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COMPARATIVE STUDY OF TOPICAL FUSIDIC ACID AND TOPICAL RETAPAMULIN IN IMPETIGO AT JLNMC, BHAGALPUR, BIHAR

Pharmacology

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ABSTRACT

As emergence of multi drug resistance, MRSA and resistant to existing therapies like fusidic acid and mupirocin is increasing prevalence, it is necessary to evaluate the efficacy of new drugs like retapamulin in treatment of resistant strains in impetigo. The study was conducted at Department of Pharmacology in collaboration with Department of Dermatology, and Out Patient department of JLNMCH, Bhagalpur, Bihar to compare Retapamulin ointment 1% twice daily with Fusidic acid 2% cream thrice daily for 7 days treatment of 100 impetigo patients of age group 2-60 years of either sex, divided in to two groups of 50 patients each. Number of the lesions counted, size of the lesions measured, and culture of the samples taken from the lesions done before and after treatment. Any adverse effects of the treatment were also recorded. Chi-square and student's unpaired t-test is used to evaluate the statistical significance between two drugs, with level of significance 0.05. Clinical and bacteriological efficacies are not significantly different between both the groups. In MRSA also, bacteriological efficacies are not significantly different between both the groups though Retapamulin shows complete cure bacteriologically in all MRSA patients. Fusidic acid is found to have lower incidence of adverse effects compared to Retapamulin.

KEYWORDS

Retapamulin, Fusidic acid, Impetigo, Clinical response, Bacteriological response

INTRODUCTION

Impetigo is a bacterial infection that involve the superficial skin. It is typically due to either Staphylococcus aureus or Streptococcus pyogenes. Impetigo is two types, contagious impetigo/nonbullous impetigo which is most common form of impetigo and bullous impetigo. The most common presentation is honey coloured scabs on the face, arms, or legs. Bullous there may be large blisters which affect the groin or armpits. Among children, impetigo is the most common bacterial skin infection and the third most common skin disease overall, behind dermatitis and viral warts.[1,2] Fever is uncommon. Risk factors include attending daycare, crowding, poor nutrition, diabetes, contact sports, and breaks in skin. With contact it can spread around or between people. Impetigo is usually diagnosed based on its appearance. Complications of impetigo are rare, but they can occur and occasionally be serious. Without treatment people typically get better within three weeks. Complications may include cellulitis, guttate psoriasis, Scarlet fever or post streptococcal glomerulonephritis. Rheumatic fever and Septicaemia are very rare. Globally Impetigo affected about 140 million people (2% of the population) in 2010.[3] It is most common in young children but can occur at any age. Aim of treatment include relieving discomfort and improving cosmetic appearance of lesions, preventing further spread within patient and to others, and preventing recurrence. Treatments should be effective, inexpensive, and have limited side effects. Topical antibiotics have the advantage of being applied only where needed, which minimizes systemic side effects. Topical antibiotic therapy is considered the treatment of choice for individuals with uncomplicated localized impetigo. Topical therapy eradicates isolated disease and limits the individual-to-individual spread. The topical agent is applied after removal of the infected crusts and debris with soap and water. Disadvantages of topical treatment are that it cannot eradicate organisms from the respiratory tract and that applying topical medications to extensive lesions is difficult.

The emergence of antibiotic resistance in hospital and community pathogens has significantly reduced usefulness of established antibiotics, a problem that has been widely publicized and poses a serious threat to public health. Antibiotics with novel mechanisms are needed to address tide of rising resistance to both systemic and topical agents. Resistance has developed to two of the most commonly used topical antibiotics worldwide, fusidic acid and mupirocin and thus stresses the need for topical agents with novel mechanisms to aid in treatment of bacterial skin infections. Retapamulin 1% ointment, a topical antibiotic in the pleuromutilin class, is approved by the US Food and Drug Administration(FDA) for use in adults and children older than 9 months to treat impetigo caused by methicillin-susceptible Staphylococcus aureus and Streptococcus pyogenes.[4] It is the first new topical antibiotic approved by the FDA since the release of mupirocin nearly 20 years ago.[5] It has potent activity against and, including strains that are resistant to beta-lactams, macrolides, and quinolones, as well as strains that are resistant to current topical therapies including fusidic acid and mupirocin. Based on these characteristics, Retapamulin ointment (1 percent) was formulated for human use, affording advantages of shorter treatment duration and a reduced frequency of dosing compared with other topical antibacterial therapies. This provides a complete course of therapy with twice daily dosing over five days. Shorter regimens and less frequent dosing are associated with improved patient preference, enhanced compliance, or both. This study is planned to evaluate the safety and efficacy of Retapamulin in comparison with Fusidic acid in treatment of impetigo.

AIMS AND OBJECTIVES

- As there is emergence of multidrug resistance, such as MRSA, this comparative study is undertaken to assess efficacy and safety of topical Retapamulin ointment and topical fusidic acid cream in the treatment of impetigo.
- This is a open label, prospective comparative study.
- Total 100 patients are enrolled into the study, 50 in each group.
- One group will be given Retapamulin ointment, and the other group Fusidic acid cream.
- Both groups are compared, and analysed in terms of efficacy and safety.
- Group receiving Retapamulin ointment expected to show better efficacy.

MATERIAL AND METHODS

This is an open label, prospective and parallel group study to evaluate efficacy and safety of topical Retapamulin ointment with topical fusidic acid in the treatment of impetigo. The study was conducted at Department of Pharmacology in collaboration with Department of Dermatology, and Out Patient department of Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar from October 2020 to September 2021. All the patients were screened and enrolled from the Dermatology Out Patient department of JLNMCH, Bhagalpur, Bihar.

INCLUSION CRITERIA

- Patients aged between 02 to 60 years of both genders.
- Patients local signs and symptoms of impetigo as pain or tenderness, purulent discharge, erythema with or without induration, swelling, localized warmth.
- Patients with number of lesions upto 10 or area of lesions not exceeding 100cmsq.

EXCLUSION CRITERIA

- Patients requiring hospitalization or parenteral antibiotic treatment.

- Patients with complicated acute bacterial skin and skin structure infections (ABSSSI) or with chronic or underlying skin condition at the site of infection (a secondarily infected atopic dermatitis, eczema, acne vulgaris, psoriasis or burn wounds) or infections involving prosthetic materials (e.g., catheter tunnel infections, orthopedic instruments).
- Patients with concomitant condition requiring non-study antibacterial therapy.
- Pregnant or breast feeding women.
- Patients unwilling or unable to comply with the study procedures.
- Significant systemic signs such as fever > 101^0F.
- The parameters were evaluated two times in the study, at the baseline, and at the end of seven days of treatment. The primary parameters include:
- Bacteriological cure assessed by culture of the samples taken from the lesions.
- Clinical cure defined as the approximate size of the lesions before and after treatment.
- Clinical cure defined as the number of lesions before and after treatment.
- Study of medication
- Group I: Retapamulin ointment 1% twice daily for 7 days.
- Group II: Topical fusidic acid 2% cream thrice daily for 7 days.

Number of participants: 50 per group.

METHOD

Initially the patients were screened for their eligibility into the study. As a part of screening, medical history of the patients was taken, physical examination, and clinical examination are done. The patients were seen two times in the study, at the baseline, and at the end of one week of treatment. General, physical and systemic examination was done and patients were enquired for incidence of adverse effects. Wound size area was determined by measuring the greatest length of the wound in two perpendicular dimensions with a standard metric ruler. The two measurements were multiplied together to provide an estimate of the overall wound size. Surrounding erythema was not included in the measurement. Collection of specimen intact pustules were cleaned with spirit and then ruptured with a sterile needle. Pus was expressed and collected on to two sterile cotton swabs. In crusted lesions, normal saline was used to clean the wound. Two swabs were rubbed over the pus or the edge of the ulcer. The swabs were then immediately transported to the microbiology laboratory for further processing. Microbiological examination of pus from the first swab was used to prepare smears and was stained by Gram's Method. The pus from the second swab was inoculated on blood agar and McConkey's agar. The culture plates were inoculated at 37°C for 24-48 hours, aerobically. Methicillin resistance was detected using oxacillin. The strains having minimum inhibitory concentration (MIC) > 4 mcg/ml for oxacillin were considered MRSA.

STATISTICALANALYSIS

All the data was presented as mean, standard deviation, and percentages of efficacies. Chi-square and student's (unpaired) t test is used to evaluate the statistical significance between two drugs. $P < 0.05$ is considered as significant.

RESULTS

Table 1 : Age distribution of patients among two groups

Age in years	Group I (Retapamulin)		Group II(Fusidic Acid)	
	No. of patients	Percentage	No. of patients	Percentage
2-10	18	36%	21	42%
11-20	16	32%	14	28%
21-30	9	18%	8	16%
31-40	5	10%	5	10%
41-60	2	4%	2	4%

Table 2 : Gender distribution among two groups

Sex	Group I (Retapamulin)		Group II(Fusidic Acid)	
	No. of patients	Percentage	No. of patients	Percentage
Male	27	54%	28	56%
Female	23	46%	22	44%

Table 3 : Presence of impetigo lesions

Area	Group I (Retapamulin)		Group II(Fusidic Acid)	
	Non-Bullous (68%)	Bullous (32%)	Non-Bullous (72%)	Bullous (28%)
Face	68	34	78	26
Arms	50	25	54	20
Legs	28	10	22	13
Trunk	8	29	6	18

Table 4 : Bacteriological response in study groups

No. of patients	Group I (Retapamulin)		Group II(Fusidic Acid)		P-value
	At Baseline	At One week	At Baseline	At One week	
S. Aureus	68	34	78	26	>0.05
S. Pyogenes	50	25	54	20	
Both	28	10	22	13	

p value >0.05 is not significant, is calculated using chi square test.

Table 5 : Clinical efficacy of retapamulin and fusidic acid by baseline pathogen

Pathogen	Group I	Group II
Staphylococcus aureus	94.2%	91.1%
Streptococcus pyogenes	89.5%	82.4%

n/N : No. of clinical successes/ number of pathogens isolated at baseline

Table 6 : Clinical response in study groups

No. of patients	Group I	Group II	P-value
Cured (Absence of Lesions)	47	46	>0.05
Not Cured (Presence of Lesions)	3	4	
Efficacy (%)	94%	92%	

p value >0.05 is not significant, is calculated using chi square test.
n/N: No. of Clinical successes / total no. of patients.

Table 7 : Bacteriological response of retapamulin and fusidic acid in MRSA patients

No. of patients	Group I	Group II	P-value
At Baseline	10	11	>0.05
At One week	0	1	
% Efficacy	100	90	

p value >0.05 is not significant, is calculated using chi square test.

(n/N: No .of bacteriological successes / No. of patients with MRSA pathogens identified at baseline)

Table 8 : Clinical response of retapamulin and fusidic acid

No. of patients	Group I	Group II	P-value
At Baseline	10	11	>0.05
At One week	1	2	
% Efficacy	90	81.8	

p value >0.05 is not significant, is calculated using chi sqaure test.

(n/N: No. of clinical successes/Total no. of patients with MRSA at base line)

Table 9 : Comparison of mean wound area between two groups

Wound Area	Group I	Group II	P-value
At Baseline	3.65±1.33	3.40±0.91	>0.05
At One week	0.24±0.97	0.35±1.20	

p value >0.05 is not significant, is calculated using unpaired t -test.

Table 10 : Incidence of adverse events in study groups

Adverse Event	Group I (Retapamulin)		Group II(Fusidic Acid)	
	Number	Percentage	Number	Percentage
Application site irritation	4	57.14%	3	75.00%
Headache	1	14.29%	0	0.00%
Diarrhoea	1	14.29%	0	0.00%
Pyrexia	1	14.29%	1	25.00%

DISCUSSION

Most data on the effectiveness of topical antibiotics focus on bacitracin, fusidic acid, and mupirocin.Retapamulin 1% ointment, a topical antibiotic in the pleuromutilin class, is approved by the US Food and Drug Administration(FDA) for use in adults and children older than 9 months to treat impetigo caused by methicillin-susceptible Staphylococcus aureus and Streptococcus pyogenes.[4] A 2003 meta-

analysis of 16 studies (1944 patients)evaluated treatments for impetigo in both adults and children.[6] Investigators conducted most of the studies in outpatient settings in the United States, United Kingdom, Northern Europe, and Canada. They expressed outcomes in terms of cure or clinical improvement within 7 to 14 days of starting treatment. Topical agents, including mupirocin, fusidic acid, and gentamicin, resulted in cure or improvement in more patients at 7 to 14 days than placebo. Definitions of cure or improvement varied among the included studies, however a 2012 Cochrane review of various interventions included 68 RCTs with a total of 5708participants, primarily from paediatric or dermatology hospital outpatient clinics in North America and Europe.[7] (Clinical cure defined as clearance of crusts, blisters, and redness as determined by investigators) or improvement at one week were the primary outcomes Mupirocin, fusidic acid, and Retapamulin all demonstrated higher rates of cure or improvement than placebo. Patients in the age group of 2 to 60 years are included in the study. Majority of the patients in group I are in age group between 2 to 10 years. 18 (36%) patients are in the age group of 2 to 10 years. 16 (32%) patients are in the age group of 11 to 20 years, 9 (18%) patients are in the age group of 21 to 30 years, 5 patients (10%) are in the age group of 31 to 40 years, and 2 (4%) patients are in the age group of 41 to 60 years.

Majority of the patients in Group II comprised of age group 2 to 10 years. 21 (42%) patients are in the age group of 2 to 10 years. 14 (28%) patients are in the age group of 11 to 20 years. 8 (16%) patients are in the age group of 21 to 30 years. 5 (10%) patients are in the age group of 31 to 40 years. 2 (4%) patients are in the age group of 41 to 60 years. In B.R.Bohaty et al. study, clinical and bacteriological efficacy of twice daily topical retapamulin ointment 1% in the management of impetigo and other uncomplicated superficial skin infections. Prospective, nonrandomized, uncontrolled, open label, single center trial conducted between April 2008 and November 2012 that evaluated efficacy of retapamulin ointment 1%, the proportion of patients aged below 18 years was 73.7%, and the proportion of those aged ≥ 18 years was 26.3%.[8] In Rortviet et al. study, impetigo is a superficial skin infection caused by bacteria and has been shown to be most common infection in children worldwide.[9] Chopra and colleagues reported increased incidence in the paediatric age group, attributing it to poorly developed epidermal barrier in children.[10] In this study, 69 % of patients are below 20 years, and 31% are above 20 years, results are consistent with previous studies. Patients of different age groups and with a small sample size makes it difficulty in concluding regarding the effect of age on clinical, microbiologic responses. In Pihu Sethi et al. a study on community associated Staphylococcus aureus and its susceptibility pattern to Mupirocin and Fusidic acid in primary pyoderma patients in India, males (72%) outnumbered females (28%).[11] In this study group I included 50 patients of which 23 (46%) are females and 27 (54%) are males. Group II included 50 patients of which 22 (44%) are females and 28 (56%) are males which is comparable to previous study. In Vinit Gupta et al. Clinicoepidemiological study of vesiculobullous disorders in paediatric age group, face is affected in 50% of patients, and 19% in lower limbs in impetigo.[12] In both the groups the Non-Bullous lesions were common and the face was the most common area for their development. In retapamulin group the total number of lesions was 215 in number and non-bullous lesions were 68% and bullous lesions were 32% and the areas that the lesions were seen most commonly in face followed by arms, trunk and legs. In Fusidic acid group the total number of lesions were 213 in number and non-bullous lesions were 72% and bullous lesions were 28% and the areas that the lesions were seen most commonly in face followed by arms, trunk and legs. Comparing to nonbullous lesions, more number of lesions noticed on trunk are bullous lesions. In this study, in 48 patients of group I, 47 patients of group II baseline pathogens identified. In both the groups the most common organism cultured at baseline is, Staphylococcus aureus ,and staphylococcus aureus is cultured in 29 patients in group 1 (Retapamulin) and 30 patients in group II (Fusidic acid), followed by Streptococcus pyogenes 13 patients in group and 13 patients in group II and both Streptococcus pyogenes, and Staphylococcus aureus were cultured in 6 patients group I and 4 patients in group II. At the end of treatment (day 7) Staphylococcus aureus cultured 1 in each group , streptococcus pyogenes cultured in 1 patient in each group, both pathogens cultured in 1 patient in group I and 2 patients in group II. In Koning S, Vanden woudenJC, Chosidow O et al. study, a placebo-controlled, randomized, double-blind trial of retapamulin, 213 patients are evaluated and at least one pathogen was isolated at baseline in 82% of subjects in each treatment group. S. aureus was the most frequently isolated pathogen, with an incidence rate of 65% in the retapamulin group and 64% in the placebo group. S. pyogenes was present in 28% of patients in the retapamulin group and 23% in the placebo group. Approximately 24% of subjects in each group had two or more pathogens isolated at baseline, the majority with both S. aureus and S. pyogenes.[13] In Oranje A, Chosidow O, Sacchidanand S et al. study, Retapamulin was also compared with fusidic acid for the treatment of impetigo in a randomized, observer-blinded, non inferiority, Phase III study, which compared the efficacy and safety of retapamulin ointment 1%, twice daily for 5 days, with topical fusidic aid ointment 2%, three-times daily for 7 days. Overall, 76.2% in each treatment group had at least one pathogen isolated at screening. S. aureus was the most frequently isolated pathogen, with an incidence rate of 65.3% in the retapamulin group and 63.8% in the fusidic acid. S. pyogenes was present in 27.5% of subjects in the retapamulin group and 23.2% in the fusidic acid group.[14] In this study, in 96% of group I patients and 94% of group II patients at least one pathogen is isolated. Over all, incidence rate of S.aureus in group I is 60.4%, in group II 63.8%. S. pyogenes is present in 27.1% of patients in group I, 27.8% in group II and both the pathogens are isolated in 12.5% in group I, 8.5% in group II. These results are comparable to previous study.

In Mc Neal et al. (2014), study of S. aureus isolates from skin and soft tissue infections in children found that 9.5% of the screened isolates exhibited retapamulin resistance, of which 57.9% were MRSA (McNeal et al., 2014).[21] In this study sensitivity for retapamulin is not seen. In this study, clinical response may be different across MRSA and MSSA but the difference is not significant between the groups. In B.R. Bohaty et al. study mean wound area is 14.43 with standard deviation of 25.38 at baseline, and at follow up of 1 week mean wound area is 4.31% with standard deviation of 17.71% in retapamulin group. And mean change % is 71.35 in retapamulin group.[8] In this study, total wound area at base line in group I is 182.4 cm2 and 171.1 cm^2 in group II. Total wound area at the end of therapy (day 7) is 12.1 cm2in group I and 17.4 cm2in group II. Mean wound area of 3.65 with standard deviation of 1.33 at base line decreased to mean wound area of 0.24 with standard deviation 0.97 after treatment in group I. Mean wound area of 3.40 with standard deviation of 0.91 at base line decreased to mean wound area of 0.35 with standard deviation 1.20 after treatment in group II. There is no statistical significant difference between the two groups.

In this study clinical and bacteriological efficacies are not significantly different between both the groups. In MRSA also and bacteriological efficacies are not significantly different between both the groups though retapamulin shows complete cure bacteriologically in all MRSA patients. Most of the studies are done in other primary pyodermas and skin and soft tissues bacterial infections along with impetigo. Only few studies are done with new topical retapamulin drug, thus limiting the availability of data. However, retapamulin is new promising drug for the treatment of multidrug resistant bacteria causing superficial skin and soft tissue infections.

CONCLUSION

In this study, per pathogen bacteriological success rates are 94.2% for S.Aureus and 89.5% for S.Pyogenes in group I and 91.1% for S. aureus and 82.4% for S. pyogenes in group II. There is no statistically significant difference between two groups in treating patients, although retapamulin shows better bacteriological success. Retapamulin is showing 94% of clinical efficacy compared to 92 % clinical efficacy of fusidic acid. There is no statistical significant difference between two groups. Clinical success rate is 90% in group I and 81.8% in group II . Bacteriological success rate is 100% in group I and 90% in group II . There is no statistical significant difference between two groups. All the adverse events observed in both groups were mild and these resolved within 24 hours after they appeared. In group I, 7 patients with adverse events are reported and 4 patients with adverse events are reported in group II. In this study clinical and bacteriological efficacies are not significantly different between both the groups. In MRSA also and bacteriological efficacies are not significantly different between both the groups though retapamulin shows complete cure bacteriologically in all MRSA patients. The results of this study are just a small step to a better understanding of the applicability of retapamulin. Hence, recommendation in future studies with variety of measurement outcome should be included.

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