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RESEARCH ARTICLE

A meta-analysis of randomized controlled trials comparing various topical anti-bacterial, anti-fungal & steroid products alone and in combinations with biopolymer and without biopolymer in skin infection conditions

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Abstract

Objective- To compare the safety, efficacy and tolerability of topical antibiotic/steroid preparations with biopolymer versus reference products without biopolymer in human population.

Materials and Methods- The data of seven different clinical studies conducted at different centers of India was obtained from the sponsor Apex Laboratories Private Limited, Chennai (India). All the data was pooled mainly into two categories- Apex products with biopolymer and Reference products without biopolymer. Further the meta-analysis was done for each study assessment scales used in the studies.

Results- Apex products with biopolymer was found to be significant for Visual analogue scale, Signs and symptoms score, Global score index, Physician global evaluation score, Patient's compliance score, Percentage wound contraction and Overall rating in comparison with Reference products without biopolymer. At the end of treatment, bacterial/fungal culture examination report was negative in 97.18%, 94.20% of patients who had been treated with Apex products with biopolymer and reference products without biopolymer respectively.

Conclusion- The present study revealed that Apex products with biopolymer was more effective than Reference products without biopolymer in achieving clinical improvement or resolution of skin infection conditions.

INTRODUCTION

Skin and soft tissue bacterial infections are one of the most common issues with ambulatory care visits totaling approximately 14.2 million in 2005 [1]. Most infections can be treated outpatient although physicians should be on alert for signs and symptoms of more severe infections. Therefore, clinical assessment of the severity of the infection, diagnosis, and knowledge of pathogen-specific antibiotic resistance is important [2].

Several bacterial microorganisms can infect the skin and soft tissue, but the most common agents are *S. aureus* and group A (*S. pyogenes*) streptococci [3,4]. The management of skin infections lends itself to more direct or topical therapy for a number of reasons, including the ability to achieve high local drug concentrations at the site of infection, the low incidence of systemic side effects due to low or no absorption, the ability to combine several agents to empirically treat a range of potential cutaneous pathogens, cost-effectiveness , patient compliance and the potential to limit anti-microbial resistance selection among other bacteria in the body compared with oral or parenteral antimicrobials [5].

Many drugs have limited efficacy because of sub-optimal pharmacokinetics and advances in drug delivery are needed to improve the pharmacokinetics of such drug. Hence biopolymer based drugs may play an important

role in development of drug formulations as they have specific advantages. It is most probably the better pharmacokinetics of the biopolymers that gives them an advantage over the conventional preparations. Hence a study was planned to compare the safety, efficacy and tolerability of topical antibiotic/steroid preparations with biopolymer of Apex Laboratories Pvt. Ltd, Vs. Reference products without biopolymer among all the patients who underwent for seven different trials conducted at Quest Life Sciences, Chennai/Kasturba Medical college hospital, Mangalore and sponsored by Apex Laboratories Pvt. Ltd, Chennai (India).

MATERIAL AND METHODS

The data of seven different clinical studies conducted at different centers of India was obtained from the sponsor Apex Laboratories Private Limited, Chennai (India). All the data was pooled mainly into two categories- Apex products with biopolymer and Reference products without biopolymer. We extracted the baseline and visit 3 data of each parameter used in the above studies and the difference between baseline and visit 3 score was entered in Microsoft Office Excel 2007 with respect to their corresponding group in addition to baseline and visit 3 scores. Further the meta-analysis was done for each study assessment scales used in the following studies:

1. Monotherapy of anti-fungal products (with biopolymer and without biopolymer)
    - Clotrimazole 1% w/w Cream (Apex) Vs Candid (Clotrimazole 1%w/w) Cream of Glenmark Pharmaceuticals Ltd.
    - Terbinafine hydrochloride 1% w/w Cream (Apex) Vs Lamisil (Terbinafine hydrochloride 1% w/w) Cream of Novartis Consumer Health.
    - Miconazole nitrate 2% w/w Cream (Apex) Vs Daktarin (Miconazole nitrate 2% w/w) Gel of Janssen-cilag Pharmaceuticals.

2. Monotherapy of anti-bacterial products (with biopolymer and without biopolymer)
    - Sofinox (Sodium Fusidate equivalent to Fusidic acid 2% w/w) Cream (Apex) Vs Fucidin (Fusidic acid 2% w/w) Cream of Leo laboratories Ltd.
    - Sofinox (Sodium Fusidate equivalent to Fusidic acid 2% w/w) Cream (Apex) Vs Soframycin (Framycetin sulphate 1% w/w) Cream of Sanofi-Aventis Pharma Ltd.
    - Sofinox (Sodium Fusidate equivalent to Fusidic acid 2% w/w) Cream (Apex) Vs Bactroban (Calcium Mupirocin 2% w/w) Cream of Glaxosmithkline Pharmaceuticals Ltd.

3. Topical monotherapy of steroidal products (with biopolymer and without biopolymer)
    - Clobetasol propionate 0.05% w/w Cream (Apex) Vs Tenovate (Clobetasol propionate 0.05% w/w) Cream of Glaxosmithkline Pharmaceuticals Ltd
    - Fluticasone propionate 0.05% w/w Cream (Apex) Vs Flutivate (Fluticasone propionate 0.05% w/w) Cream of Glaxosmithkline Pharmaceuticals Ltd
    - Betamethasone dipropionate 0.05% w/w Cream (Apex) Vs Betamil (Betamethasone dipropionate 0.05% w/w) Cream of Merck Ltd.
    - Betamethasone valerate 0.1% w/w Cream (Apex) Vs Betnovate (Betamethasone valerate 0.1% w/w) Cream of Glaxosmithkline pharmaceuticals Ltd.

4. Combination therapy of steroid + anti-bacterial (with biopolymer and without biopolymer)
    - Clobetasol propionate 0.05% w/w + Sodium Fusidate equivalent to Fusidic acid 2% w/w Cream (Apex) Vs Clonate-F (Clobetasol propionate 0.05% w/w + Fusidic acid 2% w/w) Cream of H & H Pharmaceutical Pvt. Ltd
    - Betamethsone valerate 0.1% w/w + Neomycin sulphate 0.5 % w/w Cream (Apex) Vs Betnovate-N (Betamethsone valerate 0.1% w/w + Neomycin sulphate 0.5 % w/w) Cream of Glaxosmithkline Pharmaceutical Ltd
    - Betamethsone valerate 0.1% w/w + Sodium Fusidate equivalent to Fusidic acid 2% w/w Cream (Apex) Vs Fucibet (Betamethasone valerate 0.1% w/w + Fusidic acid 2% w/w) Cream of Ranbaxy Laboratories Ltd.
    - Mometasone Furoate 0.1%w/w + Sodium Fusidate equivalent to Fusidic acid 2% w/w Cream (Apex) Vs HH Fudic (Mometasone Furoate 0.1% w/w + Fusidic acid 2%w/w) Cream of H & H Pharmaceutical Pvt. Ltd.

5. Combination therapy of steroid + anti-fungal (with biopolymer and without biopolymer)
    - Clobetasol propionate 0.05% w/w + Miconazole nitrate 2% w/w Cream (Apex) Vs Tenovate-M (Clobetasol propionate 0.05% w/w + Miconazole nitrate 2% w/w) Cream of Glaxosmithkline Pharmaceutical Ltd.
    - Beclomethasone dipropionate 0.025% w/w + Clotrimazole 1% w/w Cream (Apex) Vs Candid-B (Beclomethasone dipropionate 0.025% w/w + Clotrimazole 1% w/w) Cream of Glenmark pharmaceuticals Ltd.

6. Anti-bacterial combinations
    - Sodium Fusidate equivalent to Fusidic acid 2% w/w + Polymyxin B sulphate USP 5000 units Gel (Apex) Vs Silverex AV (Silver sulfadiazine 1 % w/w + Chlorhexidine gluconate 0.2% w/w and Aloe Vera gel 15% w/w) Cream of Rexcin pharmaceuticals Pvt. Ltd
    - Benzalkonium chloride solution 0.02% w/w + Cetrimide 0.2% w/w Cream (Apex) Vs Drapolene (Benzalkonium chloride solution 0.02% w/w + Cetrimide 0.2% w/w) Cream of Glaxosmithkline Pharmaceutical Ltd.

7. Triple drugs combinations
    - Clobetasol propionate 0.05% w/w + Sodium Fusidate equivalent to Fusidic acid 2% w/w + Miconazole nitrate 2% w/w Cream (Apex) Vs Cutiderm (Clobetasol propionate 0.05% w/w +Fusidic acid 2% w/w + Miconazole nitrate 2% w/w) Cream of Alkem Laboratory Ltd.

Study Assessments

The following scales and parameters were used in the above studies:

Visual Analogue Scale (VAS)

It was done for the assessment of pruritus by the patient. It ranges from 1 to 10, 1 being the lowest and 10 the maximum.

Visual analogue scale: 1-2-3-4-5-6-7-8-9-10 for pruritus

Signs & Symptoms Score (SSS)

Signs and symptoms were individually scored using below scale and then added together to determine the signs and symptoms score.

Signs: Erythema, Edema or Excoriation.

Scoring scale: 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe

Symptoms: Itching, Burning or Irritation.

Scoring scale: 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe

Physician Global Evaluation Score (PGES)

The overall evaluation was summarized on a five point scale on visit 1, visit 2 and visit 3.

Score: Excellent – 05, Good – 04, No change – 03, Poor – 02, Worse – 01

Global Score Index (GSI)

It is a static evaluation of overall severity of eczema at a given time. It consists of a six point scale, ranging from totally clear (0) to very severe dermatitis (5). This allows rapid overall evaluation of the disease. The scale was used to assess the severity of eczema during the screening period and on subsequent visits.

0- Normal, clear skin with no evidence of eczema
1- Skin is almost clear
2- Mild eczematous skin
3- Moderate eczema
4- Severe eczematous dermatitis
5- Very severe eczematous dermatitis

Patient's Compliance

Patients were asked for itching/irritation/pain in the wound area on visit 1, visit 2 and visit 3. The score was given based on the opinion of the patients and it is given based on the following:

0= Absent, 1= Mild, 2= Moderate, 3= Severe

Percentage Wound Contraction (PWC)

Percentage wound contraction was calculated by using the below mentioned formula and it was done in visit 1, visit 2 and visit 3.

$$\text{Percentage of wound contraction} = \frac{\text{Initial wound size} - \text{Specified day wound size}}{\text{Initial wound size}} \times 100$$

Wound Re-Epithelization Score (WRS)
Wound re-epithelization was measured and recorded on visit 1, visit 2 and visit 3 by the following score:
(Very slow– 1, Slow– 2, Moderate– 3, Rapid– 4).

Rash Site Score (RSS)
Severity of diaper rashes was evaluated using the following categorical scale:

0- None
1- Mild Erythema with minimal maceration and/or chafing
2- Moderate erythema with or without satellite papules with maceration
3- Severe erythema with papulopustules and maceration
4- Extreme erythema with erosion or ulceration

Overall Rating (OAR)
The investigator assigned and overall rating of each subject's clinical response on visit 1, visit 2, and visit 3 using following categories:

1- Cured
2- Improved
3- Unchanged
4- Worse
5- Recurred

Psoriasis Area Severity Indexes (PASI)
Based on the severity of Psoriasis, the scores were given. Higher the score will be indicating more severity.

Bacterial/Fungal Culture Skin Swab Test
Skin swab was taken from each patient first at screening from an open, excoriated or crusted infected eczema lesion to determine bacteria and medication sensitivities. The skin was swabbed with a sterile swab stick and packed in a sterile container, and then the swab was incubated in a laboratory to see which bacteria are growing and which antibiotic they were sensitive to. The same was repeated on visit 3 to check for abolition or decrease in bacterial counts.

Table 1- Sample size & Study assessment parameters for each study category

Study category	No. of patients	Scales used for study assessment
1	57	VAS, PGE, SSS, Culture examination
2	80	VAS, PGE, PCS, WCS, WRS, Culture examination
3	80	VAS, PGE, GSI, PCS, Culture examination
4	122	VAS, PGE, GSI, PCS, WCS, WRS, Culture examination
5	40	VAS, SSS, PGE, GSI, PCS, PASI, Culture examination
6	46	VAS, PGE, GSI, PCS, RSS, OAR, WCS. WRS, Culture examination
7	20	VAS, SSS, PGE, GSI, PCS, WCS, WRS, Culture examination
Total number of patients included in all the seven categories = 445		

Statistical Analysis
Using SPSS 16.0, normally distributed data were expressed as Mean ± Standard error of mean, and analyzed by one way analysis of variance (ANOVA). The non-uniform data were expressed as Median and Quartile (Q_1, Q_3) and further data analysis was done by non-parametric two independent samples test followed by Mann-Whitney U test. P-value less than 0.05 were considered as statistically significant.

RESULTS

Overall, Apex products with biopolymer were found to be significant in Visual analogue scale, Signs and symptoms score, Global score index, Physician global evaluation score, Patient's compliance score, Percentage wound contraction and Overall rating in comparison with reference products without biopolymer. At the end of treatment,

bacterial/fungal culture examination report was negative in 97.18%, 94.20% of patients who had been treated with Apex products with biopolymer and reference products without biopolymer respectively.

Table 2- Visual Analogue Scale (VAS): Baseline score-Visit 3 score

Groups	Dose	N	Mean±SEM
I	Products with Biopolymer	221	4.96±0.13***
II	Products without Biopolymer	224	4.27±0.11

***p<0.001- significant compared to products without polymer, N- Sample size, SEM- Standard error of mean

Table 3- Global Score Index (GSI): Baseline score-Visit 3 score

Groups	Dose	N	Mean±SEM
I	Products with Biopolymer	141	2.56±0.09***
II	Products without Biopolymer	111	1.94±0.07

***p<0.001- significant compared to products without polymer, N- Sample size, SEM- Standard error of mean

Table 4- Patient Compliance Score (PCS): Baseline score-Visit 3 score

Groups	Dose	N	Mean±SEM
I	Products with Biopolymer	182	2.47±0.05***
II	Products without Biopolymer	184	2.08±0.05

***p<0.001- significant compared to products without polymer, N- Sample size, SEM- Standard error of mean

Table 5- Rash Site Score (RSS): Baseline score-Visit 3 score

Groups	Dose	N	Mean±SEM
I	Products with Biopolymer	10	2.10±0.17$^{\$}$
II	Products without Biopolymer	10	2.10±0.10

$^{\$}$p>0.05- not significant compared to products without polymer, N- Sample size, SEM- Standard error of mean

Table 6- Physician Global Evaluation Score (PGES): Visit 3 score-Baseline score

Groups	Dose	N	Mean±SEM
I	Products with Biopolymer	181	3.64±0.04***
II	Products without Biopolymer	182	3.08±0.05

***p<0.001- significant compared to products without polymer, N- Sample size, SEM- Standard error of mean**

Table 7- Signs & Symptoms Score (SSS): Baseline score-Visit 3 score

Groups	Dose	N	Mean±SEM
I	Products with Biopolymer	58	4.32±0.14***
II	Products without Biopolymer	59	2.84±0.21

***p<0.001- significant compared to products without polymer, N- Sample size, SEM- Standard error of mean**

Table 8- Percentage of Wound contraction (PWC): Visit 3 %-Baseline %

Groups	Dose	N	Mean±SEM
I	Products with Biopolymer	59	82.83±3.91**
II	Products without Biopolymer	62	69.74±3.73

****p<0.01- significant compared to products without polymer, N- Sample size, SEM- Standard error of mean**

Table 9- Wound Re-epithelization Score (WRS): Visit 3 score-Baseline score

Groups	Dose	N	Mean±SEM
I	Products with Biopolymer	64	2.42±0.12$
II	Products without Biopolymer	62	2.33±0.11

$p>0.05- not significant compared to products without polymer, N- Sample size, SEM- Standard error of mean

Table 10- Overall Rating (OAR): Baseline score-Visit 3 score

Groups	Dose	N	Mean±SEM
I	Products with Biopolymer	10	3.00±0.00*
II	Products without Biopolymer	10	2.60±0.16

***p<0.05- significant compared to products without polymer, N- Sample size, SEM- Standard error of mean**

Table 11- Psoriasis Area & Severity Index (PASI): Baseline score-Visit 3 score

Groups	Dose	N	Median (Q_1, Q_3)
I	Products with Biopolymer	10	1.00 (1.00, 1.00)$
II	Products without Biopolymer	10	2.00 (2.00, 2.00)

$p>0.05- not significant compared to products without polymer, N- Sample size, Q- Quartile

DISCUSSION

The present study demonstrated that Apex products with biopolymer are more effective than reference products without biopolymer in achieving clinical improvement or resolution of skin infection conditions. This could have implications for practice, as Apex products with biopolymer are likely to have a better safety and efficacy profile than reference products without biopolymer and may achieve better compliance with treatment. The studies in this meta-analysis were selected because inclusion was based on clinical diagnosis, making its findings directly applicable to routine clinical practice. There is a lack of high quality evidence on the most effectiveness of Apex products with biopolymer in individual study categories, might be due to less number of samples in each scale used in the study. Clinical heterogeneity between studies made meta-analysis difficult. Recent advances in the field of biomaterials and their medical applications indicate the significance and potential of various microbial polysaccharides in the development of novel classes of medical materials [6]. Biopolymers seems to be an emerging area in the field of dermatological diseases particularly because of many efforts have been devoted in recent years to explore new skin substitutes and modern wound dressing materials using tissue engineering approaches [6]. Advances in drug delivery can improve the pharmacokinetics of promising drugs for many diseases and biopolymers have great potential for delivery of pharmaceuticals [7].

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