
	Not done	0	1	1	
Isolates in culture	Staphylococcus aureus alone	10	9	19	
	β-haemolytic streptococci alone	3	4	7	
	Staphylococcus aureus + β-haemolytic streptococci	2	3	5	
	No isolate	1	1	2	1.000
Bacteriological efficacy	Cure	15	14	29	
	Failure	0	1	1	

	Not evaluated	1	2	3	1.000

*p-value is significant.

The results of bacteriological profiling were equivalent in both groups. Staphylococcus aureus and Streptococcus pyogenes were the two most prevalent pathogens isolated in our study population. Bacteriological efficacy was not evaluated in 2 subjects (1 in each group) with no isolates and in 1 subject in group B because of adverse reaction.

Figure legends: Figure 1 – Subject photographs of treatment success of impetigo with twice daily 7-day therapy of topical ozenoxacin cream 1%.

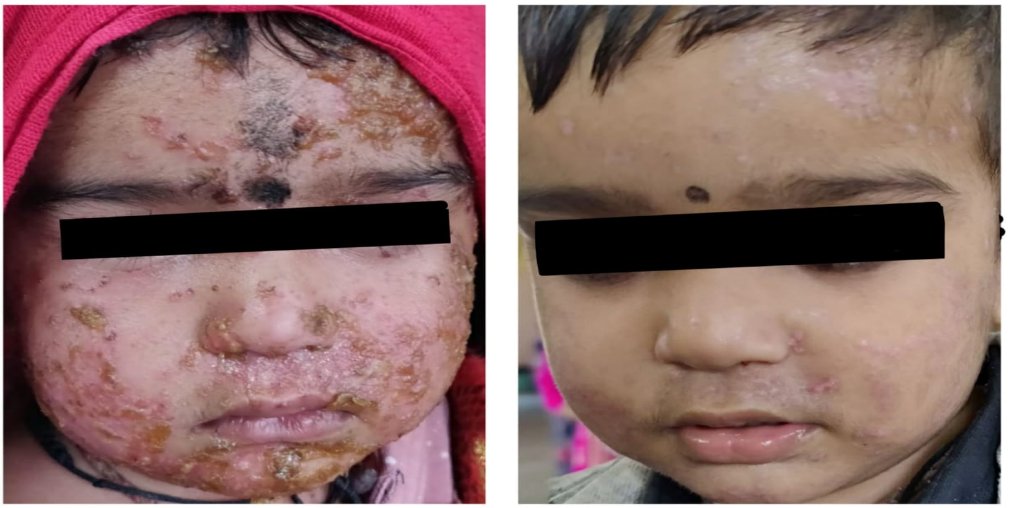

Figure 1:

Adverse effect was recorded in 1 subject using mupirocin who complained of mild itching, burning sensation and redness at the site of application. The subject was advised to stop using the topical therapy and was shifted to systemic amoxicillin/clavulanate.

Discussion

Impetigo is a prevalent superficial bacterial infection that affects the skin, with a significant worldwide illness burden exceeding 140 million cases. [4] In cases with restricted impetigo, topical antibiotic therapy is commonly began as a means to mitigate the progress of the infection and expedite its clinical resolution.

Ozenoxacin is a novel drug that acts by inhibiting DNA gyrase A and topoisomerase IV and affects DNA synthesis. This quinolone antibiotic has a bactericidal action against gram-positive organisms including MSSA (methicillin-sensitive Staphylococcus aureus), MRSA (methicillin-resistant Staphylococcus aureus), MRSE (methicillin-resistant Staphylococcus epidermidis), Streptococcus pyogenes and ofloxacin-resistant strains of Staphylococcus aureus and Staphylococcus epidermidis. [5] A cream formulation has been developed for the treatment of cutaneous bacterial infections, including impetigo.

In our study, both ozenoxacin and mupirocin were found effective in resolving the signs and symptoms of impetigo (Figure-1) and in imparting effective bacteriologic cures. However, a faster response time was obtained with ozenoxacin over mupirocin, which was advantageous in providing an early cure to the subjects. Based on the findings of Santhosh P et al, it has been shown that ozenoxacin exhibits a more expedited microbiological clearance in animal models when compared to mupirocin. However, it is important to note that no comparison human trials have been conducted thus far. [6] One further benefit of ozenoxacin is its status as a unique compound, distinct from any already existing antibiotics. Consequently, its use may be deemed safe, as there is no risk of developing resistance to other antibiotics through cross-resistance. In the Indian market, the price range of ozenoxacin 1% cream is around INR 22 to INR 28 per gramme, whereas the price range of mupirocin 2% cream is approximately INR 13 to INR 19 per gramme. But considering a lower time to cure by ozenoxacin, the total cost of treatment would be equivalent to mupirocin. However, mupirocin is available in both ointment and cream formulations, providing more options to treating physicians, whereas only cream formulation is available for ozenoxacin.

No significant adverse effects have been reported till now with ozenoxacin use while local side effects such as burning, itching and reddening have

been commonly reported with mupirocin use in studies.[7,8] In our study, both the molecules were well tolerated, except in a case of skin irritation because of mupirocin 2% cream.

The increasing prevalence of antibiotic resistance in the field of dermatology is becoming a significant cause for worry. There is a positive correlation between the duration of antibiotic usage and the likelihood of acquiring antimicrobial resistance. The phenomenon of Staphylococcus aureus acquiring resistance to mupirocin through plasmid-mediated mechanisms has been extensively described in the scientific literature.

Numerous published researches have provided evidence suggesting a positive association between the escalating clinical utilization of mupirocin and the emergence of resistance. The prevalence of mupirocin resistance is higher in methicillin-resistant Staphylococcus aureus (MRSA) strains as compared to methicillin-susceptible Staphylococcus aureus (MSSA) strains. Multiple studies have been conducted to evaluate the prevalence of Staphylococcus aureus resistance to mupirocin, revealing varying incidence rates that vary from 6.8% to 24%. [9,10]

In our study, we have obtained Staphylococcus aureus as the most common bacterial isolate, similar to other studies performed recently.[11] Choice of therapy for the treatment of impetigo should take into consideration the resistance pattern of Staphylococcus aureus. Ozenoxacin has a decreased likelihood of inducing the emergence of spontaneous resistance mutations in both quinolone-susceptible and quinolone-resistant bacterial strains. Furthermore, it has demonstrated efficacy against methicillin-resistant Staphylococcus aureus (MRSA) isolates. [12]

The limitation of our study is the recruitment of a small study population; also we had not performed sensitivity testing of our bacterial isolates. The systemic absorption of the products was also not assessed. Nevertheless, topical medicines are specifically designed to have low absorption, hence minimising the occurrence of systemic problems. [13]

Conclusion

Ozenoxacin is the first new topical antibiotic to be approved for the treatment of impetigo in the last 4 years. The current investigation has found that ozenoxacin 1% cream exhibits strong antibacterial properties and shows quicker clinical effectiveness compared to mupirocin 2% cream. Nevertheless, it is imperative to use caution and restraint in the utilisation of this unique pharmaceutical compound in order to retain its intrinsic worth. While mupirocin is widely accepted as the primary treatment option for impetigo and is offered in a more cost-effective form, ozenoxacin might potentially play a broader therapeutic role in managing localised impetigo in the event of a substantial rise in mupirocin resistance.

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