

A DOUBLE BLIND RANDOMIZED PILOT CLINICAL TRIAL COMPARING THE SAFETY, TOLERABILITY AND EFFICACY OF COMBINATION OF TOPICAL SODIUM FUSIDATE AND BETAMETHASONE VALERATE IN BIOPOLYMER VERSUS COMBINATION OF FUSIDIC ACID AND BETAMETHASONE VALERATE IN THE TREATMENT OF INFECTED ECZEMA.

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ABSTRACT : Background: Eczema or dermatitis is a reaction pattern of the skin manifesting as itching, inflammation, redness, and swelling of the skin. There is currently no cure for eczema, but the condition can be controlled with a good treatment plan and newer strategies in formulation of existing drug can improve efficacy and acceptability.

Aims: To evaluate the efficacy, tolerability and safety of topical Sodium Fusidate and Betamethasone Valerate in biopolymer Versus Combination of Fusidic acid and Betamethasone Valerate in the Treatment of Infected Eczema.

Methods: This was a 6 week study in which patients had screening and randomization visit (day 0, visit 1), treatment assessments visits at week 2 (visit 2) and week 4 (visit 3) and a follow-up visit (visit4). The blinded medication was dispensed to patients. During visit 2 (after 2 weeks), a detailed skin examination and modified eczema scoring (12 points eczema score and 12 points of infection score with total of 24 points), Visual analogue scale for pruritus and global score index were carried out. Any adverse event was recorded. During visit 3 (week 4), clinical examination and laboratory examination (Hb%, TC, DC, ESR) was performed. Adverse events and patient compliance were also recorded during these visits.

Results and Conclusions: Topical sodium fusidate and betamethasone valerate in biopolymer has shown to be more efficacious than topical sodium fusidate and betamethasone valerate. Both the combinations were well tolerable and safe.

Keywords: Infective eczema, sodium fusidate, Betamethasone valerate, Visual analogue scale, Global score index

INTRODUCTION

Eczema or dermatitis is a reaction pattern of the skin to various external and internal agents manifesting as itching, inflammation, redness, and swelling of the skin. It comprises of a variety of disorders including atopic eczema, allergic contact eczema, dyshidrotic eczema, and seborrheic eczema. The exact cause of eczema is unknown, but it is linked to allergies and an abnormal response of the immune system. Exposure to triggers, such as stress, allergens, and skin irritants, precipitate a flare-up of eczema in sensitive people (Homey B, et al., 2006; McGirt LY, et al., 2006; Leung D, et al., 2008). Eczema is a common condition, affecting about 10 percent to 20 percent of the world's population, according to the American Academy of Dermatology (Akdis CA, et al., 2006). The appearance, severity, symptoms, and triggers of eczema vary between individuals. Atopic Eczema does though frequently occur and reoccur during infancy and childhood and may resolve in adulthood. People who are more likely to develop eczema include those with a personal or family history of allergies, allergic rhinitis or asthma. Clinical features of eczema can include itching followed by the development of erythema, edema, oozing, vesiculation, crusting, erosion, lachenification and scaling.

Uncomplicated eczema is generally not a serious condition, but itching and scratching can lead to increased inflammation, open breaks in the skin, and a secondary bacterial infection or fungal infection of the surrounding skin and tissues. Bacterial infection like impetigo, pyoderma, and cellulitis can potentially serious. In 90% of the isolates, *S. aureus* can be implicated in this condition (Leung DY, et al., 2000; Hauser C, et al., 1985). A diagnosis of eczema can often be made by taking a thorough health history, including symptoms, and performing a physical exam. For suspected cases of allergic contact dermatitis, skin patch testing may be performed. In a patch test, small amounts of common allergens are applied methodically to the skin to determine what substances are triggering an allergic response, leading to the eczema. There is currently no cure for eczema, but the condition can be controlled with a good treatment plan individualized to a person's medical history, specific type and severity of eczema, and other factors. Treatment begins with the prevention of flare-ups. This includes an integrated plan to reduce exposure to irritants and allergens and minimize skin dryness. A variety of topical and oral medications may be prescribed to reduce inflammation and cure secondary infections (Boguniewicz M, et al., 2006; Leung DYM, et al., 2006; Howell MD, et al., 2006; Salt BH, et al., 2007; Stalder JF, et al., 1992). Phototherapy may be helpful in erosive cases of atopic dermatitis. A combination of treatments that include lifestyle changes with medications and other treatments as appropriate is the most effective way to best control eczema. Various glucocorticoid preparations are being used alone or in combination with antibiotics in the management of infected eczema. The combination of the glucocorticoid with antibiotic seems to be better than use of drugs alone (ramsay CA, et al., 1996; Leyden JJ, et al., 1977). The sodium fusidate and betamethasone preparation of Apex laboratories is claimed to be superior to other market preparations because of biopolymer content in Apex preparations.

Objective of the study

To evaluate the efficacy, tolerability and safety of topical Sodium Fusidate and Betamethasone Valerate in biopolymer Versus Combination of Fusidic acid and Betamethasone Valerate in the Treatment of Infected Eczema in patients of either sex.

Primary Outcome: - To assess the percentage of patient achieving good, moderate and mild improvement in eczema after two and four weeks of topical treatment with the one of the study drug (visit 2 and visit 3).

Secondary Outcome:-To assess the overall improvement in terms of:

Visual analogue scale for pruritis (Nunnally JC, et al., 1994; Wewers ME, et al., 1990).

- Global score index at the end of two and four weeks of treatment.

- Percentage of patients adhering to 4 weeks of treatment measured by the dropout rate at the end of 4weeks of treatment (visit 3).

- Any adverse events detected at 2nd week (visit 2) and 4th week (visit 3)

MATERIAL AND METHODS

Trial Design:

Patients of either sex, age >18 years, patient with modified eczema area and severity score and infection score of 6 and who were not on treatment with any topical or systemic anti-infective/steroid preparation for more than two consecutive days in the past 1 week prior to screening visit or any other type of topical and systemic medications for eczema were included in the study. Patients with Severe infected eczema involving significant surface area of the body (>20%), with co-existing skin disorders, with immunocompromised individuals like known HIV positive patients, diabetes mellitus etc., patients with known osteoporosis, peptic ulcer and tuberculosis were excluded from the study. The protocol was approved by the Institutional Review Board and written informed consent was obtained from all the patients.

This was a double blind phase IV clinical trial with two treatment groups. The study was conducted after obtaining the approval from the Manipal University Ethics Committee. Patients were enrolled from the dermatology clinic of Kasturba Hospital. This was a 6 week study in which patients had screening and randomization visit (day 0, visit 1), treatment assessments visits at week 2 (visit 2) and week 4 (visit 3) and a follow-up visit (visit4). In the screening visit patient was assessed for eligibility clinically and baseline investigations was collected for hematology. Patients were randomized in the same visit. The blinded medication was dispensed to patients and instructions were given to them about 'how to use it'. During visit 2 (after 2 weeks), a detailed skin examination and modified eczema scoring (12 points eczema score and 12 points of infection score with total of 24 points), Visual analogue scale for pruritis and global score index were carried out. Any adverse event was recorded in the CRF. During visit 3(week 4), clinical examination and laboratory examination (Hb%, TC, DC, ESR) was performed. Adverse events and patient compliance were also recorded during these visits. Photography of the lesions was taken in all the visits.

Investigational Products (IP)

Formulation A: - Combination of Topical Sodium Fusidate and Betamethasone valerate in biopolymer

Formulation B: -Combination of Fusidic acid and Betamethasone valerate

Each patient after successful screening received the IP kit which contains either A or B, blinded medication (4 tubes). Successful screening patient was assigned predetermined numbers and will be assigned to one of the arm on the same day (visit 1).

Patient visits and dosing: - Patients were given IP as mentioned before on visit 1 and visit 2. Patient was instructed apply one of the cream twice (2 tubes) in the morning (8:00am) and night (8:00pm) over the affected area.

Statistical Analysis

Percentage of patients achieving good, moderate and mild improvement, turning microbial negative and dropout rates after two and four weeks in either groups was compared by wilcoxon paired 't' test. Mean VAS scoring and global scoring index in these two groups was compared by Wilcoxon signed-rank test using SPSS statistical Package, version 14. Age, sex, adverse effects and laboratory abnormalities were presented in the form of Descriptive statistics for each group.

RESULTS

In present study, two investigational drugs (topical sodium fusidate and betamethasone valerate and topical sodium fusidate and betamethasone valerate in biopolymer) were evaluated for its efficacy in treatment of infective eczema. Total of 18 patients were enrolled in the study of which investigational drugs were assigned randomly, wherein the patient and principal investigator were unaware of the contents of the coded drugs.

In 18 patients, 10 have undergone treatment with topical sodium fusidate and betamethasone valerate and 8 have undergone treatment with topical sodium fusidate and betamethasone valerate in biopolymer. Mean age of the patients undergoing treatment with topical sodium fusidate and betamethasone valerate was 39.5 ± 20 years and for that of topical sodium fusidate and betamethasone valerate in biopolymer were 30.5 ± 9.54 years. The study patients constitute of 12 males (66%) and 6 females (33%).

Primary outcomes:

The magnitude of improvement was seen in both the treatment groups. Percentage of patients achieving cure and marked improvement combined were more in topical sodium fusidate and betamethasone valerate in biopolymer group as compared to topical sodium fusidate and betamethasone valerate group (Chart 1,2).

Chart 1

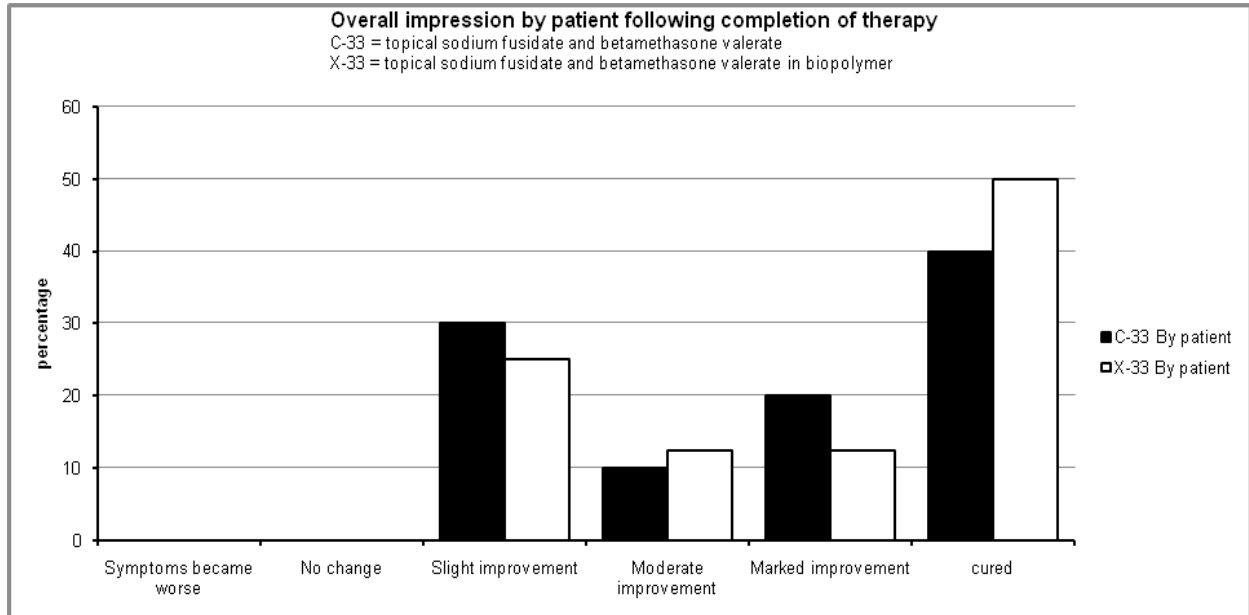
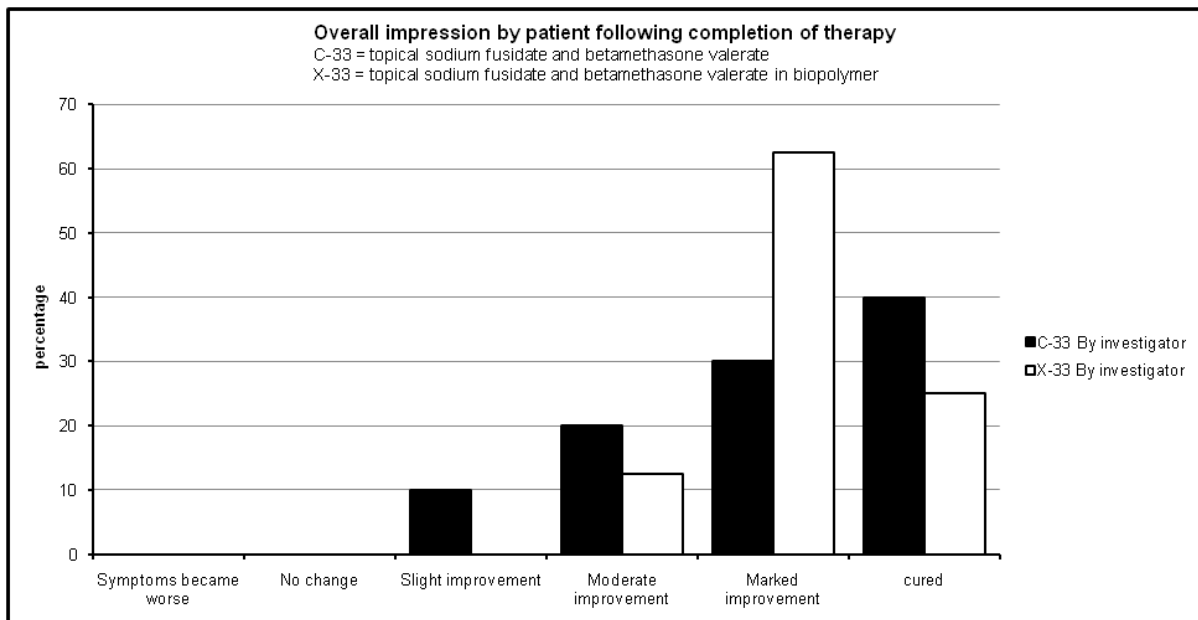


Chart 2



Secondary outcomes

The reduction in itch score (visual analogue score, 0-10) was analyzed using wilcoxon paired test. There was significant reduction in itch, as measured by visual analogue score, in 2nd, 3rd and 4th visit as compared to the 1st visit in both the treatment groups (Table 1). Between the group comparison for the reduction in itch score was done by comparing absolute difference in itch scores (VAS visit 1 – VAS visit 4) by Mann-Whitney U test. Both the groups were equally effective in reducing the itch symptoms (**p-value= 0.640**).

Table 1: Visual analogue score (VAS) for itch in the treatment groups in infective eczema patients by wilcoxon signed-ranked test (Median, IQR)						
	TOPICAL SODIUM FUSIDATE AND BETAMETHASONE VALERATE			TOPICAL SODIUM FUSIDATE AND BETAMETHASONE VALERATE IN BIOPOLYMER		
	No. of patients	(Median, IQR)	p-value	No. of patients	(Median, IQR)	p-value
Visit 1	10	5 (4,6)		8	5 (2.75, 6)	
Visit 2	10	1.5 (0.75, 4)	0.005*	8	2 (1, 4.25)	0.024*
Visit 3	10	1.5 (0, 3.25)	0.005*	8	0.5 (0, 2.5)	0.012*
Visit 4	8	0.5 (0, 2.7)	0.018*	7	0 (0, 5)	0.027*

IQR- Interquartile range; * p-value significant <0.05 as compared to 1st visit

There was significant improvement in global health score (1-7) as assessed by investigator, in 2nd, 3rd and 4th visit as compared to the 1st visit in both the treatment groups (Table 2). Between the group comparison for the improvement in global health score was done by comparing absolute difference in global scores (Global scores visit 4 – Global scores visit 1) by Mann-Whitney U test. Both the groups were equally effective in improving global health (p-value= 0.807).

Table 2: Global health status score in the treatment groups in infective eczema patients by wilcoxon signed-ranked test (Median, IQR)						
	TOPICAL SODIUM FUSIDATE AND BETAMETHASONE VALERATE			TOPICAL SODIUM FUSIDATE AND BETAMETHASONE VALERATE IN BIOPOLYMER		
	No. of patients	(Median, IQR)	p-value	No. of patients	(Median, IQR)	p-value
Visit 1	10	4 (3.75, 5)		8	4 (3.25, 4.75)	
Visit 2	10	6 (5, 7)	0.01*	8	6 (5, 6)	0.016*
Visit 3	10	6 (5.75, 6.25)	0.022*	8	6.5 (4.5, 7)	0.011*
Visit 4	8	6.5 (4.5, 7)	0.017*	7	7 (4, 7)	0.016*

IQR- Interquartile range; * p-value significant <0.05 as compared to 1st visit

Dropout rates: The dropout rates were calculated at the end of 4 weeks i.e. visit 3 are 0 for each group. Adverse events: None of the groups reported any adverse events with use, throughout the study. Laboratory abnormalities: 2 patients in topical sodium fusidate and betamethasone valerate in biopolymer and 1 patient in topical sodium fusidate and betamethasone valerate group had raised ESR. Other laboratory parameters, in study patients, like Total leukocyte count, differential count, blood urea, fasting blood sugar and serum creatinine were within normal limits.

Discussion

Fusidic acid shows a narrow antibacterial spectrum, it is quiet effective against Gram-positive bacteria; especially *S. aureus*, and has also shown to be effective against both MSSA and MRSA isolates (Verbist L, 1990; Bishop EJ, and Howden BP 2007).

The combination of betamethasone valerate and fusidic acid has shown to be cosmetically acceptable treatment cream as compared to other combination like betamethasone valerate and clioquinol and also showed better bacteriological response (Hill VA et al., 1998). There was improvement in symptoms in both the treatment groups. In this study, as per the patient's assessment, 20% reported marked improvement and 40% reported to be cured when they were subjected to Topical sodium fusidate and betamethasone valerate group. Whereas in Topical sodium fusidate and betamethasone valerate in biopolymer group, 12.5% reported marked improvement and 50% reported to be cured. As per the investigator's assessment, 30% reported marked improvement and 40% reported to be cured when they were subjected to Topical sodium fusidate and betamethasone valerate group. Whereas in Topical sodium fusidate and betamethasone valerate in biopolymer group, 62.5% reported marked improvement and 25% reported to be cured. The better response with the Topical sodium fusidate and betamethasone valerate in biopolymer group may be due to its biopolymer content. The addition of biopolymer claims to complement and enhance the therapeutic value of the formulation, forms a micro film at the site of application and immobilizes microbes with its cationic charge.

All the subjects of both the groups took medications all the four weeks showing 100% compliance. All the laboratory parameters, in study patients, like Total leukocyte count, differential count, blood urea, fasting blood sugar and serum creatinine were within normal limits and none of the groups reported any adverse events with the use of medication, throughout the study. Both the formulations were well accepted by the patients.

Conclusion:

In this study, from the results obtained, it is clear that percentage of patients with infective eczema achieving cure and marked improvement combined were more in topical sodium fusidate and betamethasone valerate in biopolymer group as compared to topical sodium fusidate and betamethasone valerate. Further, both the groups were equally effective in reducing the itch symptoms of these patients. Both the groups were equally effective in improving overall global health. Topical sodium fusidate and betamethasone valerate in biopolymer has shown to be more efficacious than topical sodium fusidate and betamethasone valerate and well tolerable and safety on par with the comparator.

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