

To evaluate the efficacy and safety of “RV2427B” cream in Irritant dermatitis care

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ABSTRACT

Background: The treatment of various irritant dermatitis involves the elimination of the casual or favoring factor, the control of aggravating factors, and administration of topical agents. Even though corticosteroids are extensively used in these conditions to reduce the inflammation, it can also result in undesirable side effects. Hence, there is a need for a non steroidal topical agent to be used in these conditions. **Aims:** To evaluate the efficacy and tolerance of repairing cream “RV 2427B” in children and adults in irritant dermatitis care. **Materials and Methods:** In this phase III open labeled, multicenter, non-controlled, non-randomized trial, irritant dermatitis in children and adults either due to diaper rash, pityriasis alba and irritant dermatitis (eczema), perioral dermatitis, perleche or intertrigo were administered; repairing cream RV 2427 B containing a) 4 % zinc oxide, b) 2.5 % dry colloidal oat extract, (c) 0.5 % oat oil, (d) 0.2% copper sulfate, and (e) 0.1 % zinc sulfate to be applied twice-daily in the affected area. The subjects were evaluated on day 7 and day 21 for both efficacy and tolerance and last visit for cosmetic acceptability. The trial was conducted in accordance with the good clinical practices (GCP) after obtaining ethical clearance from respective Institutional Review Boards. Statistical evaluation was by variance analysis and student test for the quantitative variables, chi-square test for the qualitative variables. **Results:** Of the 136 enrolled subjects, 95 completed the study. After 21 days of treatment, 84% of the subjects assessed by the investigator and 76% by the self-assessment for the cream found effective. Investigational product was considered to be safe after 7 and 21 days of use. **Conclusion:** Repairing cream “RV 2427 B” is effective and safe in the management of irritant dermatitis.

Key words: Irritant dermatitis, repair cream, zinc oxide

INTRODUCTION

The term “irritant dermatitis” in a broad sense represents response to the physical / toxic effects of a wide range of environmental exposures. Dermatitis arises when the defense or repairing capacity of the skin is exhausted or when the penetration of chemicals excites an inflammatory response. The 3 main factors involved in the pathogenesis of irritant dermatitis are, disturbed barrier function, epidermal cell change, and release of inflammatory mediators and cytokines.^[1]

Dermatological conditions like diaper rash, perioral dermatitis, perleche, intertrigo, many a times, are because of the irritant factors. Condition like pityriasis alba although considered as an endogenous eczema, presents as scaly hypopigmented macules on the face, and application of emollient creams helps in its treatment.

The treatment of this irritant dermatitis involves the elimination of the causal or favoring factor, the control of aggravating factors, and administration of topical agents. Even though corticosteroids are extensively used in these conditions to reduce the inflammation, it can also result in undesirable side effects. In cases of diaper dermatitis, the occlusion of the wet diaper raises the absorption of the topical steroid and may lead to purple nodules termed granuloma gluteale infantum.^[2] Condition like perioral dermatitis may be precipitated by topical corticosteroids.^[3] It has been suggested that topical corticosteroids including hydrocortisone should be discouraged from prolonged usage on the face.^[4] So, there is a need for non steroid cream in conditions mentioned above, which helps in correcting the skin barrier function and limit the passage of irritants and allergies.

The repairing cream “RV 2427B” was designed to treat irritated skin, it contains the following

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components: a) 4 % zinc oxide, b) 2.5 % dry colloidal oat extract, (c) 0.5 % oat oil, (d) 0.2% copper sulfate, and (e) 0.1 % zinc sulfate. Among these, zinc oxide, zinc sulfate, and copper sulfate are known for their soothing, anti-microbial, and re-generating properties. Oat extract and oat oil are natural anti irritants that reduce the inflammatory phenomenon.^[5]

This phase III open-labeled, multicenter, non-controlled, non-randomized trial was intended to evaluate the efficacy and tolerance of repairing cream "RV 2427 B" in children and adults either due to diaper rash, pityriasis alba and irritant dermatitis (eczema), perioral dermatitis, perleche or intertrigo. Pityriasis alba was included at the insistence of sponsors.

MATERIALS AND METHODS

Inclusion criteria:

- Male or female adults
- Women of child-bearing age practicing effective contraceptive method
- Children (age > 1 month) and adults suffering from irritant dermatitis on face and or body (diaper rash, perioral dermatitis, pityriasis alba and irritant dermatitis, perleche, and intertrigo). The inclusions of the patients were at the investigators discretion with relation to extent of involvement.
- Willing to give an informed consent in case of adults and from parents in case of children

Exclusion criteria:

- Pregnant women
- Children below 1 month age
- Use of a cosmetic product other than that studied on irritant dermatitis
- Known hypersensitivity to one of the ingredients in the product tested
- Participation in another clinical trial during present trial
- Presence of superadded infection necessitating antibiotic treatment
- Antibiotic, anti-viral, anti-fungal treatment or corticosteroids initiated within 3 days of inclusion

This trial was conducted at 5 dermatology departments: Bangalore Medical College (BMC) and St. John's Medical College (SJMC), Bangalore, Jagdguru Shivaratareshwara Medical College (JSS), Mysore, Father Muller Medical College (FMMC) and K. S. Hegde Charitable Hospital (KSHEMA), Mangalore from September 2006 - December 2007.

Ethical consideration: The trial was conducted in accordance with the good clinical practices (GCP) after obtaining permission from the respective institutional review boards (IRB) according the clinical research guidelines established by the basic

principles defined in the U.S.21 CFR part 312, 120 ICH – GCP and enunciated in the declaration of Helsinki.

Study design: On day 0, all subjects who met inclusion / exclusion inertia, who consented to participate in this study, were administered 2 tubes of repairing cream to be applied twice-daily (morning and evening) to the affected area. The subjects were evaluated on day 7 (D-7) and days 21 (D21) post-treatment. All subjects were evaluated for both efficacy and tolerance and last visit for cosmetic acceptability. (Overall study design is represented in Table 1). Evaluation criteria was divided as objective (cracks, desquamation, erythema, exudation) and subjective (pruritus, burning, tightness, tingling), this was used to evaluate the efficacy and tolerance. For minors subjective, opinions of a parent were considered. Assent forms were also signed by the appropriate minors. The patients were issued subject dairies, and the tubes were instructed to return after the completion of the study. Patients were instructed not to take any oral medications.

Efficacy and safety measurements: The primary evaluation criteria were assessed as improvements in clinical data using objective signs (on a 4-point scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe) and subjective signs (with an analogical scale graduated from 0 (absence of symptoms) to 10 (of maximum intensity) by comparing paired measurements from D0 and D7. The secondary evaluation criteria were assessed as improvements in clinical data using objective and subjective signs by comparing paired measurements from D0 and D21. Global efficacy and tolerance were assessed based on the measurements by the investigator (using the following scale: 3 = Very effective, 2 = Effective, 1 = Not very effective, 0 = Not effective at all). All subjects were informed at the beginning of the study to consult the investigator in case they notice any unpleasant reaction during the study period. Global

Table 1: The study design

	D0	D7	D21
	VISIT VI	VISIT V2	VISIT V3
Information, signature of consent	X		
Verification of the inclusion criteria	X		
Past medical history	X		
Assignment of subject numbers	X		
General clinical examination	X	X	X
Evaluation of the main criterion	X	X	X
Evaluation of the secondary criteria	X	X	X
Collection of adverse events		X	X
Distribution of the follow up notebook	X	X	
Recovery of the follow up notebook		X	X
Distribution of the products under study	X		
Recovery of the products under study			X

assessment of tolerance was done by the investigator at D7 and D21 (using a scale: 3 = Very good tolerance, 2 = Good tolerance, 1 = Bad tolerance, 0 = Very bad tolerance). The self-assessment of the global efficacy of the tested product by the subject or by the legal guardian in case of a child under 18 years of age, at D7 and D21, was done using a follow up notebook given to the subject at D0. Also, assessment of the cosmetic acceptability of the tested product was done at D21. For safety assessment, any adverse or intercurrent event (were graded by the investigator using a 3-point intensity scale; mild: Awareness of signs or symptoms, but easily tolerated; moderate: Uncomfortable enough to cause interference with usual activity; severe: Incapacity with inability to work or do usual activity), which occurred during the study period was recorded. In infants, response was obtained by parents.

Statistical analysis: Statistical inferential tests for objective and subjective data were assessed by comparing the responses on D7 and D21 from baseline (D0) using paired test procedures. Objective signs were all measured using qualitative scale, and McNemar Bowker test were used for comparisons. Subjective data were quantitative values measured using visual analogue scale (between 0 to 10). For quantitative values, a paired student test was carried out; Wilcoxon signed rank test was also used to check the robustness of distribution assumption in the paired t – test. For all statistical tests, type I error was fixed at 5%. Supportive statistical summaries were presented in the tables and charts for all measurements.

RESULTS

A total of 136 subjects were enrolled into the study, and 95 subjects completed the study. The diagnosis of subjects was as follows; 66 (48%) subjects had eczema (Pityriasis alba and irritant dermatitis), 18 (13%) had perioral dermatitis, 27 (20%) had diaper rash, 8 (5%) had perleche, and 17 subjects had intertrigo (13%).

Among the 95 subjects who completed the study, 82 subjects completed all the 3 visits and the remaining completed only 2 visits and withdrew from study due to completed resolution of lesion.

Among 136 subjects, 61 (44.8%) subjects were males and 75 (55.2%) were females. Subjects in the age group of less than 18 were 54 (40%), and those above 18 were a total of 82 (60%) subjects.

Objective data: Primary comparison- There were marked improvements in clinical sign after 7 days of treatments in all objective sign endpoints, these improvements were all statistically significant when the paired measurements were compared from D0 and D7 using McNemar Bowker test procedure. Secondary comparison – The improvements in clinical signs continued after 21 days of treatment in all objective sign end points; more than 63.0% reduction in erythema symptom was observed at

D7 visit and 80.7% of improvement on visit (D21). Similarly, the improvement of desquamation symptoms were observed on D7 (68.9%) and D21 (85.5%) visits. About 50.6% reduction of severity in cracks and 24.1% improvement in sweating was observed. Although less number of subjects (55) was available with paired observation in D0 and D21, this clinical improvement in both groups was statically significant in all objective signs when compared from D0 and D21 using Mc Nemar – Bowker test procedure.

Subjective data: On primary comparison, there was marked improvement in clinical signs after 7 days of treatment in all 4 subjective sign end points (burning sensation, pruritus, tightness, and tingling); these improvements were all statically significant when the paired measurements were compared from D0 and D7 using paired t-test procedure. Wilcoxon and signed rank test procedure also corroborated with the significant results observed using the paired t-test. Secondary comparison showed significant improvements in clinical signs continued after 21 days of treatment in all 4 subjective endpoints. There was marked improvement in clinical signs after 7 days and 21 days of treatment in subjective sign end points, especially the burning sensation and pruritus. The improvement was about 75.38% and 90.0%, respectively, on D21 visit. However, other subjective signs, i.e. tightness and tingling, showed an average improvement of about 60% reduction in severity on D21 visit.

Global efficacy: More than 86% (102) (adding very effective and effective) of the subjects assessed by the investigator as well as by self assessment 79% (94) (adding very effective and effective) found the cream effective or very effective after 7 days of treatment. After 21 days of treatment, 84% (adding very effective and effective) of the subjects assessed by the investigator and 76% by the self-assessment found the cream effective or very effective [Tables 2 and 3].

Table 2: Distribution of subject by global efficacy: Investigator's opinion

Visit \ Count (%)	Not Effective at all	Not Very Effective	Effective	Very Effective	Total
Day 7 (V2)	4 (3.4%)	13 (10.9%)	98 (82.4%)	4 (3.4%)	119 (100%)
Day 21 (V3)	2 (2.4%)	11 (13.3%)	69 (83.1%)	1 (1.2%)	83 (100%)

Table 3: Distribution of subject by global efficacy: Subject's opinion

Visit \ Count (%)	Not Effective at all	Not Very Effective	Effective	Very Effective	Total
Day 7 (V2)	7 (5.9%)	18 (15.1%)	89 (74.8%)	5 (4.2%)	119 (100%)
Day 21 (V3)	7 (8.4%)	13 (15.7%)	62 (74.7%)	1 (1.2%)	83 (100%)

Tolerance: Almost everyone in the study had good to very good tolerance of the cream after 7 (97%) and nearly similar after 21 days of treatment (94%).

Safety: The investigational product was considered as safe since most of the subjects had either good or very good tolerance.

Cosmetic acceptability: Majority of the subjects (84%) evaluated after 21 days treatment found ease of application, ease of use, and practicality of packing were satisfying to very satisfying. At visit, three (71.4%) of patients mentioned that they would like to continue to use the product.

DISCUSSION

In this phase III open-labeled, multicenter, uncontrolled, randomized trial repairing cream mainly containing zinc oxide and colloidal oat extract revealed the beneficial effects in the management of irritant dermatitis. The dermatological conditions included in this trial were diaper rash, perioral dermatitis, pityriasis alba, irritant dermatitis (eczema), perleche, and intertrigo. In all these conditions the barrier repair function of the skin is impaired.

In diaper dermatitis, factors like moisture, friction, urine, feces, and sometimes micro organism, result in dermatitis. The barrier function of the skin is affected, with resultant increase in irritant chemical penetration and pathogen replication.^[6] Perleche or cheilitis is an irritant dermatitis due to lips licking, cosmetics, and medications.^[7] A number of agents have been implicated in the pathogenesis of perioral dermatitis.^[3]

Zinc oxide is a relatively weak anti-bacterial agent and is used in the form of powder and ointments. An inflamed skin is usually associated with pain, burning, or itching, and locally applied agents which relieve these uncomfortable sensations are known as soothing preparations. Application of cream containing emollients are useful in these conditions.^[8] Zinc oxide is used in the past in conditions like acute eczema, seborrheic dermatitis, neurodermatitis, in which it has the soothing action.^[9] In angular stomatitis when applied, zinc oxide ointment helps in preventing maceration due to the constant presence of saliva. Zinc oxide is also a component of many anti pruritic formulations available as lotion, liniments, and ointments.^[10]

In this trial, the beneficial effects of RV 2427 B cream are shown in irritant dermatitis. In diaper dermatitis, zinc oxide ointments are considered as the first line therapeutic agent in primary diaper dermatitis.^[11] Wananukul S *et al.*, in a multicenter study, indicated that ointment containing dexpathenol and zinc oxide was beneficial in the treatment of irritant diaper dermatitis.^[12,13]

This trial repairing cream "RV 2427 B," containing zinc oxide and colloidal oat extract as main ingredients, demonstrated

an overall efficacy rate of more than 82% in the treatment of various irritant dermatitis. More than 90% of the patients demonstrated good tolerance for this product.

Limitations of the study:

1. Inclusion of pityriasis alba, which is considered as an endogenous eczema. The only justification for using this condition is the requirement of a non-steroidal cream for the remission. These cases also didn't have oozing from the lesions, and only scaling and erythema, if any, were considered for evaluation.
2. The statistical analysis was done after compiling the data from all the centers.

CONCLUSION

This study shows that repairing cream "RV 2427 B" is effective, safe, and cosmetically acceptable in the treatment of irritant dermatitis of the skin. As this cream doesn't include any steroids, there will not be any restrictions in using this product. However, double blind, placebo controlled trials in individual dermatosis may help in further emphasizing the efficacy of this product.

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