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Original Research Article

A randomized open label parallel group study comparing the safety, effectiveness and adherence between 2% fusidic acid cream versus 1% retapamulin ointment in children with impetigo

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ABSTRACT

Background: Impetigo is a contagious bacterial skin infection that affects both adults and children. Topical antibacterials such as mupirocin and fusidic acid are the most commonly used in both primary and secondary impetigo. Clinical trials have shown high efficacy of retapamulin in the treatment of secondary impetigo. However, its use in primary impetigo is limited. To this purpose, we compared the safety, efficacy and adherence to treatment of fusidic acid with retapamulin in primary impetigo.

Methods: A total of 50 patients with a clinical diagnosis of primary impetigo, between 2-12 years of age, having <10 lesions, 3/5 signs and symptoms, skin infection rating score ≥4 and pus score ≥ one were involved. Patients who were having secondary impetigo leions were excluded. Twenty-five patients received 2% fusidic acid cream three times a day, and the remaining 25 patients received 1% retapamulin ointment two times a day for seven days. Skin Infection Rating Scale (SIRS) was used to assess the severity of disease at baseline and end of treatment. Clinical success was considered when SIRS score of zero each for pus, crust and pain and 0/1 each for erythema and itching. Clinical failure is a SIRS score of ≥1 for pus.

Results: Baseline disease characteristics such as a number of lesions, the severity of disease (SIRS) and pus scores were statistically similar between the two groups. The clinical improvement observed with both fusidic acid and Retapamulin (20/25, 80%) and (21/25, 84%) treatments was not statistically different ($p>0.05$). Both drugs were well tolerated.

Conclusions: Both fusidic and retapamulin showed similar clinical success in patients with primary impetigo. Since fusidic acid has anti-inflammatory property and its treatment is cost-effective, it can be considered as first-line treatment and retapamulin in fusidic acid-resistant impetigo.

Keywords: Adherence, Fusidic acid, Infection rating scale, Retapamulin, Secondary impetigo, Skin

INTRODUCTION

Impetigo is a contagious bacterial skin infection that affects both adults and children.[1] Impetigo is primary which occurs as a result of the direct bacterial invasion of previously normal skin, in particular by Staphylococcus aureus and Streptococcus pyogenes, or more commonly as secondary when the underlying skin disease such as eczema is infected.[2] Impetigo can be a clinically significant problem, as the untreated disease can persist and spread causing local outbreaks. Also, the streptococcal disease may have serious long-term sequelae, such as

glomerulonephritis.[3] In general practice, it is considered the third most common dermatological condition diagnosed among children between the ages of 6 and 11 years.[1] Impetigo is believed to be associated with a high spontaneous cure rate. The rate of resolution for placebo arms in controlled studies varies (clinical cure rates from 13 to 52% have been reported.[4] Topical antibacterials such as mupirocin and fusidic acid are commonly used to accelerate clinical cure, thereby preventing recurrences in infected individuals and minimising the spread of infection to others.[5]

Also, a more rapid clinical cure will mean that affected children miss less schooling and do not have to be withdrawn from child care in an attempt to limit the spread of infection. Topical agents may be considered more appropriate than oral/systemic antibacterials for the treatment of impetigo, at least for localised disease (involvement of 5-10 lesions) as the beneficial nonpathogenic bacteria in the digestive tract, are unaffected by topical treatment. The common adverse events associated with oral antibacterial therapy including nausea, vomiting and diarrhoea may be avoided by using topical agents.[5]

Moreover, there is a reduced risk of drug-drug interactions when using a topical antibacterial, compared with a systemic, oral antibacterial agent.[5] Retapamulin ointment, 1%, is a novel, semisynthetic member of the pleuromutilin class of antibacterials, appears to be a promising drug for treatment of impetigo and other SITLs resulting due to *S.* aureus and *S. pyogenes*.[6] The drug with its novel site of action, topical formulation, and shorter duration of action and less frequent dosing will help to ensure compliance and also prevent the development of resistance to antibacterial agents. The drug is safe and has poor systemic absorption. Retapamulin is a convenient and safe therapeutic option for the treatment of impetigo and SITLs for all age groups including children.[7] *In vitro*, retapamulin has excellent activity against *S. aureus* and *S. pyogene*s and has limited potential for resistance development.[8-10] Retapamulin was significantly more effective than placebo in inducing the clinical response in subjects with secondary impetigo of pediatric and adult subjects.[5] Plain fusidic acid cream or ointment used two or three times daily in SSTIs such as impetigo are clinically and bacteriologically effective, with minimal adverse events. Development of resistance to fusidic acid has remained generally low or short-lived and can be minimised by restricting therapy to no more than 14 days at a time.

Moreover, it is the empirical therapy, prescribed for impetigo and cost-effective.[11] A study showed that topical fusidic acid and mupirocin in staphylococcal skin infections had shown little difference in clinical outcome.[12] To this purpose, we compared the safety, effectiveness and adherence to treatment of fusidic acid with retapamulin in primary impetigo in a randomised open-label parallel group study.

METHODS

The study was conducted at Narayana medical college in collaboration with the department of dermatology. Included patients were patients with a clinical diagnosis of primary impetigo, between 2-12 years of age, afebrile, Impetigo lesions <10,3/5 signs and symptoms, skin infection rating score ≥4 and pus score ≥1 (Table 1) and patients or their parent/legal guardian willing and able to comply with the protocol. Patients were excluded if they were, patients aged <2 years and >12 years, impetigo lesions >10 at baseline, having secondary impetigo, or having a history of hypersensitivity to fusidic acid or retapamulin, or using systemic antibiotic or systemic corticosteroid within one week before baseline , use of topical corticosteroid, topical antibiotic, or topical antifungal within 48hours before baseline and use of any other topical products (including antibacterial soaps) applied on or near the affected area of impetigo.

Table 1: Skin infection rating scale.

Item	Category	Score	Scale
1	Erythema	0	Absent
		1	Minimal
		2	Moderate
		3	Severe
2	Pus	0	Absent
		1	Minimal
		2	Moderate
		3	Severe
3	Crusting	0	Absent
		1	Minimal
		2	Moderate
		3	Severe
4	Pain	0	Absent
		1	Minimal
		2	Moderate
		3	Severe
5	Itching	0	Absent
		1	Minimal
		2	Moderate
		3	Severe

Study procedures

In the first visit, patients were screened for study enrollment after taking informed consent by the guardian. Eligible patients were randomised either to topical fusidic acid cream or retapamulin and began treatment all on the same day. Patients received either 2% fusidic acid cream three times a day for seven days or 1% retapamulin ointment two times a day for seven days. First, follow up was seven days after treatment with either fusidic acid or retapamulin. Second, follow up was done for those patients who did not have a successful clinical response at first follow-up on day-14. Safety was determined by either patient spontaneously reported adverse reactions or adverse findings by the physicians. Compliance to

treatment was assessed by the number of missed topical applications and patient who has completed 80% of treatment was considered as compliant.

Measurement of clinical outcomes

Skin Infection Rating Scale (SIRS) was used to assess the severity of disease at baseline and the end of treatment and day-14 follow-up. SIRS evaluate 5 Signs and symptoms: pus, crust, erythema, itching, and pain on a scale (0-3): 0= absent, 1 = mild, 2 = moderate, 3 = severe.

Clinical success was determined by sufficient resolution of signs and symptoms of infection of the target lesion such that no additional antimicrobial therapy is required to treat the impetigo, as evidenced by the SIRS score of zero each for pus, crust and pain and 0/1 each for erythema and itching. Clinical improvement was determined by a SIRS score of zero for exudate/pus which does not meet all the criteria for clinical success. Clinical failure is a SIRS score of ≥1 for pus.

Statistical analysis

Data were collected in a preformed case record form; data was then entered into Microsoft Excel spreadsheet 2016, then it was cleaned for typographical errors, duplicate entry and records were homogenised for further statistical analysis. Statistics were performed using IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp. Tabulations of results were made, data were presented as mean standard deviation and actual numbers and percentages. Chi-square test was used to draw inferences between two groups on categorical data and unpaired t-test and repeated measures ANOVA was used to draw inferences on continuous data. A two tailed p value less than 0.05 was used for significance testing.

RESULTS

A total of fifty patients participated in this study, 25 patients received 2% fusidic acid cream, and 25 patients received 1% retapamulin ointment as shown in Figure 1. The mean age of the patients was 6.0±2 years. The skin infection rating scores were shown in Table 2 and Figure 2. There were 23/50 (46%) female and 27/50 (54%) male children. 2/50 (4%) were dropped out of the study, the reason for dropout is lost to follow-up. We observed that 41/50 (82%) of patients had the clinical success of treatment (Figure 3), which is defined as a reduction in pus, crust and pain of skin infection rating scale to zero from the baseline value as. 7/50 (14%) of our patients experienced treatment failure after seven days. These patients were given oral cephalexin for five days along with topical therapy.

All these initial clinical failure patients had complete resolution of signs and symptoms after oral antibiotic therapy. None of our patients had any complications or treatment-related adverse events. There were no clinical recurrences in any treatment groups. Only 2/50 (4%) were missed topical applications of treatment and were considered as non-compliant as shown in Table 3.

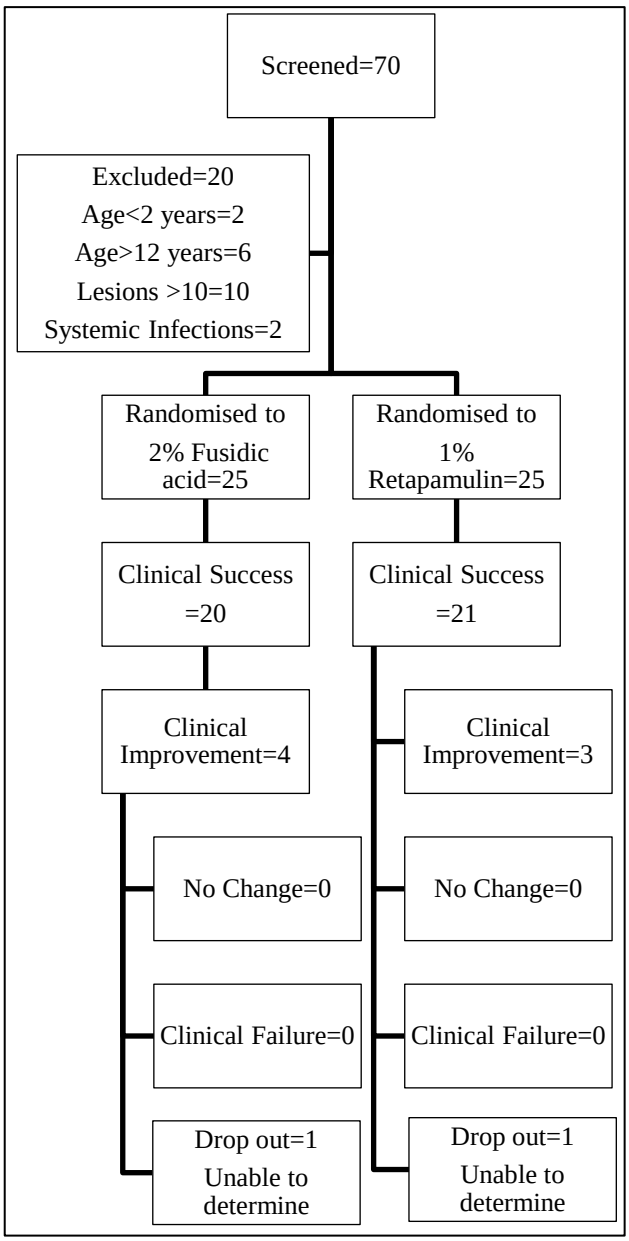

Figure 1: Consort diagram showing patient flow through the clinical study.

When we compared the clinical symptoms and signs before and after the treatments between the two groups, we found that the number of skin lesions, SIRS, pus score and pain scores (Figure 2) are statistically (P>0.05) similar between the fusidic acid and retapamulin treatments (Table 4).

We also noticed that the clinical success, safety and compliance were similar (P>0.05) between the two groups (Table 5). The number of non-responders (clinical failures) to treatments was more with fusidic acid as compared to retapamulin groups at the end of treatment.

Table 2: Clinical characteristics of all patients with primary impetigo.

All patients	Count	Mean	SD	Median	Range
Age	50	6	2	6	9
Treatment Duration	50	7	0	7	0
Number of lesions at baseline	50	5	2	5	6
Number of lesions at end	50	0	1	0	3
SIRS at baseline	50	7	3	7	12
SIRS at end	50	1	2	1	7
Pus Score at baseline	50	2	1	2	3
Pus Score at baseline	50	0	0	0	1
Pain Score at baseline	50	1	1	1	3
Pain Score at end	50	0	0	0	1

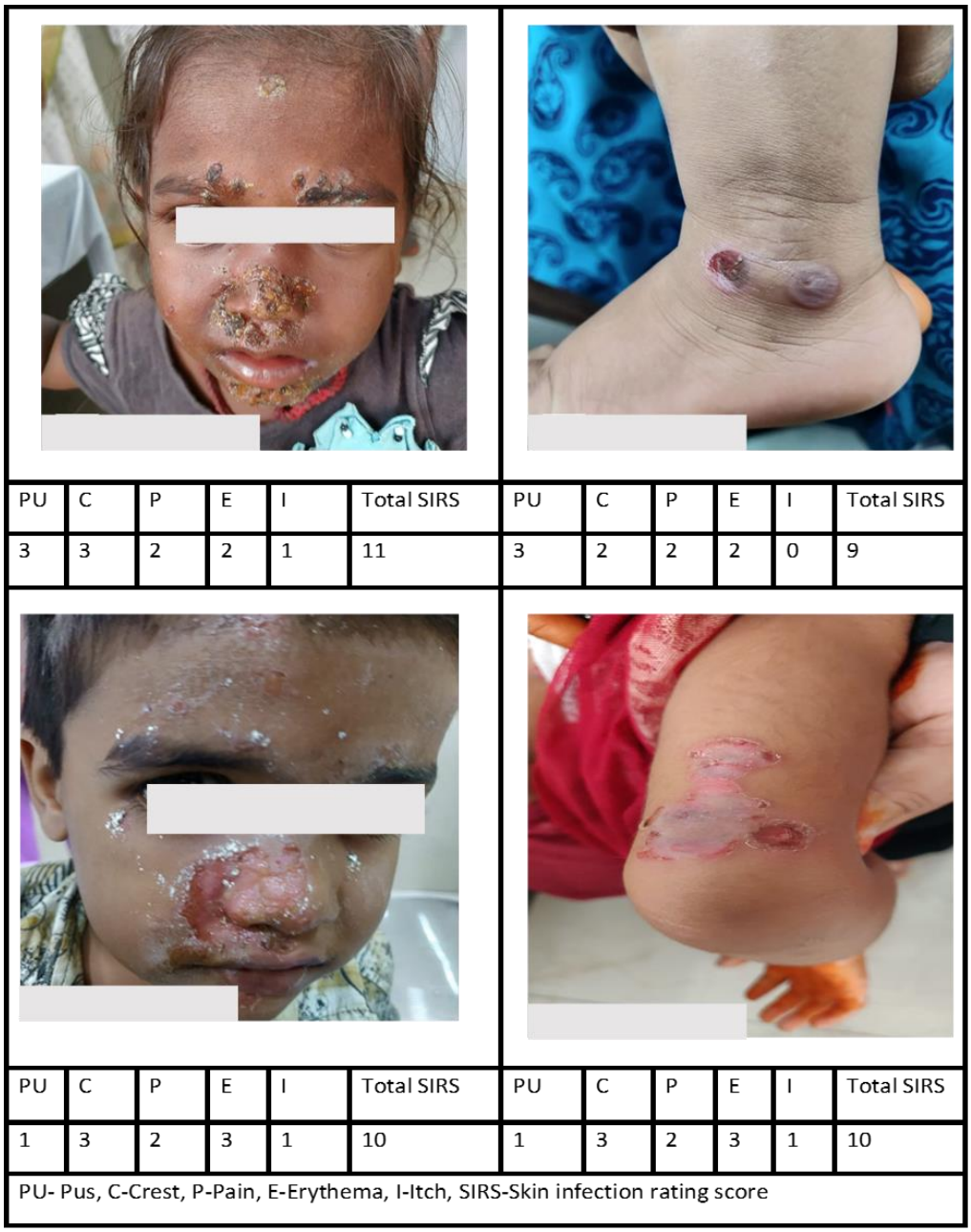

Figure 2: The individual symptoms, and signs of impetigo infection measured on skin infection rating scale.

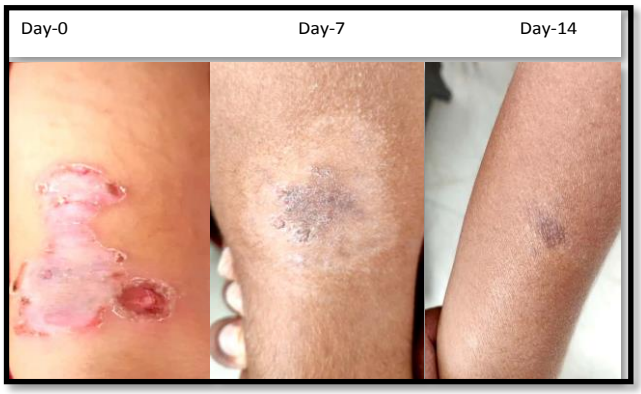

Figure 3: The healing status of impetigo lesions after treatment.

Table 3: Clinical outcomes of all patients with primary impetigo.

All patients		n	%
Gender	Female	23	46.00%
	Male	27	54.00%
	Total	50	100.00%
Clinical Success	Drop Out	2	4.00%
	No	7	14.00%
	Yes	41	82.00%
	Total	50	100.00%
Compliance	No	2	4.00%
	Yes	48	96.00%
	Total	50	100.00%

Table 4: Comparison of clinical characteristics of patients between 2% fusidic acid cream and 1% retapamulin ointment.

	2% Fusidic acid		1% Retapamulin		P value
Age	6±2	6	7±3	8	<0.05
Number of lesions at baseline	5±1	5	4±2	5	>0.05
Number of lesions at end of treatment	0±1	0	0±1	0	>0.05
SIRS at baseline	7±3	7	7±3	7	>0.05
SIRS at end	1±2	1	1±2	1	>0.05
Pus Score at baseline	2±1	2	2±1	2	>0.05
Pus Score at end	0±0	0	0±0	0	>0.05
Pain Score at baseline	3±1	2	2±1	1	>0.05
Pain Score at end	0±0	0	0±0	0	>0.05

Table 5: Comparison of Clinical outcomes of patients between 2% fusidic acid cream and 1% retapamulin ointment.

	2% Fusidic acid		1% Retapamulin		P value
Gender					
Female	12	48.00%	11	44.00%	>0.05
Male	13	52.00%	14	56.00%	
Total	25	100.00%	25	100.00%	
Clinical Success					
Drop out	1	4.00%	1	4.00%	>0.05
No	4	16.00%	3	12.00%	
Yes	20	80.00%	21	84.00%	
Total	25	100.00%	25	100.00%	
Compliance					
No	1	4.00%	1	4.00%	>0.05
Yes	24	96.00%	24	96.00%	
Total	25	100.00%	25	100.00%	

DISCUSSION

Impetigo is a highly contagious superficial bacterial infection of the skin that affects mostly children. Most cases are caused by *Staphylococcus aureus*, *Streptococcus pyogenes*, or a mixture of both organisms. The most commonly used topical antibacterials are mupirocin and fusidic acid, and meta-analysis shows that there is no difference between their efficacy.[7] Retapamulin is indicated for impetigo and mild secondary skin infections arising from lacerations, abrasions, sutured wounds, psoriasis or dermatitis.[13] We compared the safety and effectiveness of retapamulin versus fusidic acid in a total of 50 patients with a clinical diagnosis of primary impetigo, between 2-12 years of age, having <10 lesions, 3/5 signs and symptoms, skin infection rating score ≥4 and pus score≥ 1. Clinical success was defined as drying up

(without crusts) or resolution of the lesion by the end of seven days of treatment.

Fusidic acid is a unique member of the fusidane class of steroid antibiotics, that has a time-tested safety, used topically in acute bacterial skin and skin structure infections where staphylococci are the predominant pathogens.[14] They have good penetration into the cutaneous surface and high concentration at the site of infection.

Till 2002 the effectiveness of fusidic acid has never been assessed in comparison with placebo. However, a recent study showed that the proportion of children cured clinically at one week was 55% in the fusidic acid cream group and 13% in the placebo group. [15] In our study, we also found that the efficacy at the end of 7 days of treatment with fusidic acid was 80%, one patient dropped out of the study, and the remaining patients received oral cephalexin for five days along with topical therapy.

Retapamulin is a novel pleuromutilin group of antibiotics which has an excellent spectrum of activity and appears to be a promising drug for impetigo. Clinical cure of impetigo with retapamulin is well defined when compared with placebo. The success rate was 85.6% as compared to 52.1% in placebo.[16] To date, there is only one study comparing retapamulin and Fusidic acid, showing no statistical differences between the two products for the treatment of impetigo.[13] Our study has also found similar success rates on a comparison between these two treatments. We observed that the magnitude of success was lower than this study. The possible reasons for the lower magnitude of success could be narrow inclusion criteria such as children under 12 years of age. Noncompliance is more common in school going children, and improper application of topical antibacterial might also have influenced the outcome.

Around 14% of our patients experienced treatment failure after seven days. These patients were given oral cephalexin for five days along with topical therapy. All these initial clinical failure patients had complete resolution of signs and symptoms after oral antibiotic therapy. The possible reasons for clinical failure include, Site of the lesion on face or limbs may affect the treatment response as it may hamper the time of contact of antibiotic with the lesion and procedure of topical application-before application, lesion crusts should be removed by soaking in soapy water - providing this does not cause discomfort. This allows the antibiotic to come into direct contact with the bacteria rather than being wasted on inert, dry, exfoliating skin. It is also possible that alcohol-based antiseptics can also exacerbate skin dryness and fissures.[17] None of our patients had experienced any complications since all our patients had non-bullous lesions and lower SIRS scores at presentation.

Ours is a single centre study with a small group of the pediatric population, with lower SIRS scores and treatment outcomes were measured on subjective factors such as erythema, purulence, crusting, oedema, and pain. Observer-blinding could have eliminated variability in the quantification of response. However, it was not feasible due to practical reasons. The microbiologic response was also not evaluated due to financial reasons.

CONCLUSION

In our study, we observed that both fusidic acid and retapamulin had statistically similar success rates in the treatment of non-bullous impetigo. Since fusidic acid has additional anti-inflammatory property and its treatment is cost-effective, it has to be considered as first-line treatment and retapamulin in fusidic acid-resistant impetigo.

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