Comparative Study of Topical Fusidic Acid and Topical Retapamulin in Impetigo

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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. An open label, prospective, parallel group study was conducted in outpatient department of Dermatology in Osmania General Hospital 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 into 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 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

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**I. 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.

1.1 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.

II. Patients 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.

2.1 Source of data

The study was conducted at Department of Pharmacology in collaboration with Department of Dermatology, and Out Patient clinics of Osmania General Hospital.

The study was started after getting written approval from Osmania Medical College Institutional Ethics Committee.

2.2 Study period

The study period was from October 2015 to September 2016.

All the patients were screened and enrolled from the Dermatology Out Patient clinics of Osmania General Hospital Hyderabad.

2.3 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.

2.4 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 °F.

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.

2.5 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.

2.6 Number of participants: 50 per group.

2.7 Informed consent process
Written informed consent was taken from all the patients who are above 18 years of age, before taking them into the study. For patients above 12 years of age, written consent along with either of the parent was taken, for taking part in the study. For children aged between 8 to 12 years oral consent was taken from the child and written consent from either of the parent for taking part in the study. For children aged below 2 years and below 8 years written informed consent was taken from both the parents before participation into the study.

III. Methodology
The present study was conducted as a prospective, open label, in subjects diagnosed with impetigo, patients screening and recruitment was carried out at the out-patient Department of Dermatology in Osmania General Hospital. The study was initiated after obtaining approval from the Osmania Medical College Institutional Ethics Committee.

Written informed consent for participating in the study has been taken from the patients. They were explained in detail the study procedure. 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.

3.1 Statistical analysis
The statistical analysis was carried out with GraphPad prism 7 Software. 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.

IV. Observations And Results

<table>
<thead>
<tr>
<th>S.No</th>
<th>Age</th>
<th>Group I (Retapamulin)</th>
<th>Group II (Fusidic Acid)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>%</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>1</td>
<td>2 to 10 yrs</td>
<td>18</td>
<td>36%</td>
</tr>
<tr>
<td>2</td>
<td>11 to 20 yrs</td>
<td>16</td>
<td>32%</td>
</tr>
<tr>
<td>3</td>
<td>21 to 30 yrs</td>
<td>9</td>
<td>18%</td>
</tr>
<tr>
<td>4</td>
<td>31 to 40 yrs</td>
<td>5</td>
<td>10%</td>
</tr>
<tr>
<td>5</td>
<td>41 to 60 yrs</td>
<td>2</td>
<td>4%</td>
</tr>
</tbody>
</table>
Comparative Study of Topical Fusidic Acid and Topical Retapamulin in Impetigo

Figure 1: Age distribution of patients among two groups

Table 2: Gender distribution among two groups

<table>
<thead>
<tr>
<th></th>
<th>Group I (Retapamulin)</th>
<th>Group II (Fusidic Acid)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
<td>22</td>
</tr>
</tbody>
</table>

Figure 2: Gender distribution in group I (Retapamulin)

Figure 3: Gender distribution in group II (Fusidic Acid)
Table 3: Presence of impetigo lesions

<table>
<thead>
<tr>
<th>Area</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-Bullous (68%)</td>
<td>Bullous (32%)</td>
</tr>
<tr>
<td>Face</td>
<td>68</td>
<td>34</td>
</tr>
<tr>
<td>Arms</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>Legs</td>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td>Trunk</td>
<td>8</td>
<td>29</td>
</tr>
</tbody>
</table>

Table 4: Bacteriological response in study groups

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Group I</th>
<th>Group II</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At Base Line</td>
<td>At One Week</td>
<td>At Base Line</td>
</tr>
<tr>
<td>S.Aureus</td>
<td>29</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>S.Pyogenes</td>
<td>13</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Both</td>
<td>6</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

Note: 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

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.Aureus</td>
<td>94.2%</td>
<td>91.1%</td>
</tr>
<tr>
<td>S.Pyogenes</td>
<td>89.5%</td>
<td>82.4%</td>
</tr>
</tbody>
</table>

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

Table 6: Clinical response in study groups

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Group - I</th>
<th>Group - II</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured (Absence of Lesions)</td>
<td>47</td>
<td>46</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Not Cured (Presence of Lesions)</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Efficacy (%)</td>
<td>94%</td>
<td>92%</td>
<td></td>
</tr>
</tbody>
</table>

Note: p value >0.05 is not significant, is calculated using chi square test.
Comparative Study of Topical Fusidic Acid and Topical Retapamulin in Impetigo

Figure 6: Clinical success rate of retapamulin and fusidic acid in study groups

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

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Group I</th>
<th>Group II</th>
<th>P &gt; 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Base Line</td>
<td>10</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>At One Week</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>% Efficacy</td>
<td>100</td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>

p value >0.05 is not significant, calculated using chi square test.
(n/N: No. of bacteriological successes / No. of patients with MRSA pathogens identified at base line)

Table 8: Clinical response of retapamulin and fusidic acid

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Group I</th>
<th>Group II</th>
<th>P &gt; 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Base Line</td>
<td>10</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>At One Week</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>% Efficacy</td>
<td>90</td>
<td>81.8</td>
<td></td>
</tr>
</tbody>
</table>

p value >0.05 is not significant, calculated using chi square test.
(n/N: No. of clinical successes / Total no. of patients with MRSA at base line)

Figure 7: Clinical and bacteriological success rate of retapamulin and fusidic acid in MRSA patients

Table 9: Comparison of mean wound area between two groups

<table>
<thead>
<tr>
<th>Wound Area</th>
<th>Group I</th>
<th>Group II</th>
<th>P &gt; 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Base Line</td>
<td>3.65 ± 1.33</td>
<td>3.40 ± 0.91</td>
<td></td>
</tr>
<tr>
<td>At One Week</td>
<td>0.24 ± 0.97</td>
<td>0.35 ± 1.20</td>
<td></td>
</tr>
</tbody>
</table>

p value >0.05 is not significant, calculated using unpaired t-test.
Comparative Study of Topical Fusidic Acid and Topical Retapamulin in Impetigo

V. 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 5708 participants, primarily from pediatric 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. 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.
Comparative Study of Topical Fusidic Acid and Topical Retapamulin in Impetigo

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 difficult 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 was 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 I (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 Koning S, Vanden woudenJC, Chosidow O et al. study, clinical efficacy by baseline pathogen was calculated as total number of clinical success by total number patients with baseline pathogens isolated, and per pathogen bacteriological success are 88.4% for S.Aureus and 88.2% for streptococcus pyogenes in retapamulin, and 52.9% for S.aureus, 37.5% for S.pyogenes in placebo group.[13]

In Oranje A, Chosidow O, Sacchidanand S et al. study, clinical efficacy by baseline pathogen was calculated as total number of clinical success by total number patients with baseline pathogens isolated, and per pathogen bacteriological success are 99.1% for S.aureus and 97.8% for streptococcus pyogenes in retapamulin, and 92.8% for S.aureus, 88.9% for S.Pyogenes in fusidic acid.[14]
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. In this study per pathogen bacteriological success rates are consistent with the previous studies.

In Koning S, Vanden woudenJC, Chosidow O et al. study, retapamulin ointment 1%, twice daily for 5 days, was significantly more effective than placebo in inducing clinical response (clinical success rates of 85.6% [119 out of 139] versus 52.1% [37 out of 71] for placebo in the intent-to-treat [ITT] population at end of therapy [day 7]; p < 0.0001). At follow-up (day 14), the clinical success rate (ITT population) was 75.5% for retapamulin and 39.4% for placebo (p < 0.0001).[13]

In Oranje A, Chosidow O, Sacchidanand S et al. study, the efficacy of retapamulin ointment and fusidic acid in the per-protocol clinical (PPC) population at the end of therapy was similar. Retapamulin treatment was associated with a clinical success rate of 99.1% (314 out of 317), compared with 94.0% (141 out of 150) for fusidic acid.[14] In group I, 47 patients out of 50 completely cured (absence of lesions) and 3 patients are not cured (presence of lesions). In group II, 46 patients out of 50 are completely cured (absence of lesions) and 4 patients are not cured (presence of lesions). Retapamulin is showing 94% of clinical efficacy compared to 92% clinical efficacy of fusidic acid. There is no statistical significant difference between two groups. In this study per pathogen bacteriological success rates are consistent with the previous studies.

In B.R. Bohaty et al. in his study, efficacy of topical retapamulin in the management of impetigo and other uncomplicated superficial skin infections, is evaluated. MRSA is isolated in 7 patients out of 38 patients enrolled into the study contributing to 19.4% of total pathogens isolated in the study at base line and MSSA isolated in 52.8% of the total patients.[8]

In the same study clinical response for MRSA was 71.4% and bacteriological response was 100% in retapamulin. In this study out of 50 patients in each group, MRSA (Methicillin-resistant Staphylococcus aureus) identified in 10 patients in group I, 11 patients in group II. In this study, clinical success rate is 90% in group I (Retapamulin) and 81.8% in group II (Fusidic Acid). Bacteriological success rate is 100% in group I (Retapamulin) and 90% in group II (Fusidic Acid). There is no statistical significant difference between two groups though retapamulin shows better clinical and bacteriological success rates than fusidic acid.

Studies reported by Senthilkumar[15] and Venniyil et al.[16] from south India with prevalence of MRSA of 46% and 78%, respectively.

In Pihu Sethi et al. study conducted in primary pyoderma patients, prevalence of MRSA was 39.5%. MRSA was seen to be more common in southern part of India than in the west (20.33%) or north (18.88%).[17] In this study, out of total baseline S.aureus pathogens, 28.6% of MRSA is isolated in group I and 32.3% in group II. In this study, overall 30.4% of MRSA is isolated at baseline. These results are comparable to previous studies. The reason for the difference in prevalence in various parts of the country could be the different strains of S. aureus causing the disease. The generous use of antibiotics in current times could be the cause for the increased rate.[18]

Gorwitz et al. (2008), recent study of multiple centers throughout the United Stated found that MRSA was the cause of 78% of the staphylococcal-related infections of the cutaneous and soft tissues.[19]

Orange et al. (2007) have reported an increasing resistance of MRSA isolates to common topical agents such as mupirocin and sodium fusidate.[14]
In Rennie et al. (1999- 2005) study, of the 2302 S. aureus strains tested, 65 (2.8%) were resistant to fusidic acid; 240 (10.4%) were methicillin-resistant (MRSA), of which 10 (4.2%) were resistant to fusidic acid.[20]
In this study sensitivity for fusidic acid is not done, but 3 patients are not responded in this study for fusidic acid. Data is insufficient to comment on fusidic acid resistance. Clinical data on retapamulin resistance is incomplete.

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 cm$^2$ and 171.1 cm$^2$ in group II. Total wound area at the end of therapy (day 7) is 12.1 cm$^2$ in group I and 17.4 cm$^2$ in 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.

A study by Koning et al. in 2002 examined the effect of twice-daily povidone-iodine shampoo with either fusidic acid cream or placebo cream applied 3 times daily for up to 14 days in the treatment of impetigo. Treatment with fusidic acid cream plus povidone-iodine shampoo was found to be more effective than the placebo cream/povidone-iodine combination, with the size of the affected area in the placebo group actually increasing in size after one week of treatment. Interestingly, at treatment week 2, the percentage reduction in size was 90% for the fusidic acid group and 38% for the placebo combination group. However, at follow-up at week 4, the percentage reduction was comparable for both groups, 99% for the fusidic acid group and 95% for the placebo group, probably representing the natural course of resolution of the disease.[22]

In this study, percentage reduction in wound size is 93.7% in group I and 89.8% in group II at the end of therapy, which is comparable to the previous study.

Topical antibiotics have the advantage of being applied only where needed, minimizing antibiotic resistance and avoiding gastrointestinal and other systemic adverse effects.[7,23] The length of time of topical treatment varies based on product, but in clinical trials, a seven-day course was more effective than placebo for resolution of impetigo.[6,7]

Three topical antibiotic preparations recommended for impetigo are mupirocin 2% cream or ointment, Retapamulin 1% ointment, and fusidic acid. Empiric treatment considerations have changed with the increasing prevalence of antibiotic-resistant bacteria. Methicillin-resistant S. aureus (MRSA), macrolide-resistant streptococcus, and mupirocin-resistant streptococcus are now documented.[5,24] Retapamulin is a novel pleuromutilin antibacterial and the first new topical antibacterial in nearly 20 years.[5]

Retapamulin is registered as a 1% ointment for the short-term topical treatment of uncomplicated superficial bacterial skin and skin structure infections caused by S. aureus and methicillin sensitive S. pyogenes in primary impetigo, secondarily infected traumatic lesions and secondarily infected dermatoses in patients older than nine months of age.[7] Retapamulin is effective against Gram-positive organisms, including S. aureus, S. pyogenes, S. agalactiae, β-haemolytic streptococci, S. Viridans, coagulase-negative staphylococci and some Gram-negative organisms.[25] Retapamulin has been shown to be more effective than clindamycin, ceftriaxone and metronidazole against bacteroides fragilis, Clostridium perfringes and propionibacterium acnes; all anaerobes.[7] Retapamulin is only indicated for the treatment of methicillin-sensitive strains of S. aureus (not methicillin-resistant S. aureus).[13] Pathogens that are resistant to antibacterial classes, such as clindamycin, are still susceptible to Retapamulin, despite the existence of some cross resistance.[13]

In Koning S, Vanden woundenJC, Chosidow O et al. study, there was a similar rate of overall adverse events between retapamulin (24.5% [34 out of 139]) and placebo (25.4% [18 out of 71]). Pruritus at the application site was the most common treatment-related adverse event, which was reported by nine (6.5%) patients in the retapamulin group and one (1.4%) patient in the placebo group.[13]

DOI: 10.9790/0853-1809060821 www.iosrjournals.org 17 | Page
In Oranje A, Chosidow O, Sacchidanand S et al. study, a similar proportion of subjects in each treatment group reported at least one adverse event (retapamulin: 16.2% [56 out of 345]; fusidic acid: 14.5% [25 out of 172]).

The most common adverse effect associated with retapamulin administration in children enrolled in clinical trials was application site irritation (1.9% of patients). Other adverse effects, reported in similar rates in both Retapamulin and control subjects, included application site pruritis (1.9%), diarrhea (1.7%), nasopharyngitis (1.5%), headache (1.2%), pyrexia (1.2%), and eczema (1%). In adults who received retapamulin during clinical trials, headache was the most frequently reported adverse effect, occurring in 2% of patients. Retapamulin treatment has not been seen to be associated with any major side effects. The most common treatment related adverse effect noted was application site irritation.[26]

There have been few reports of patients developing contact dermatitis secondary to application of retapamulin; however, in all these patients the dermatitis responded to discontinuation of retapamulin.[27]

In this study, 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.

Most common adverse event reported is application site irritation in both the groups. In group I, application site irritation is seen in 4 patients i.e., 57.14% of total adverse events reported, headache is seen in 1 patient i.e., 14.29% of total adverse events reported, diarrhea is seen in 1 patient i.e., 14.29% of total adverse events reported, and pyrexia is seen in 1 patient i.e., 14.29% of total adverse events reported. In group II, application site irritation is seen in 3 patients i.e., 75% of total adverse events reported, and pyrexia is seen in 1 patient i.e., 25% of total adverse events reported.

In Koning S, van Suijlekom-Smit LW, Nouwen JL, et al. study fusidic acid cream in the treatment of impetigo in general practice, adverse effects observed in this double blind placebo controlled are pain, redness, burning, itching at the application site of cream.[22]

Among adverse events, higher incidence was noted among those treated with cephalexin and placebo while the sodium fusidate had the lowest incidence of symptoms.

Overall incidence of adverse events shows retapamulin was well tolerated and safe for those patients in clinical trials and most adverse reactions were of mild to moderate severity. Relative lower incidence of any adverse events was found among patients with impetigo or with secondary skin infections treated with retapamulin than treated with other treatment; however this was not statistically significant. Noteworthy to mention is that there were no serious and fatal adverse events among patients treated in the trials included.

In Oranje A, Chosidow O, Sacchidanand S et al. study, most subjects in both treatment groups were compliant with the dosing regimen. Only one subject (0.3%) in the retapamulin group used less than 80% of the prescribed doses of study medication, compared with seven (4.1%) in the fusidic acid group.[14]

In group I, 4 patients did not turn up after 3 days of treatment out of which 3 patients did not give any reason for not participating in the study and 1 patient was withdrawn from the study because of the adverse event.

In group II, 3 patients did not turn up after 4 days of treatment out of which 3 patients did not give any reason for not participating in the study and 1 patient was withdrawn from the study because of the adverse event.

Most patients in both the treatment groups were compliant with the dosing regimen. In group I, 98% compliance is seen and in group II 97% compliance is seen.

Retapamulin has also been found to be non-inferior to fusidic acid in a large multicentric non-inferiority blinded RCT with similar clinical and bacteriological response rates: retapamulin (99.1%, 99.2%) and fusidic acid (94%, 93%).[14] There have been no comparative clinical studies with any other topical antibiotic such as mupirocin. When compared to a placebo in a double blind randomized trial. Retapamulin was found to be superior (success rate 85.6% vs. 52.1%).[13]

Although, no statistically significant difference were noted among the trials, the direction of beneficial effect in the clinical success favours those patients treated with Retapamulin. Thus, the effect of Retapamulin is superior against placebo but not with sodium fusidate. The population profile particularly the age have may also affected the heterogeneity.

One study included paediatric patients while the others have adults. Sample size may also have effects.

Earlier evidences came from case series, where as randomized control trials are started at 1994, which has clearly stated that FA is as effective as other oral antibiotics in skin and soft tissue infections along with similar or greater tolerability.[28]
Bacteriological efficacy, which is defined as eradication of the pre treatment pathogen or no swab being taken at the end of the treatment because no pathological material was present.

A Cochrane review revealed that, topical FA is equally or more effective than oral antibiotics for impetigo patients.[29]

It was applied over skin, three times per day in pyoderma. Fusidic Acid has similar clinical and bacteriological efficacies compared with other drugs.

In Jackson et al. (1966), response rate was 100% in fusidic acid impetigo treatment.[30]

In Cassels-Brown et al. (1981), comparative study of fusidic acid and neomycin bacitracin cream done, response rate was 100% in fusidic acid group and 90% in neomycin bacitracin cream impetigo treatment.[31]

In Morley and Munot et al. (1988), comparison of topical fusidic acid and mupirocin done in impetigo, response rate was 88% in fusidic acid group and 84% in mupirocin group respectively in impetigo treatment. In these studies, fusidic acid ointment is as effective as mupirocin ointment and patients considered it is more acceptable because of greasiness of the mupirocin ointment.[32]

In Christensen, Anehus et al. (1994), comparison of fusidic acid and hydrogen peroxide done in impetigo, response rate was 82% in fusidic acid group and 72% in hydrogen peroxide cream group impetigo treatment.[33]

In Koning et al. (2002), response rate was 87% in fusidic acid group and 59% in placebo cream with povidone-iodine group in impetigo treatment in comparison of both these drugs.[22]

From above studies it can be understood that response rate was decreased for fusidic acid over the time period, could be due to raising prevalence of fusidic acid resistance as one of the causes.

In this study, 92% clinical efficacy of fusidic acid is seen, which is consistent with the previous studies.

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.

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 pyoderma 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.

VI. 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.
6.1 Strengths of the study
- Culture and sensitivity of the samples are done to get the better results.
- Study of a new topical antibiotic Retapamulin for the treatment of the MRSA causing impetigo.

6.2 Limitations
- Limited source of data with the same measurement outcome, as retapamulin is a new drug.
- Inclusion criteria included only lesions less than 10, not included widespread disease.
- High heterogeneity of data as it included age group between 2-60 years.
- A complete pharmaco-economic analysis, including direct costs were not done since the subjects could not recall their expenses and loss of earnings
- Sensitivity for fusidic acid and mupirocin resistance of the pathogens not done, if they were done results would have been more accurate.

6.3 Recommendations
- Study should be carried out with bigger sample size for the results to be more accurate.
- As retapamulin is a new drug more studies comparing with oral antibiotics are recommended.
- As retapamulin is a new drug studies comparing with topical preparations like mupirocin are recommended.
- Study of retapamulin for extensive disease of impetigo, as it is now approved for 100 cmsq of area of the lesions.
- Study of retapamulin for other skin and soft tissue bacterial infections.
- Study of retapamulin with natural therapies combination, non antibiotic therapies can also be focused.
- Studies evaluating the treatment of widespread impetigo as a primary objective are limited. So it is recommended to researchers to focus on this area.

References
Comparative Study of Topical Fusidic Acid and Topical Retapamulin in Impetigo


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