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Single-center, prospective, and observational study on the management and treatment of impetigo in a pediatric population

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Abstract. – OBJECTIVE: Ozenoxacin is a new antibiotic used to treat non-bullous impetigo. The aim of this study is to evaluate the microbiological and clinical efficacy of topical ozenoxacin 1% cream after 5-day twice-daily treatment, in pediatric patients with impetigo.

PATIENTS AND METHODS: This observational and prospective study included patients aged 6 months to 18 years, with non-bullous impetigo. Efficacy was measured using the Skin Infection Rating Scale (SIRS) and microbiological culture at the first visit (T0), at the second visit after 72 hours (T1) and after 5 days (T2). Safety and tolerability were also evaluated.

RESULTS: A total of 50 patients was enrolled. A reduction of SIRS score >10% after 72 hours of treatment was noticed in all patients, while a complete reduction was assessed after 5 days in all the population. Microbiologic success rates for ozenoxacin at T1 was 92% (four patients had original pathogens in the specimen culture from the skin area), whereas at T2, it was 100%.

CONCLUSIONS: Topical ozenoxacin has strong efficacy in treating impetigo in pediatric patients. Ozenoxacin's clinical and microbiological rapid onset of response led to consider this antibiotic a novel efficacy option for the treatment of impetigo.

Key Words:
Impetigo, Pediatric, Dermatology, Skin, Infection.

Introduction

Skin diseases represent about 15% of evaluations to the pediatric emergency room and about 20% of consultations by general practitioners[1]. Among the skin diseases, impetigo is one of the most common skin infections. Gram-positive bacteria are the most commonly responsible for these diseases, particularly *Staphylococcus aureus*. The prevalence of impetigo is high, and more than 150 million people are estimated[2,3] to be affected worldwide at the same time. Bacterial multidrug resistance has been a serious issue for healthcare systems in recent decades, and there have been many attempts to overcome this problem, which is still present today[4,5].

Topical antibiotic therapy is the treatment of choice in most cases of impetigo, although antibiotic resistance (mainly to methicillin) has increased rapidly in recent years[6]. Few formulations of topical antibiotics are available in Italy, and most of these molecules have developed resistance over the years, causing therapeutic failures and the spread of resistance. *Staphylococcus aureus-resistant* phenotypes have reached a prevalence of up to 50% in southern Europe, and there is growing concern over the continued spread of methicillin-resistant *Staphylococcus aureus* (MRSA)[7].

New antibiotics such as ozenoxacin, a new quinolone recently introduced and effective against bacteria resistant to quinolones and methicillin, can offer a valid therapeutic alternative[8-11]. Clinical data in the context of "real life" are needed to better assess the clinical efficacy of ozenoxacin in the management of pediatric patients with NBI and its microbiological clearance rate.

The aim of this study was to evaluate the clinical efficacy, safety, and tolerability of Ozenoxacin in pediatric patients with impetigo.

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Patients and Methods

This is a single-center, prospective, and observational study. Patients aged between 6 months and 17 years and 364 days, with a diagnosis of non-bullous impetigo, evaluated at the Pediatric Emergency Department or the General Pediatric Clinic of the Fondazione Policlinico Universitario A. Gemelli - IRCSS between June 2020 and June 2021 were enrolled. Parents or guardians signed an informed consent for children's participation.

Patients with impetigo, without any previous clinical evaluation and with no therapy at the time of the first visit, were initially evaluated clinically using the Skin Infection Rating Scale (SIRS) score, an evaluation based on 7 signs/symptoms: blistering, exudate, and/or pus, crusting, erythema and/or inflammation, itching and/or pain, on a scale of 0 (absent) to 3 (severe) (possible range of scores, 0-15) (Figure 1).

During the first evaluation, a swab of the wound was performed. All isolates were tested for susceptibility to erythromycin, clindamycin, fusidic acid, mupirocin, ozenoxacin, levofloxacin, ciprofloxacin, retapamulin, penicillin, and vancomycin using prepared dry panels (Sensititre™, Thermo Fisher Scientific, Segrate, Milan, Italy).

Item	Score	Scale	Definizione
Vesicles	0	Absent	No evidence of vesicles
	1	Minimal	Few vesicles raised on careful evaluation
	2	Moderate	Fluid-filled vesicles uncomfortable for the patient
	3	Severe	Large area covered with many vesicles which may include large bullous vesicles
Exudate/pus	0	Absent	No evidence of exudate or pus
	1	Minimal	Small amounts of fluid/pus
	2	Moderate	Moderate exudate / pus infected area
	3	Severe	Large infected areas and draining exudates
Crusting	0	Absent	No evidence of crust formation
	1	Minimal	Some areas show some signs of crusted lesions
	2	Moderate	Crusting present throughout the infected area
	3	Severe	Thick crust over the entire impetiginous area
Erythema / inflammation	0	Absent	Normal skin tone and color; no signs of erythema or inflammation
	1	Minimal	Pink skin with minimal signs of inflammation
	2	Moderate	Red skin with evident signs of inflammation
	3	Severe	Red skin and severe inflammation
Itching /pain (adult and pediatric patients capable of self-assessment)	0	Absent	No signs of itching or pain
	1	Minimal	Some evidence of scuffing or rubbing and minor discomfort
	2	Moderate	Scratches and annoying painful lesions
	3	Severe	Extensive scratching and pain that interferes with daily activities or sleep
Itching /pain (pediatric patients unable to report symptoms)	0	Absent	No signs of itching or pain. Normal behavior
	1	Minimal	Some scratch marks. The patient cries more than usual with no effect on normal activities/behaviour
	2	Moderate	Evidence of scratching and the patient crying more than usual interfering with normal activities/behaviour
	3	Severe	Extensive scratching and inconsolable crying interfering with normal activity/behavior and/or sleep

Figure 1. Skin Infection Rating Scale.

They were prepared using the broth microdilution method, as recommended by the Clinical and Laboratory Standards Institute (CLSI)[12,13].

The range of concentrations tested were: ozenoxacin (0.001-4 mg/l), ciprofloxacin (0.06-16 mg/l), clindamycin (0.015-16 mg/l), erythromycin (0.06-16 mg/l), fusidic acid (0.03-16 mg/l), levofloxacin (0.06-16 mg/l), mupirocin (0.06-256 mg/l), penicillin (0.03-0.5 mg/l), retapamulin (0.015-2 mg/l), and vancomycin (0.25-2 mg/l). Two quality-control strains (*S. aureus* ATCC 29213 and *S. pneumoniae* ATCC 49619) were also included in the study.

Subsequently, patients began treatment for impetigo according to clinical practice. Patients were instructed to perform a subsequent evaluation at the General Pediatric Clinic 72 hours and 5 days from the start of treatment. At the second evaluation, patients who met the inclusion criteria were enrolled. In particular, inclusion criteria were: patients aged between 6 months and 17 years and 364 days, with a diagnosis of non-bullous impetigo, defined as maculopapular lesions that turn into thin-walled blisters that break quickly, leaving superficial erosions, sometimes itchy or painful, covered with classic honey-colored crusts, classified as primary or secondary, the latter more widespread; patients on therapy with ozenoxacin (Dubine 10 mg/g) for less than 72 hours; patients who had undergone a swab for culture examination of the skin lesion site of impetigo and an antibiogram; patients that had been assessed according to the SIRS scale at onset.

Exclusion criteria were: patients with other skin infections other than non-bullous impetigo; infections with Gram-negative pathogens; patients on antibiotic therapy.

After 5 days of treatment, the clinical response to topical therapy with ozenoxacin (Dubine 10 mg/g), defined as a ≥10% reduction in the SIRS score from baseline (primary endpoint), was determined and evaluated in the first 50 patients enrolled. Secondly, the clinical efficacy and microbiological efficacy (the latter by performing a culture test and determining the minimum inhibitory concentrations (MIC) of the microdilution broth) of the therapy with ozenoxacin was evaluated with respect to baseline. Any adverse events that could occur during the study were collected and reported, according to current clinical practice.

The primary outcome of this study was to evaluate the clinical efficacy of ozenoxacin using the SIRS score at the end of treatment lasting 5 days (reduction of the SIRS score ≥10% compared to baseline), in pediatric patients with impetigo. The secondary outcome was to evaluate the clinical efficacy of ozenoxacin (using the SIRS score) after 72 hours from the start of treatment. Safety and tolerability were also evaluated.

Statistical Analysis

Based on the primary objective, the sample size is calculated assuming to be able to observe a percentage of responding patients equal to 90%[14], with a margin of error equal to 9% and a confidence level of 95%. A sample size of N = 43 patients was obtained, to which a 10% dropout was added, reaching the final size of N = 50 patients. The sample was described in its clinical and demographic characteristics through descriptive statistical techniques. In particular, the quantitative variables were represented through the following measures: minimum, maximum, range, mean and standard deviation. The qualitative variables were represented with tables of absolute and percentage frequencies. The normality of continuous variables was verified with the Kolmogorov-Smirnov test.

The primary objective was achieved by calculating the percentage of patients responding to treatment after 5 days. Comparisons between the effectiveness of the different antibiotics was carried out with the Chi-square test and the ANOVA test ($p<0.05$).

Results

A total of 50 patients with non-bullous impetigo were enrolled in this study; 18 were female, 32 were male, the mean age was 8.2 years, and the median age was 7 years. Characteristics of patients enrolled, SIRS score at baseline (T0), and reduction of SIRS at T1 (72 hours) and T2 (5 days) are shown in Table I.

Our results show that all enrolled patients had a reduction in SIRS score at T2 (5 days) higher than 10%, in particular, all the patients had a reduction of 100% of SIRS score at T2 (primary outcome). All the patients enrolled had a reduction in SIRS score higher than 10% also at T1 (72 hours), in particular the minimal reduction was 33.3%. One patient showed a reduction of 100% in SIRS score at 72 hours after topic therapy with ozenoxacin.

A total of 61 clinical isolates of *S. aureus* (n = 37), coagulase-negative staphylococci (n = 23) and *S. dysgalactiae* (n = 1) was collected. Species in the coagulase-negative staphylococci group were *Staphylococcus capitis* (n = 3), *Staphylococcus epidermidis*

(n = 6), *Staphylococcus haemolyticus* (n = 4), *Staphylococcus hominis* (n = 7), *Staphylococcus pasteuri* (n = 1), *Staphylococcus saprophyticus* (n = 1) and *Staphylococcus warneri* (n = 1). *S. aureus* and *S. epidermidis* isolates were also stratified by methicillin (n = 30 - susceptible *S. aureus* [MSSA]; n = 7 - resistant *S. aureus* [MRSA]). Isolates were identified using a MALDI Biotyper (Bruker Daltonik GmbH, Leipzig, Germany).

Table II shows MIC_{50} and MIC_{90} values for ozenoxacin (OZNX) and 9 comparator antimicrobial agents against 61 strains isolated from clinical skin specimens.

OZNX has strong antibacterial activity against *S. aureus*. The minimum inhibitory concentration $(MIC)_{90}$ of OZNX against methicillin-susceptible *S. aureus* (MSSA; 30 strains) and MRSA (7 strains) isolated were ≤0.008 and 0.25 μg/mL, respectively, whereas the MIC_{50} of OZNX for MSSA and MRSA were ≤ 0.004 and 0.03 μg/mL, respectively, and the MIC ranges were < 0.001-0.12 and 0.004-0.25 μg/mL, respectively (Table I). The maximum OZNX MIC (0.25 μg/mL) was observed even for LVFX-resistant (MIC: ≥4 μg/mL) *S. aureus*. OZNX has a higher antibacterial activity than other tested antibiotics with a statistically significant difference (p<0.05).

Table III shows the antibacterial activity of ozenoxacin and comparators against coagulase-negative *Staphylococcus* (CNS) species. Of the 23 CNS isolates included in the study, 6 (26%) were methicillin-resistant (MR-CNS), and 17 (74%) were methicillin-susceptible (MS-CNS). Only one MS-CNS isolate was nonsusceptible to levofloxacin. Ozenoxacin was highly active against all CNS isolates (MIC_{50} = ≤ 0.008 μg/mL; MIC_{90} = 0.03 μg/mL), inhibiting 83% of isolates at a MIC of ≤ 0.004 μg/mL, with a statistically significant difference (p<0.05).

Ozenoxacin had higher activity against methicillin-resistant CNS isolates (MIC_{50} = 0.004 μg/mL and MIC_{90} = 0.008 μg/mL against both) compared to mupirocin (MIC_{50} = 0.25 μg/mL and MIC_{90} = 0.5 μg/mL against both) and fusidic acid (MIC_{50} = 0.25 μg/mL and MIC_{90} = 16 μg/mL against both). Ozenoxacin was highly active against the *S. dysgalactiae* isolate tested, with a MIC of 0.03 μg/mL. Ozenoxacin showed lower MICs against isolates than fusidic acid, mupirocin, erythromycin, clindamycin, ciprofloxacin, or levofloxacin, as established by the MIC_{90} level. Additionally, against the levofloxacin-nonsusceptible *S. aureus* isolates (MIC: ≥ 4 μg/mL), ozenoxacin proved to be the most powerful compound.

No strain showed an evident reduced susceptibility to OZNX.

The microbiologic response after treatment with ozenoxacin was evaluated at visit 1 (72 h from the start of treatment) and visit 2 (5 days from the start of treatment).

Microbiologic success/eradication was defined as the absence of the original pathogens identified in the specimen culture from the affected area at baseline (T1) with or without the presence of any new microorganisms. Microbiologic failure/persistence was defined as the presence of the original pathogens in the specimen culture from the affected area at baseline with or without the presence of any new microorganisms.

Microbiologic success rates for ozenoxacin at T1 was 92% (four patients had original pathogens in the specimen culture from the skin area), whereas at T2, it was 100%. No side effects were evaluated during the 5 days-course treatment.

Discussion

Impetigo is a bacterial skin infection mainly caused by *Staphylococcus Aureus* and *Streptococcus pyogenes*, leading to highly contagious lesions that can spread rapidly by direct contact[15-17].

Ozenoxacin belongs to a new generation of topical antibiotics with potent selective inhibition of DNA replication and is structurally characterized as a nonfluorinated quinolone[18,19].

In our study, the efficacy and safety of ozenoxacin in the pediatric population with non-bullous impetigo were examined by pooling data for patients aged 6 months to <18 years of age. Ozenoxacin demonstrated a clinical and microbiological response after 5 days of therapy of 100% and early bacteriologic eradication after 3 days of treatment, with a reduction of SIRS score higher than 33.3% in all the study population.

Although the primary outcome that we were pre-set at the beginning of enrollment to evaluate the efficacy of ozenoxacin was the reduction of SIRS by at least 10% at 5 days (T2), our results showed not only 100% reduction of SIRS at T2, but also an early bacteriologic eradication with a minimal reduction in 3-day SIRS (T1) of 33.3% and one patients with a reduction of 100% of SIRS at T1. Microbiologic success rates for ozenoxacin at T1 was 92%, whereas at T2 was 100%. These results were consistent with a previous multicenter randomized controlled clinical trial by Gropper et al[20], published in 2014.

Furthermore, in accordance with the present results, previous studies[21] have demonstrated that ozenoxacin exhibited high activity *in vitro* against staphylococci and streptococci, regardless of susceptibility to other fluoroquinolones or methicillin, with MIC_{50} and MIC_{90} as 0.004 and 0.25 ug/ml, respectively.

Ozenoxacin's spectrum of activity *in vitro* against staphylococci and streptococci, regardless of susceptibility to methicillin or levofloxacin, is reflected in the efficacy that this drug shows from a clinical point of view for the treatment of impetigo[22,23]. Schachner et al[24] conducted a review in 2021 evaluating that ozenoxacin 1% cream is an important option for treating impetigo for pediatric and adult populations, combined with its favorable features, such as a low dosing frequency and a 5-day treatment regimen, and these data match our results. Moreover, the incidence and intensity of adverse events can vary among the classes of antimicrobials. For novel molecules such as oxenoxacin, the literature is lacking data, but a tendency to irritation, sensitization, phototoxicity, or photoallergy has been reported[25,26].

Due to the rapid bactericidal activity of ozenoxacin, as indicated in this analysis, its early microbiological eradication activity may have critical importance in restricting the transmission of impetigo, a highly contagious condition[18,27,28].

Limitations

The major limitation of this study is the small sample size. Nonetheless, few data are nowadays available on the treatment of this highly frequent and contagious disease with ozenoxacin. The relevant findings here reported can impact the daily clinical practice, due to the excellent results obtained both after three and five days.

Conclusions

The consistent clinical and rapid bacteriologic effects demonstrated by ozenoxacin cream 1% in a pediatric population, support its use as an important empirical therapeutic option for patients with impetigo.

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Authors' Contributions

LC and SF looked up the literature and wrote the initial draft. AG and LC revised the manuscript. AC, LDS and SF supplement the materials. AG, AC, and AC developed the study design and conceptualization. BF, AO, and DT collected and processed data. All authors reviewed and agreed on the final manuscript.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

Ethical Approval

The authors state that the study was approved by the Ethics Committee of our institution (Università Cattolica del Sacro Cuore), n°3321.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Informed Consent

All enrolled patient's parents or guardians signed an informed consent for children's participation. Informed consent of parents or guardians are available from the corresponding author on request.

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