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Review Article

Topical ozenoxacin 1% cream in impetigo: A systematic review and meta-analysis

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Abstract

Impetigo is a prevalent bacterial skin infection of the youngsters. Ozenoxacin is a new quinolone topical antibacterial agent that was developed as a 1% cream for the treatment of impetigo. The purpose of this study, which included a systematic review and meta-analysis, was to map the research and present the effectiveness of ozenoxacin 1% topical cream for treating impetigo. From the beginning to the end of the study period [July 2022], a thorough search was conducted on the PubMed, Google Scholar, Cochrane library, and Science Direct databases. According to clinical judgment and bacteriological testing, relevant studies that reported the success rate of ozenoxacin 1% topical cream in treating impetigo were included. Meta-analysis was done using the open-source software "R". The odds ratio was calculated along with the 95% confidence interval. To assess the level of certainty of the generated result, the GRADEpro tool was used. This systematic review as well as meta-analysis included 4 clinical trials, two from Spain and two from the United States of America, with an approx. of 1,874 cases, 957 of which used ozenoxacin 1% topical cream and 917 of which used placebo treatment. The fixed effect model showed that the use of ozenoxacin 1% topical cream is more effective than the use of placebo based on clinical judgment [OR=2.16, 95% CI (1.77−2.65); P=<0.001; I^2=1%] and based on bacteriological culture testing results [OR=4.15, 95% CI (3.08–5.57); P=<0.001; I^2=27.5%]. There is no evidence of publication bias or heterogeneity. The generated evidence is classified as having a high level of certainty. With a high certainty level of evidence, this meta-analysis showed that ozenoxacin 1% topical cream effectively treats impetigo over a placebo for both children and adult patients.

Key words
Antibacterial; Efficacy; Impetigo; Ozenoxacin 1% cream; Placebo; Quinolones.

Introduction

Impetigo is an extremely infectious prevalent bacterial skin infection that most commonly affects young children and infants,[1] and less frequently in adults. [2] The overall prevalence of

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impetigo is approximated to be 11.2%, with children (12.3%) being 2.5 times more likely than adults (4.9%).[3] Warm and moist climates, poor socioeconomic status, densely populated environments, nutritional deficiencies, and participation in sports, for example, is a major threat factor for impetigo.[1] *Staphylococcus aureus* (S. aureus) is the most common pathogen responsible for impetigo, but *Streptococcus pyogenes* is also present, either separately or in conjunction with S. aureus. Erythematous pustules or vesicles (red sores) that speedily advance to superficial erosions with a honey-colored crust characterize the condition. Lesions on the face, neck, and hands are common, but they can extend to other areas of the body due to scraping or be allowed to pass on to close contacts. Because it is highly contagious, the disease is especially dangerous in schools and daycare centers.[2] Clinical practice guidelines recommend utilizing topical antimicrobial compounds to treat localized impetigo areas and oral antibiotics to treat multiple or extensive lesions that do not respond to topical therapy, as well as systemic infection.[4] Topical treatments achieve a maximum local concentration of drug directly to the area of infection, enhancing the antibiotic's capability to overcome point mutation resistance. Furthermore, topical treatments are designed to be mildly absorbed, lowering the toxic side impacts of oral therapies.[5]

As a result, topical applications is favoured for localized, straightforward impetigo and it is more efficacious than a placebo.[6] It has also been discovered to be as effective as or more efficacious than oral therapy, with outbreaks affecting a large number of people being administered orally[4] or when it is unsuitable to use topical therapy (i.e., for more generalized or severe infections).[7]

In December 2017, the FDA authorized ozenoxacin for the treatment of impetigo in patients over the age of 2 months and older.[8] In 2018, ozenoxacin 10 mg/g was accepted for sale in Spain,[9] and in May 2019, ozenoxacin 1% topical cream was authorised in 12 European Union countries.[10] Ozenoxacin (Xepi) is a topical non-fluoridated quinolone antibiotic prescribed for the treatment of bullous or non-bullous impetigo in adults and children over the age of two months.[11] Ozenoxacin has a dual inhibitory effect, preventing DNA replication by binding irrevocably either to DNA gyrase or topoisomerase IV. This usually causes quick bacterial cell death, indicating that the treatment is bactericidal.[12,13] Quinolones have broad-spectrum, potent antibacterial activity and are bactericidal against both gram-positive and gram-negative microbes. Ozenoxacin has bactericidal activity against gram-positive microbes such as MSSA (methicillinsensitive Staphylococcus aureus), MRSA (methicillinresistant Staphylococcus aureus), MRSE (methicillinresistant Staphylococcus epidermidis), Streptococcus pyogenes, Propionibacterium acnes, and ofloxacinresistant strains of S. aureus and S. epidermidis.[13-15]

Ozenoxacin has superlative antimicrobial properties and relatively lower minimum inhibition concentrations than other quinolones like ofloxacin, nadifloxacin, and levofloxacin.[14] Ozenoxacin does not stimulate cytochrome P450 enzymes in vitro because uptake throughout the body is negligible and no drug interactions have been reported.[16] Despite the fact that ozenoxacin is a comparatively recent antibacterial agent, it has been utilized in clinical practice. However, no meta-analysis was carried out to generate evidence about its effectiveness among the user population. This systematic review and meta-analysis were carried out in order to map the effectiveness of ozenoxacin 1% topical cream in patients with impetigo and recognize the efficacy of ozenoxacin.

Materials and Methods

Research protocol This systematic review as well as the meta-analysis protocol have been described and registered in the International Prospective Register of Systematic Reviews (PROSPERO), and the registration number is (CRD42022337716).

Research design and search strategy We strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA) guidelines in this systematic review as well as meta-analysis.[17] From inception to June 2022, we searched PubMed, Google Scholar, Cochrane Library, and ScienceDirect for all published studies that investigated the outcome of ozenoxacin 1% topical cream for treating impetigo. The search was performed in the search bar using the Boolean operator (AND, OR, NOT) and the possible MeSH and non-MeSH terms. Search terms and strategies are detailed in **(Table 1)**. PICOS framework was followed for the literature search as follows:

P (people): infant, child, or adult.
I (intervention/exposition): 1% ozenoxacin cream.
C (comparison): retapamulin 1% ointment OR other creams OR vehicle cream OR placebo cream.
O (outcome): impetigo OR impetigo contagiosa.
S (study design): randomized clinical trials.

Following inclusion criteria evaluation, two independent reviewers (MD and GF) screened abstracts and titles and checked full texts for eligible studies for this systematic review as well as meta-analysis. Any differences of opinion in among two independent critics were resolved during a dialogue with a third reviewer. EndNote 20.2.1 software was used to retrieve the eligible studies, remove duplicates, and manage the records.

Table 1 Searching strategies for PubMed, Google Scholar, Cochrane Library, and ScienceDirect.

PubMed	*Search strategy*
#1	Impetigo contagiosa [MeSH]
#2	Impetigo [MeSH]
#3	#1 OR #2
#4	Ozenoxacin 1% cream [MeSH]
#5	Xepi 1% cream [MeSH]
#6	#4 OR #5
#7	Infant [MeSH]
#8	Child [MeSH]
#9	Adult [MeSH]
#10	#7 OR #8 OR #9
#11	#3 AND #6 AND #10
Google Scholar	*Search strategy*
#1	all in the title: Impetigo contagiosa OR "Impetigo" AND "Ozenoxacin 1% cream" OR "Xepi 1% cream" AND "Infant" OR "Child" OR "Adult."
Cochrane Library	*Search strategy*
#1	Impetigo contagiosa [ti, ab, kw]
#2	Impetigo [ti, ab, kw]
#3	#1 OR #2
#4	Ozenoxacin 1% cream [ti, ab, kw]
#5	Xepi 1% [ti, ab, kw]
#6	#4 OR #5
#7	Infant [ti, ab, kw]
#8	Child [ti, ab, kw]
#9	Adult [ti, ab, kw]
#10	#7 OR #8 OR #9
#11	#3 AND #6 AND #10
ScienceDirect	*Search Strategy*
#1	((Impetigo contagiosa OR "Impetigo" "Ozenoxacin 1% cream" OR "Xepi 1% cream" AND "Infant" OR "Child" OR "Adult."))

Eligibility criteria

Inclusion criteria The following were the inclusion criteria: randomized controlled clinical trials with full-text available that reported the outcome of the ozenoxacin 1% topical cream for the therapies of impetigo, the study should report the cure of the condition at 7 days and 14 days of start treatment based on at least clinical assessment and bacteriological findings, studies written in English language were considered eligible for the analysis

Exclusion criteria In the non-randomized clinical trial, studies reporting cure after 7 days

or 14 days using other combined therapy with ozenoxacin 1% cream, conference abstracts, proceedings, letters, commentaries, and studies in translations numerous different than English have also been prohibited.

Data extraction

Two unbiased critics (AA and SB) extracted data from the included studies. The reviewers used the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument for data extraction.[18] The following information was extracted using a predetermined data form: authors, years of publications, country, study setting, research design, study population, number of patients, types of treatments, duration of treatments, time of assessment of the outcome, and outcome of the treatment, treatment-emergent adverse event. The data was entered directly into a Microsoft Excel spreadsheet.

Evaluation of study quality and threat of bias

Evaluation of quality The modified Jadad scale was employed to assess the article's quality.[19] The scale assesses the quality of the clinical trials based on participant randomization, blinding, dropouts, eligibility criteria, adverse event reporting, and statistical analysis description. The scale score ranged between 0–8, and a study scored ≥3 was considered good quality.

Evaluation of the bias threat Two peer review authors (MD and GF) assessed the bias threat independently in the included studies using the approach recommended by the Revised Cochrane threat of bias tool for randomized trials (ROB 2). The threat of Bias 2 (RoB 2) tool replaces the original threat of bias tool.[20]

The instrument is divided into five disciplines where bias may be introduced into the outcome: Bias again from random assignment phase; bias from deviance from planned intervention programs; bias from overlooking outcomes; bias in results; as well as bias in the sampling of such outcomes reported. Each component of the threat of bias tool in the included researches will be classified as "Low," "High," or "Some concerns" **(Figure 1)**. **Definition of the outcome of interest**

Success or failure in clinical trials The primary outcomes of interest will be the clinical assessment and reporting of cure or failure after 7 days of starting the treatment of ozenoxacin 1% cream. If the treated lesions observed on day 1 are completely resolved and the SIRS scores

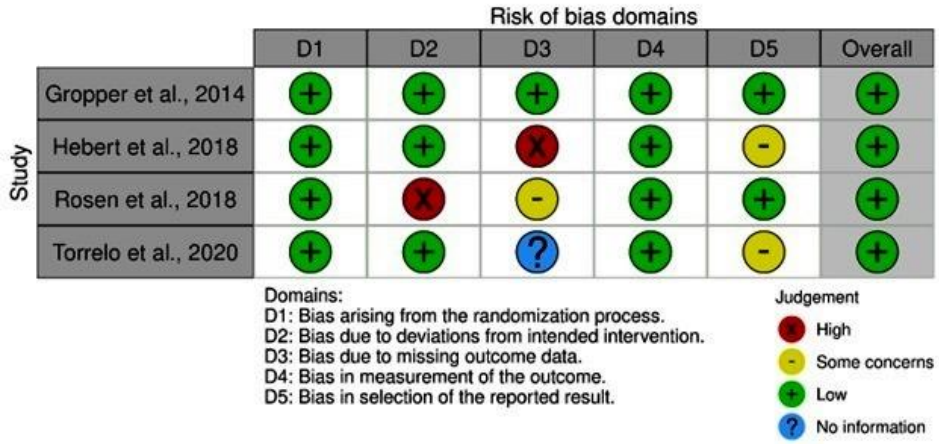

Figure 1 Assessment of Risk of Bias using RoB2.

are 0 for blistering, exudate, and/or pus, crusting, itching, and/or pain, and 1 for erythema and/or inflammation, the case is considered clinically successful. If the patient's total SIRS score decreases by more than 10% from baseline, the patient is considered "improved" (not fulfilling the criteria of individual SIRS scores for cure). Patients who were judged to have improved or failed were classified as failures.[21]

Microbiological assessment Bacteriological assessments were done on day 6 or 7 starting the treatment. The result is considered eradicated and successful if the primary organism detected on day 1 is absent from the cultured samples collected on day 6 or 7. If the primary organism detected on day 1 is present at the treatment's end, it is considered a bacteriological failure or persistent infection.[8]

Statistical analysis

The meta-analysis and subgroup analysis in this study were carried out using the "meta" package statistical software "R 4.0.3" (The R Foundation for Statistical Computing, Vienna, Austria) and the "metabin" function.[22] The heterogeneity of the researches enrolled in the meta-analysis was assessed using Cochrane Q and I^2. Cochrane Q, with $P<0.010$ and $I^2>50\%$, demonstrated the existence of heterogeneity in the research that included.

A fixed-effect model (Mantel-Haenszel method) was utilized for analysis if there was no significant inter-study heterogeneity. The random-effects model was used in all other cases. The effictivness of ozenoxacin 1% topical cream for managing impetigo was calculated using the aggregated OR and 95% confidence interval. To evaluate publication bias, Egger's test and a funnel plot were utilized. A statistical significance finding is considered if a two-sided *P*-value <0.05.

Grading the quality of evidence

The degree of certainty of this generated evidence was determined using the GRADEpro Guideline Development Tool profiler online tool.[23] The GRADEpro tool rates evidence, beginning with a greater degree of assurance and decreasing as the bias threat, including reporting bias, inconsistent results, indirectness of evidence, and inaccuracy, becomes significant.

Ethical consideration

Because no paramount data are obtained, no ethical clearance was obtained was required for such a systematic review or meta-analysis.

Results

Study selection The preliminary search for the related articles from the database retrieved 72 articles after removing duplicates and non-relevant studies; the remaining 11 studies were relevant. Of these, 4 were review articles, excluded. After screening, 7 studies were sought for retrieval and fully assessed for eligibility, yet 3 further were removed due to 1 being non-relevant (pharmacokinetic study) and 2 being of low quality. This means that the total number of studies used in the meta-analysis was four **(Figure 2)**.

Features of the studies included Four studies enrolling 1,372 cases treated with ozenoxacin 1% topical cream in impetigo were admissible for participation in this systematic review as well as meta-analysis. All studies are randomized clinical trials, including 2 studies from Spain[10,24] and two from the United States of America.[21,25] Three studies recruited infants aged ≥2 months besides adults,[8,21,25] while one

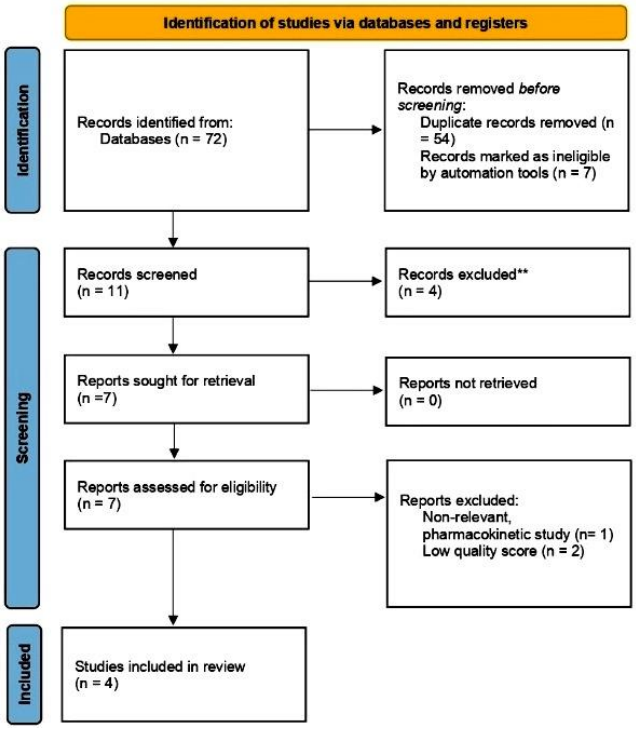

Figure 2 PRISMA flow diagram showing the number of articles identified in the systematic review and meta-analysis of ozenoxacin 1% cream for the treatment of impetigo.

study[10] recruited infants aged ≥6 months and ≤18 years **(Table 2)**. All the enrolled researches were high-quality researches based on the Jadad scale score for interventional studies **(Table 3)**.

Efficacy of topical ozenoxacin 1% topical cream versus placebo using primary end-point clinical judgment The clinical outcome of ozenoxacin 1% topical cream was evaluated on the sixth or seventh day of treatment. It was evaluated in four included research findings, 957 patients were allocated to the ozenoxacin 1% topical cream arm and 917 patients assigned to the placebo arm. The meta-analysis revealed that using ozenoxacin 1% topical cream is superior to using placebo [OR= 2.16, 95% CI (1.77 2.65); P=<0.001] **(Figure 3)**. A template with a fixed effect was used, and there is no heterogeneity observed [I^2=1%, Q=3.04; P=0.384]. The funnel plot revealed that the studies had a symmetrical distribution **(Figure 4)**, and Egger's test yielded

Table 2 Description of included studies.

Author, year	Country	Study Settings	Ozenoxacin 1% arm No. of patients enrolled	Placebo arm No. of patients enrolled	Duration of treatment	Outcome assessment time
Gropper et al., 2014 [8]	Spain	27 centers in 5 countries (Germany, Romania, South Africa, Ukraine, and USA)	(155 patients); Children 2 ≥ months and adults	(156 patients)	5 days/BID	6-7 days
Hebert et al., 2018 [25]	USA	53 centers in 7 countries (Germany, Romania, South Africa, Ukraine, Spain, Russia, and USA)	(357 patients); Children 2 ≥ months and adults	(354 patients)	5 days/BID	6-7 days
Rosen et al., 2018 [21]	USA	34 centers in 6 countries (USA, Russia, South Africa, Germany, Romania, and Spain)	(206 patients); Children 2 ≥ months and adults	(206 patients)	5 days/BID	6-7 days
Torrelo et al., 2020 [10]	Spain	South Africa, the USA, Germany	(239 patients); Children ≥ 6 months ≤ 18 years	(201 patients)	5 days/BID	6-7 days

Table 3 Quality assessment of included studies by using a modified version of Jadad scale.

Author, year	Randomization /appropriate	Blind/ appropriate	Withdrawals and drops	Inclusion and exclusion criteria	Adverse effect description	Statistical analysis	Total
Gropper et al., 2014 [8]	1/1	1/1	1	1	1	1	8
Hebert et al., 2018 [25]	1/1	1/1	1	1	1	1	8
Rosen et al., 2018 [21]	1/1	1/1	1	1	1	1	8
Torrelo et al., 2020 [10]	1/1	0/-1	1	1	1	1	5

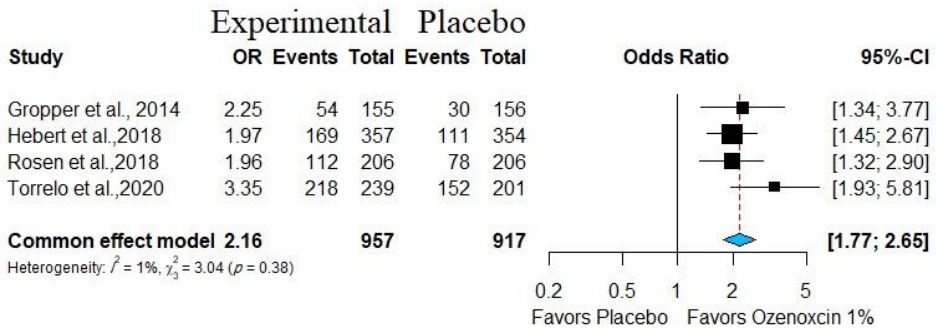

Figure 3 Forest plot showing the meta-analysis of ozenoxacin 1% cream vs. placebo in primary end-point clinical judgment.

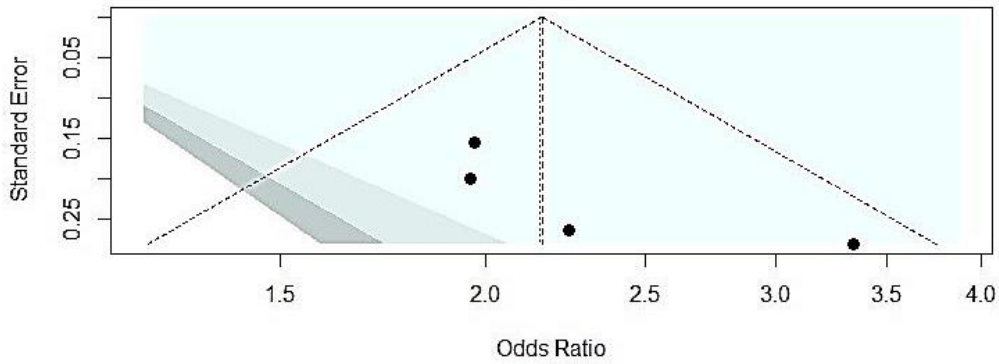

Figure 4 Funnel plot for studies in primary end-point clinical judgment.

no results (P=0.204).

Efficacy of topical ozenoxacin 1% topical cream versus placebo using bacteriological assessment All four clinical trials have compared the effect of ozenoxacin 1% topical cream with a placebo in treating impetigo and assessed the outcome based on the bacteriological culture testing on the 6th or 7th day of treatment. This outcome was assessed in 702 patients allocated to the ozenoxacin 1% topical cream arm compared to 670 patients allocated to the placebo arm. This meta-analysis using a fixed effect model showed that topical treatment with ozenoxacin 1% topical cream is more effective than placebo [OR=4.15, 95% CI (3.09–5.58); P= 0.001] notwithstanding the of the age of the individual **(Figure 5)**. There is no inter-study heterogeneity [I2=27.5%, Q=4.14, P=0.247]. We followed fixed effect models and no further heterogeneity analysis was required. We looked for signs of publication bias using a funnel plot, which revealed a symmetrical pattern of distribution of the research **(Figure 6)**. This is supported by a quantitative Egger's test, which revealed no evidence of reporting bias (P=0.553).

Grade certain of the generated evidence The current generated finding evidence was of high certainty for both outcomes measured, according to the GRADEpro tool. The effectiveness of ozenoxacin 1% topical cream in treating impetigo was stronger than placebo (based on patient assessment judgments and bacteriological testing results) **(Table 4)**.

Discussion

This meta-analysis found that using ozenoxacin 1% topical cream 2 times a day for five days is more effective than a placebo in treating impetigo. This is true whether the patient is a child or an adult. This meta-analysis generated

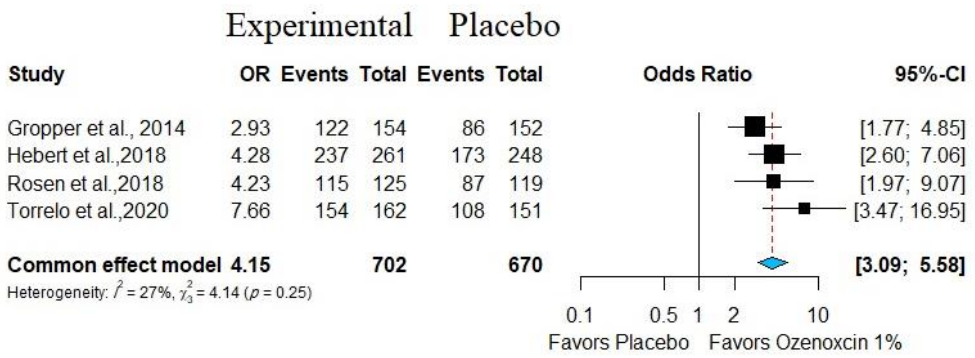

Figure 5 Forest plot showing the meta-analysis of ozenoxacin 1% cream vs. placebo using bacteriological assessment.

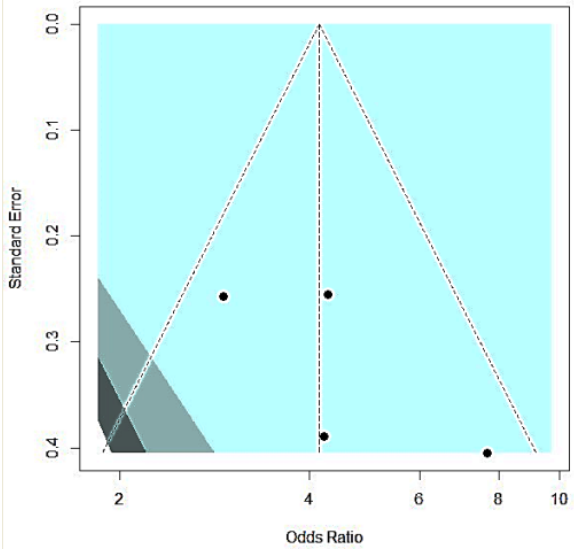

Figure 6 Funnel plot for studies using bacteriological assessment

Table 4 GRADE table efficacy of ozenoxacin 1% cream vs. placebo in the treatment of impetigo among children and adults patients.

No. of studies	*Study design*	*Risk of bias*	*Inconsistency*	*Indirectness*	*Imprecision*	*Publication bias*	*Ozenoxacin 1% cream*	*Placebo*	*Overall quality of evidence*	*Comment*
Primary outcome										
4	Randomized clinical trials	Not serious	Not serious	Not serious	Not serious	Not suspected	628/702 (89.5%)	454/670 (67.8%)	⊕⊕⊕⊕ High	OR=4.15 (95% CI 3.09–5.58)
Bacteriological Testing										
4	Randomized clinical trials	Not serious	Not serious	Not serious	Not serious	Not suspected	553/957 (57.7%)	371/917 (40.4%)	⊕⊕⊕⊕ High	OR=2.16 (95% CI 1.77–2.65)

GRADE Working Group grades of evidence.
Note: High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Note: Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Note: Low certainty: our confidence in the effect estimate is limited: the true effect may differ substantially from the effect's estimate.
Note: Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
OR: Odds Ratio.
CI: Confidence Interval

evidence about the efficacy of the newly topical antibiotic ozenoxacin 1% topical cream for treating impetigo for the first time. The currently generated evidence is highly certain, and there is almost no inter-study heterogeneity in this meta-analysis, which may reflect the high quality of the included studies. Furthermore, there is also no evidence of reporting bias, which ensured that the majority of the published literature was included up to date.

Impetigo is one of the soft tissue and skin infections induced mainly by *S. aureus* and *S. pyogenes*.[9] Many studies have found that the prevalence of cutanous infections caused aureus isolates with resistance to mupirocin antibiotics

and fucidic acid is increasing.[26,27] This necessitates a new antibiotic to overcome this resistant pattern of *S. aureus*. Ozenoxacin 1% topical cream showed clinical efficacy against *S. aureus* strains, including MRSA strains, fucidic acid, or mupirocin-resistant strains.[13-15] Perhaps this point makes ozenoxacin superior to other classical antibiotics such as fucidic-acid and mupirocin; However, this is not clinically tested and proven.

The selection of the articles in this study is based primarily on clinical judgments and bacteriological culture testing results. Therefore, our findings may provide clinicians in remote areas with the best evidence for using ozenoxacin 1% topical cream to treat impetigo. Ozenoxacin 1% topical cream was used in patients with localized impetigo and was not evaluated in patients with widespread impetigo. However, the recommended treatment of widespread impetigo is still a systematic antibiotic over topical antibiotics.

Although the purpose of this point of the research is not to evaluate the adverse reactions of ozenoxacin 1% cream, however, it is worth mentioning that two studies out of four have not reported any adverse events related to the ozenoxacin 1% topical cream,[10,24] while a total of two patients in the remaining two studies have reported a worsening of a previous seborrheic dermatitis and rosacea.[21,25] This may ensure the patients' tolerability and safety of the ozenoxacin 1% cream, especially the children.

We are striving to the maximum of our abilities, it represents an initial systematic review as well as meta-analysis of ozenoxacin 1% topical cream efficacy in impetigo. Our findings can benefit dermatologists and policymakers, which could help them provide the best treatment to their patients. The inclusion of high-quality researches is a strong point of our meta-analysis. We thought that reduced the inter-research heterogeneity to the minimum. Moreover, there is no evidence of publication bias.

Further study is needed to include more high-quality studies that assess the efficacy of ozenoxacin 1% topical cream in more broad lesions.

Conclusion

With a high certainty level of evidence, this meta-analysis showed that ozenoxacin 1% topical cream effectively treats impetigo over a placebo for both children and adult patients.

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