Original Research Article

An evaluation of safety and efficacy of nadifloxacin 1% ointment versus mupirocin 1% ointment in Indian children with skin and soft tissue infection

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Received: 06 October 2019

Revised: 16 November 2019

Accepted: 06 December 2019

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ABSTRACT

Background: Although nadifloxacin has been shown to be effective in the treatment of skin & soft tissue infections (SSTI), there is a paucity of data comparing its efficacy and safety with other antibacterials, especially in Indian paediatric population. Therefore, objective of this study was to compare the safety and efficacy of nadifloxacin with mupirocin in children with SSTI.

Methods: This was a single-centre, open label, randomized, parallel group, comparative study in 60 children of <12 years of age with SSTI. Test group (n=30) received nadifloxacin 1% ointment and reference group (n=30) received mupirocin 1% ointment, to be applied twice daily. Patients were followed up at day 4, 8 and 15. Efficacy of the study drugs was evaluated by clinical and bacteriological cure rate. Safety was assessed by reporting of adverse events.

Results: Baseline characteristics of enrolled patients were comparable between treatment groups and all 60 patients completed the study. At Day 15, 100.0% cases among nadifloxacin group and 96.7% cases among mupirocin group achieved clinical cure (p=0.313). The most common bacteria found in culture were Gram positive cocci in both the groups (86.7% in nadifloxacin and 58.8% in mupirocin group). None of the cases in any of the groups showed bacteriological presence at day 15. No adverse event was reported in any of the treatment groups during the study duration.

Conclusions: Nadifloxacin was found to be equally efficacious and safe to mupirocin in the treatment of SSTI in Indian pediatric population.

Keywords: Bacteriological cure, Clinical cure, Mupirocin, Nadifloxacin, Pediatric, Skin and soft tissue infections

INTRODUCTION

Skin and soft tissue infections (SSTIs) involve microbial invasion of the skin and underlying soft tissues. The estimated incidence rate of SSTIs is 24.6 per 1,000 person-years.¹ A study from India reported that the prevalence of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) was 40-42% in 2008-2009.² Common superficial bacterial infections of the skin include impetigo, folliculitis, furunculosis, and acne.

Topical antibacterials are used to accelerate clinical cure, prevent recurrences in affected individuals and to minimize the spread of infection. They are considered more appropriate as they target only infected area and thus avoid the side effects of oral treatment and the associated drug interactions. Mupirocin and fusidic acid are the common topical antibacterial agents used for these bacterial skin infections.³ However, emergence of resistance to these commonly used agents is becoming common in clinical practice. The prevalence of such

resistance was found to be as high as 37.7% to mupirocin and 51.9% to fusidic acid in one study.⁴ The prevalence of MupRH (high-level mupirocin resistance) in India among MRSA has been found to vary between 0 and 38.46% in different studies.⁵ Therefore, other classes of topical antibacterial agents are required for the effective treatment of SSTI.

Nadifloxacin was approved in Japan since 1993 and in India as antibacterial and anti-acne topical medicine since 2002.^{6,7} Nadifloxacin acts by inhibiting the configuration of negative supercoiling of bacterial DNA, catalyzed by DNA gyrase. DNA gyrase is an enzyme present in every bacterium and is essential for DNA replication, transcription, and recombination. Inhibition of this enzyme leads to bactericidal activity of nadifloxacin.⁸

Nadifloxacin, a topical fluoroquinolone, has been shown to be effective against aerobic Gram-negative, Gram-positive (including MRSA and coagulase-negative *Staphylococci*), and anaerobic bacteria.⁸ However, there is a paucity of data comparing efficacy and safety of nadifloxacin with other antibacterials for treatment of skin infections especially in pediatric population in India. Therefore this study was carried out to evaluate the efficacy and tolerability of nadifloxacin 1% ointment vs mupirocin 1% ointment in pediatric patients with SSTI.

METHODS

Study design and participants

This was a single-centre, open label, randomized, parallel group, comparative study in children (n=60) with skin and soft tissue infection (SSTI). Study was conducted at Lifepoint Hospital, Pune, India. Patients randomized to test group (n=30) received nadifloxacin 1% ointment while those randomized to reference group (n=30) received mupirocin 1% ointment. Study was conducted in accordance with ICH-GCP and all the pertinent Confidential and Proprietary local regulations. The study was performed in accordance with the Declaration of Helsinki. The study has been registered with clinical trial registry of India (CTRI/2018/03/012411).

Subjects who met the following inclusion criteria were included in the study: 1) Male or female child <12 years of age, 2) children suffering from mild to moderate bacterial SSTI including, but not limited to, impetigo, secondarily infected wounds, folliculitis, infected atopic dermatitis or furunculosis and 3) Child's parent willing to provide written informed consent; child >5 years willing and providing assent for inclusion in study. Patients who had any of the following criteria were excluded from the study: 1) History of hypersensitivity to quinolones or mupirocin, 2) Receipt of any topical treatment at the same site within 1 week prior to study entry, 3) Receipt of any systemic antimicrobials within 1 week prior to study entry, 4) Receipt of any investigational drug within 4 weeks prior to study entry, 5) Patients with presence of any concomitant disease or health problem that

may interfere in study assessments or endanger patient safety during study treatment and 6) Any other significant illness.

Study procedure

The study comprised of screening period (visit 1), treatment period (visit 2 and 3) and follow-up period (visit 4). After baseline evaluation and laboratory investigations by investigator at visit 1 (day 1), eligible patients were randomised into test or reference group and provided medicines as described below. Randomization was done on the basis of a predetermined computer-generated randomization list.

Test group patients (n=30) received nadifloxacin ointment (twice daily) and reference group patients (n=30) received mupirocin ointment (twice daily). All patients received study drugs for 7 days and were evaluated for safety and efficacy at visit 2 (day 4±1) and visit 3 (day 8±1). If the recovery was not complete at visit 3, then same study drugs were continued and patients were evaluated at visit 4 (day 15±2). However, all patients who did not show complete recovery even on day 14 were followed up till complete recovery, but only the evaluation performed up to day 14 was considered for data analysis. During the treatment period, data pertaining to primary and secondary endpoints were evaluated and laboratory samples were collected for efficacy assessment. The maximum study duration per patient was 17 days. Safety of study drugs was assessed based on the reporting of adverse events. Parents (and children) were instructed on capturing any local adverse experience in the patient diary and assessed by the investigator for any adverse events during study visits.

Efficacy of the study drugs was evaluated by primary and secondary efficacy endpoints as described below:

Primary end-points

Clinical cure rate

Clinical features of SSTI such as erythema, exudation, swelling, pruritus, crusting, pain and tenderness were evaluated for their severity on each study visit till end of study treatment on the 4-point scale (0 - absent, 1 - mild, 2 - moderate and 3 - severe). Clinical cure was defined as absence (score of 0) for all clinical features of SSTI.

Proportion of children with clinical cure were compared between both treatment groups at each treatment visit.

Secondary end-points

Bacteriological cure

Bacterial culture was evaluated from the sample taken from SSTI site before starting the study medication and at the visit 4. Absence of the prominent bacteria, seen in

baseline culture, at the visit 4 culture was considered as bacteriological cure. Proportion of children with bacteriological cure was compared between both treatment groups at each treatment visit.

Statistical considerations

For this study, it was estimated that sample size of 30 subjects per group was sufficient between test and reference group at a significance level of 95%.

Continuous variables were summarized by treatment group using summary statistics (number of observations, mean, and standard deviation, median, minimum and maximum). Categorical values were summarized by treatment group using frequencies and percentages. These summaries were presented for the safety and per protocol populations. In this study all p values were reported based on two-sided test and these statistical tests were interpreted at 5% level of significance.

Efficacy analysis

The primary efficacy variable of proportion of children with clinical cure was compared between both treatment groups at each treatment visit by using Chi square test. Secondary efficacy variable of proportion of children with bacteriological cure was compared between both treatment group at each treatment visit by using Chi-square test.

Safety analysis

Proportion of children found to have adverse events was compared between both treatment groups.

RESULTS

Total 60 patients were enrolled in the study (30 in test and 30 in reference group) and all the patients completed the study. There were no major protocol violations which led to

withdrawal of subjects from the study. Compliance with both the study medications was found to be satisfactory.

Demographic data and baseline characteristics

Analysis of the study population stated that age of the enrolled patients was ranging from 0.40-12.00 years with average age being 6.92 years among nadifloxacin and 7.89 years among mupirocin group which was comparable ($p=0.245$). In nadifloxacin group, male:female patients were 60:40(%) and in mupirocin group 70:30(%), however, the difference was not statistically significant ($p=0.416$). Mean height and weight of the study patients was within normal limit and comparable between both groups (Table 1).

Efficacy endpoints

Primary end-points

Clinical cure rate

Although few patients had clinical cure at day 4, it was not statistically significant in both groups. At Day 8, 40.0% cases among nadifloxacin group and 36.7% cases among mupirocin group had significant change in clinical cure from baseline respectively. The change in clinical cure was numerically more in nadifloxacin group compared to mupirocin group ($p=0.790$). At Day 15, 100.0% cases among nadifloxacin group and 96.7% cases among mupirocin group achieved clinical cure, which showed no statistical difference ($p=0.313$) between two treatment groups (Table 2).

Analysis of individual parameters (erythema, exudation, swelling, pruritus, crusting, pain and tenderness)

Figure 1 and 2 show comparison of visit-wise percentage of patients with each of the individual clinical parameters between two groups.

Table 1: Demographic data and baseline characteristics.

Parameter		Nadifloxacin	Mupirocin	p value
No. of cases		N=30	N=30	
#Age (years)	Mean	06.92	7.89	0.245 (NS)
	SD	03.75	02.64	
	Range	00.40 -11.60	00.90-12.00	
@Sex (%)	Male	18 (60.0)	21 (70.0)	0.416 (NS)
	Female	12 (40.0)	09 (30.0)	
#Height (cm)	Mean	116.87	120.17	0.537 (NS)
	SD	21.60	19.49	
	Range	54.00 -142.00	56 -148.00	
#Weight (kg)	Mean	20.27	19.36	0.581 (NS)
	SD	6.64	6.08	
	Range	8 - 31.00	8.00 -36.20	

By Student t test, @ By Chi Square test, NS Not Significant

Table 2: Comparison of proportion of patients with clinical cure rate between two groups.

Clinical cure rate	Nadifloxacin (N=30)								Mupirocin (N=30)							
	Baseline		Day 4		Day 8		Day 15		Baseline		Day 4		Day 8		Day 15	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
Yes	-	-	1	3.3	*12	40.0	*30	100.0	-	-	2	6.7	*11	36.7	*29	96.7
No	30	100	29	96.7	18	60.0	-	-	30	100	28	93.3	19	63.3	1	3.3
p value			0.313(NS)		*0.001		*0.001				0.150(NS)		*0.001		*0.001	
p value (b/w groups)									(-)		0.553(NS)		0.790(NS)		0.313(NS)	

* $\leq p$ 0.05 Significant; $p > 0.05$ Not Significant **Figure 1: Comparison of percentage of patients without erythema between treatment groups.** **Figure 2: Comparison of percentage of patients without exudation between treatment groups.**

At Day 15, 100.0% cases in nadifloxacin group and 96.7% cases in mupirocin group did not have erythema, exudates, swelling and pruritus which showed a significant improvement from baseline among both the groups (Figure 1, 2, 3 and 4). When compared, there was no statistically significant difference ($p=0.313$) between

two groups for each of these parameters. Improvement in swelling and pruritus occurred as early as day 4 in both treatment groups (Figure 3 and 4). At Day 4, 33.3% cases among nadifloxacin group and 26.7% cases among mupirocin group had no swelling, while 33.3% cases among nadifloxacin group and 36.7% cases among mupirocin group had no pruritus.

Figure 3: Comparison of percentage of patients without swelling between treatment groups. **Figure 4: Comparison of percentage of patients without pruritus between treatment groups.**

Figure 5: Comparison of percentage of patients without crusting between treatment groups.

Figure 6: Comparison of percentage of patients without pain between treatment groups.

At Day 15, 100.0% cases among nadifloxacin group and 96.7% cases among mupirocin group had no crusting, pain and tenderness which showed a significant improvement from baseline in both the groups (Figure 5,

6 and 7). There was no significant difference ($p=0.313$) between two groups in terms of improvement in any of these parameters. Improvement in tenderness occurred as early as day 4, when 26.7% cases among nadifloxacin group and 23.3% cases among mupirocin group had no tenderness (Figure 7).

Figure 7: Comparison of percentage of patients without tenderness between treatment groups.

Efficacy endpoints

Secondary end-point

Bacteriological cure rate

At baseline, 15/30 and 17/30 of the cases showed a bacteriological presence in test and reference group, respectively, which was comparable (Table 3). The most common bacteria found in culture were Gram positive cocci in both the groups (86.7% in nadifloxacin group and 58.8% in mupirocin group). At Day 15, none of the cases showed a bacteriological presence among both the group which showed a significant ($p<0.001$) fall from baseline in both the groups. If compared, the change was same among both the groups and the difference was not significant.

Table 3: Comparison of percentage of cases with bacteriological cure between two groups.

Bacteriological presence	Nadifloxacin (N=15)				Mupirocin (N=17)			
	Baseline		Day 15		Baseline		Day 15	
	No.	%	No.	%	No.	%	No.	%
Yes	15	100.0	-	-	17	100.0	-	-
p value	*0.001				*0.001			

By Chi-Square Test; * $p<0.05$ Significant

Safety endpoints

No adverse event was reported in any treatment group during the study duration. As an additional safety parameter, signs and symptoms of arthropathy were

assessed by the investigator at each visit (day 4, 8 and 15), which included joint pain, reduced movement/stiffness, pain on movement, joint swelling and tenderness over joint. However, none of the patient

reported presence of these signs and symptoms in any treatment group at any visit.

DISCUSSION

Skin and soft tissue bacterial infections are common problem seen in clinical practice. Several bacterial microorganisms can infect the skin and soft tissue, but the most common agents are *S. aureus* and group A (*S. pyogenes*) *streptococci*.¹ Most SSTIs could be managed on an outpatient basis and are easily treatable. Therapeutic options include incision and drainage and/or antimicrobial therapy which may be oral, topical or occasionally parenteral. The topical antibiotics are preferred over oral or parenteral antimicrobials for a number of reasons including the ability to achieve high local drug concentrations at the site of the infection, the low incidence of systemic side effects, cost-effectiveness, patient compliance, and the potential to limit antimicrobial resistance selection among other bacteria in the body.^{9,10}

In general, the selection of topical antibiotic agent is dependent on the probable microorganism causing the infection. Mupirocin is a frequently used topical agent for treatment of SSTI.¹¹ Nadifloxacin is a highly potent quinolone antimicrobial agent developed by Otsuka Pharmaceuticals (Tokyo, Japan) with broad-spectrum activity against a wide variety of pathogenic bacterial species. Although the agent was initially investigated for oral or parenteral use as it was highly potent, its pharmacokinetic properties made it unsuitable for systemic administration. However, it was found to be very active in a 1% cream form, leading to the development of a topical formulation.^{12,13} In vitro and clinical studies have already proven the safety and efficacy of nadifloxacin in the treatment of acne vulgaris and other bacterial skin infections.¹⁴ Nadifloxacin has also been reported to be effective against bacteria, like MRSA, that have developed resistance to other available anti-microbial drugs.¹⁵

Many *in vitro* studies have assessed the activity of nadifloxacin against bacterial skin infection causing organisms. Nenoff et al. conducted an *in vitro* study that compared and assessed the activity of nadifloxacin with various other anti-bacterials against aerobic and anaerobic Gram-positive bacteria including *S. aureus*, coagulase-negative *Staphylococci* (CNS), *Streptococcus spp.*, *Propionibacterium granulosum*, and *Propionibacterium acnes* strains. The results demonstrated nadifloxacin to be highly active against all bacteria except some of the CNS strains.¹⁶

Fluoroquinolones are extensively used in adults and have proven to be highly effective and safe. However, the evidence for their use in children is less robust. Studies in juvenile animals demonstrated the development of arthropathy and damage to immature cartilage of weight-bearing joints.¹⁷ However, number of studies have shown

good safety profile in children. Levofloxacin has been studied in children with community-acquired pneumonia (CAP) and has been shown to be comparable to standard antimicrobial agents. Retrospective and prospective reviews of ciprofloxacin use in patients with cystic fibrosis have not demonstrated an increased incidence of adverse musculoskeletal events which was confirmed with the use of MRI or plain radiographic studies. Few large studies have shown a low incidence of arthralgia in children (1.5-1.8%), which were generally mild to moderate in severity, self-limiting, and often occurred in patients with cystic fibrosis. However, incidences of arthropathy can also be secondary to their underlying disease process in cystic fibrosis and therefore making it difficult to quantify drug effect. Although the safety data of nadifloxacin is available in pediatric patients (single arm and PMS studies only), comparative studies with other anti-bacterial are largely missing.^{15,17} Therefore, the present study provided the important data on clinical use of topical nadifloxacin in comparison with mupirocin in Indian pediatric population with skin and soft tissue infection (SSTI).

The results of this study showed that nadifloxacin is well tolerated and efficacious in the treatment of children with skin and soft tissue infection (SSTI). There was a significant reduction in severity for all the symptoms of bacterial infections (including erythema, crusting, exudation, swelling, pruritus, pain, and tenderness) in the nadifloxacin group as well as mupirocin group. Clinical cure rate among nadifloxacin group was found to be 100%. Further, nadifloxacin showed good efficacy against both *Staphylococci* and *Streptococci* pathogens and bacteriological cure was achieved in 100% patients. Kimata reported use of nadifloxacin cream for atopic dermatitis in children caused by MRSA and found eradication in all 18 patients treated with nadifloxacin.¹⁵ Likewise, Asada et al. reported eradication rate of 100% with nadifloxacin in single-species Gram-positive *cocci* infections and 86.9% for the multi-species infections in 78 patients treated for folliculitis and sycosis vulgaris infections. These eradication rates are similar to what is reported in this study demonstrating the good efficacy of nadifloxacin in SSTI. In this study, nadifloxacin was found to be well-tolerated and no adverse event was reported in any patient. In a study reported by Hausteiner et al, 101 patients with impetigo, secondarily infected wounds, folliculitis, sycosis vulgaris, and impetiginized dermatitis were treated with topical nadifloxacin 1% cream and only 3 adverse events were reported (itching, erythema and inflammatory swelling).¹³ The post-marketing surveillance study of nadifloxacin 1% cream, in 329 enrolled patients at 125 centres across India, reported only two AEs (burning and itching) and no serious AE was reported.

CONCLUSION

In the present study, nadifloxacin ointment was found to be equally efficacious as mupirocin ointment in providing

relief from all the symptoms of bacterial skin infections (including erythema, crusting, exudation, swelling, pruritus, pain, and tenderness) in Indian pediatric population with SSTI. Treatment with nadifloxacin ointment also resulted in complete clinical and bacteriological cure which was comparable to mupirocin ointment. None of the patient reported any adverse event with nadifloxacin and no other major safety concern was found in this study in pediatric population. Thus, nadifloxacin can be used as a promising therapeutic option for the treatment of SSTI in pediatric patients without any major safety risk.

ACKNOWLEDGEMENTS

Authors are thankful to Eupraxia Consulting for medical writing support in developing this manuscript.

Funding: Funding sources research grant from Wockhardt Ltd., India

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Janbandhu S, Chaudhary S, Chaudhary S, Puppallwar G, Jain R. An evaluation of safety and efficacy of nadifloxacin 1% ointment versus mupirocin 1% ointment in Indian children with skin and soft tissue infection. *Int J Contemp Pediatr* 2020;7:236-42.