

Evaluation of the efficacy and safety of “Diaper Rash Cream” in the management of infantile irritant diaper dermatitis (IIDD)

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Abstract

Infantile irritant diaper dermatitis (IIDD) is an inflammation of the infantile skin covering the groin, lower stomach, upper thighs and buttocks. Infantile irritant diaper dermatitis may become difficult to treat, if the area becomes infected or the infant develops allergy to medications applied to the area. This study was conducted to evaluate the efficacy and safety of “Diaper Rash Cream” in the management of IIDD.

The study was a prospective, phase III clinical trial, conducted as per the good clinical practice guidelines. A total of 15 infants, who were suffering from IIDD, and whose parents were willing to give informed written consent were included in the study.

At the initial visit, a detailed medical history was obtained by interviewing the parents regarding any dermatological problem, or any adverse effect following the use of any baby product previously in the infant. Then, a detailed physical examination of the infant was done including the dermatological system. Before beginning the study, the “Diaper Rash Cream” was applied in a test dose and observed for the development of any immediate hypersensitivity manifestations, for a period of 30 minutes. If there were no immediate hypersensitivity manifestations, the parents were advised to apply the “Diaper Rash Cream” once daily, after bath for a period of 2 weeks, on the skin covering the groin, lower stomach, upper thighs and buttocks. All the infants were followed up on the 7th and 14th day of application, and at each follow-up visit, a detailed clinical examination was done. All the adverse events, either reported or observed by the parents were recorded along with information about the onset, severity, duration and site of the adverse reaction. The signs and symptoms of immediate skin irritation and delayed hypersensitivity reactions were evaluated as per the standard reference guidelines.

There was a significant improvement in the clinical manifestations of IIDD in all the included infants, in 3 days, and there was complete recovery from the clinical manifestations of IIDD, after a week’s application, in all the included infants.

There was a significant reduction in itching in 10 babies, from the 3rd day onwards, and all the infants were relieved of itching from the 5th day. There was also a significant reduction in 7 babies, with regard to erythematous scaly diaper area, which often involves papulovesicular or bullous lesions, fissures, and erosions from the 3rd day onwards, and all the infants were relieved of papulovesicular or bullous lesions, fissures, and erosions by the 6th day. Also, there were no clinically significant adverse reactions, with excellent compliance.

The positive benefits observed in this study might be due to the synergistic action of the active ingredients of the formulation viz. anti-inflammatory activities (of Aloe vera, Vitex negundo and Rubia cordifolia), antibacterial activities (of Zinc calx, Aloe vera, Vitex negundo and Rubia cordifolia), wound healing activities (of Aloe vera), and antioxidant activities (of Vitex negundo, Prunus amygdalus and Rubia cordifolia). Therefore, it can be concluded that “Diaper Rash Cream” is effective and safe in the management of IIDD.

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Introduction

Diapers are used for the care of infants, young children and incontinent or paralyzed individuals, to prevent fecal soiling and for social convenience. However, the use of diaper poses a risk of developing “irritant diaper dermatitis”, which is commonly known as “diaper rash”. Recent innovations in diaper technology have led to development of super absorbent disposable diapers,

emollient delivering diapers, and breathable diapers, and these newer types of diapers reduce the incidence of diaper dermatitis. The non-biodegradable material used in super absorbent diapers is, however, a matter of serious concern because of its toxic effects and environmental pollution.¹

Infantile irritant diaper dermatitis is an inflammation of the infantile skin covering the groin, lower

stomach, upper thighs and buttocks. Infantile irritant diaper dermatitis may become difficult to treat, if the area becomes infected or the infant develops allergy to medications applied to the area.

The "Diaper Rash Cream" is a polyherbal formulation recommended for the prevention and treatment of irritant diaper dermatitis, and contains the powders of Zinc calx, extract of *Aloe vera* and the oils of *Prunus amygdalus*, *Vitex negundo* and *Rubia cordifolia*. This study was conducted to evaluate the efficacy and safety of "Diaper Rash Cream" in the management of IIDD.

Aim of the study

This study was planned to evaluate the clinical efficacy and safety (short- and long-term) of "Diaper Rash Cream" in the management of IIDD.

Study design

The study was a prospective, phase III clinical trial, conducted at the Well Baby Clinic, at the Department of Pediatrics, Medical College and Hospital, Kolkata, from September to December 2004, as per the good clinical practice guidelines.

Methods and materials

Inclusion and exclusion criteria

A total of 15 infants, who were suffering from IIDD, who were born at term, with a birth weight of more than 2500 grams (having appropriate gain in weight, length, and head circumference, and a normal psychomotor development on pediatric physical examination), and whose parents were willing to give informed written consent were included in the study. Infants who were under some medication for systemic or topical disease, and those babies, whose parents were unwilling to give written informed consent before entering the study, were excluded from the study.

Study procedure

The parents who brought their infants for routine check up at the Well Baby Clinic were informed about the study product, its effects, duration of study period, their

responsibilities, the importance of compliance, ethical aspects, and overall plan of the study. Informed consent was obtained in writing from the parents of all the included infants.

At the initial visit, a detailed medical history was obtained by interviewing the parents regarding any dermatological problem, or any adverse effect following the use of any baby product previously in the infant. Then, a detailed physical examination of the infant was done including the dermatological system.

Before beginning the study, the "Diaper Rash Cream" (Batch No.: 40601-RD) was applied in a test dose and observed for the development of any immediate hypersensitivity manifestations, for a period of 30 minutes. If there were no immediate hypersensitivity manifestations, the parents were advised to apply the "Diaper Rash Cream" once daily, after bath for a period of 2 weeks, on the skin covering the groin, lower stomach, upper thighs and buttocks.

All the infants were followed up on the 7th and 14th day of application, and at each follow-up visit, a detailed clinical examination was done. The parents were advised to discontinue the product, if they noticed any adverse effect.

Adverse events

All the adverse events, either reported or observed by the parents were recorded along with information about the onset, severity, duration and site of the adverse reaction. The signs and symptoms of immediate skin irritation and delayed hypersensitivity reactions were evaluated as per the standard reference guidelines. The scoring scales for various adverse effects were as follows: Scoring scale for evaluating erythema: no erythema – 0, very slight erythema – 1, well defined erythema – 2, moderate to severe erythema – 3, and very severe erythema – 4. Scoring scale for evaluating edema: no edema – 0, very slight edema – 1, slight edema – 2, moderate edema – 3, and severe edema – 4. Scoring scale for evaluating pruritus and urticaria: nil

pruritus and urticaria – 0, very slight pruritus and urticaria – 1, well defined pruritus and urticaria – 2, moderate to severe pruritus and urticaria – 3, and severe pruritus and urticaria – 4.

The relation of adverse events to the study product was predefined as "Unrelated" (a reaction that does not follow a reasonable temporal sequence from the time of application of the product and not localized to the whole site of application), "Probable" (follows a known responsible pattern to the suspected product, but could have been produced by the baby's clinical state and localized at the site of application), "possible" (follows a known responsible pattern to the suspected product that could not be reasonably explained by the known characteristics of the baby's clinical state and localized at the site of application).

Results

There was a significant improvement in the clinical manifestations of IIDD in all the included infants, in 3 days and there was complete recovery from the clinical manifestations of IIDD, after a week's application, in all the included infants.

There was a significant reduction in itching in 10 babies, from the 3rd day onwards, and all the infants were relieved of itching from the 5th day. There was also a significant reduction in 7 babies, with regard to erythematous scaly diaper area, which often involves papulovesicular or bullous lesions, fissures, and erosions from the 3rd day onwards, and all the infants were relieved of papulovesicular or bullous lesions, fissures, and erosions by the 6th day. Also, there were no clinically significant adverse reactions, with excellent compliance.

There were no clinically significant adverse reactions (either reported by the parents or observed by the investigators) during the entire study period. There were no dropouts, and the overall compliance to the product use was excellent.

Discussion

Infantile irritant diaper dermatitis, a frequent condition, is a form of contact dermatitis, occurs due to the interaction of multiple factors (increased wetness, elevated local skin pH, fecal enzymes and microorganisms), and manifests as an erythematous rash. Increased wetness in the diaper area makes the skin more susceptible to damage by physical, chemical, and enzymatic mechanisms. Wet skin increases the penetration of irritant substances. The urease enzyme found in the stratum corneum liberates ammonia from cutaneous bacteria, which has an irritant effect on nonintact skin. Lipases and proteases in feces mix with urine on nonintact skin and cause an alkaline surface pH, adding to the irritation. (Feces in breastfed infants have a lower pH, and breastfed infants are less susceptible to diaper dermatitis.) The bile salts in the stools enhance the activity of fecal enzymes, adding to the effect.^{2,3}

Candida albicans has been identified as a contributing factor to diaper dermatitis, and the infection often occurs after 48-72 hours of active eruption. *Candida albicans* has been isolated from the perineal area in as many as 92% of children with diaper dermatitis. Other microbial agents have been isolated less frequently, perhaps more as a result of secondary infections. In a clinical study, Ferrazzini et al. investigated the relevance of *Candida* sp. and *Staphylococcus aureus* colonization in IIDD and determined the correlation between the extent of colonization and the severity of disease. The results showed a significant, positive correlation between severity of disease and extent of *Candida* spp. colonization at all swab locations (the colonization by *Staphylococcus aureus* was nonsignificant).⁴ In a study by Dorko et al. the occurrence of *Candida* spp. was determined in infants, with diaper dermatitis, and the most frequently isolated species was *Candida albicans*, followed by *C. parapsilosis*, *C. tropicalis*, *C. pulcherrima*, *C. guilliermondii*, and

C. zeylanoides. Other organisms present in the mixed culture from the diaper area were *Staphylococcus aureus*, *Escherichia coli*, and few strains of streptococci (groups B and D), and *Proteus mirabilis*. Infants diapered exclusively in disposable diapers showed less rash than those diapered exclusively or sometimes in cloth diapers.⁵

The principle of treatment of diaper dermatitis is to keep the skin in the nappy area as dry as possible with frequent nappy change, and absorbent disposable diapers are known to reduce the incidence of diaper dermatitis. Absorbent disposable diapers do not allow urine to come into contact with the skin, and can hold large amounts of urine. For all practical purposes these diapers only need to be changed when they become soiled with feces or they get so heavy that they are down near the child's ankles.⁶

This study observed complete recovery from IIDD in all the included babies, after a week's application. Also, there were no clinically significant adverse reactions, with excellent compliance. The positive benefits observed in this study might be due to the synergistic action of the active ingredients of the formulation.

Zinc has been widely used in the treatment of diaper dermatitis and various studies have demonstrated the antibacterial efficacy of zinc oxide. Collipp et al. observed significant reduction in the incidence of diaper rash, with oral zinc supplementation.⁷ In another study, Collipp et al. noted that IIDD was associated with reduced hair zinc, and infants with the least hair had lower zinc levels than infants with the most hair.⁸ Baldwin et al. conducted a study to determine the clinical benefits of a novel disposable diaper designed to deliver a zinc oxide and petrolatum-based formulation continuously to the skin during use. They evaluated the prevention of skin irritation and barrier damage from a standard skin irritant in an adult arm model. The

results revealed that, exposure to the formulations directly on adult skin prior to an irritant challenge was associated with significant reduction in skin barrier damage and skin erythema, and greatest reductions were seen for the zinc containing formulations. Wearing of the formulation treated diaper was also associated with a significant reduction in skin erythema and diaper rash compared to the control product.⁹

The principle constituents of *Aloe barbadensis* are anthraquinones (aloe-emodin and aloin A (barbalin),¹⁰ cinnamoyl, p-coumaroyl, feruloyl, caffeoyl aloesin, aloemannan,¹¹ acemannan, verectin,¹² elgonica dimer A and bisbenzopyran.¹¹ *Aloe vera* has anti-inflammatory, antifungal, immunosuppressive, and wound healing properties. The active ingredients of *Aloe vera* have been found to exhibit immunosuppressive, anti-inflammatory activities, bradykinin degrading and cell proliferation-stimulating activities.¹² Ali et al. found that anthraquinones from *Aloe vera* are responsible for the antifungal activity.¹³ The constituents of *Aloe barbadensis* have wound healing properties.^{14,15} Davis et al. evaluated the extracts of *Aloe vera* for topical anti-inflammatory activity, and the results showed that small amounts of *Aloe vera* given topically inhibit inflammation induced by a moderate amount of irritant.¹⁶ Another study by the same author demonstrated the antioxidant and anti-inflammatory effects of aloesin derivative (isorabaichromone) in *Aloe vera*. As *Aloe vera* has long been used to promote wound healing, the inhibitory effects of aloesin derivatives for cyclooxygenase (Cox)-2 and thromboxane (TXA 2) synthase were examined and the participation of p-coumaroyl and feruloyl ester groups in the aloesin skeleton was demonstrated, which explain, the wound healing effects of *Aloe vera*.¹⁷ Bautista-Perez et al. demonstrated the antibradycinin effect and hence anti-inflammatory activities of *Aloe vera*.¹⁸ In a study by Vazquez et al. the aqueous extract of *Aloe vera* gel inhibited

prostaglandin E2 production from arachidonic acid. The chemical tests performed on the aqueous extract for anthraglycosides, reductor sugars and cardiotonic glycosides were positive.¹⁹

Prunus amygdalus is a rich source of antioxidants (tocopherols, squalene and phytosterols).²⁰ Kayano et al. documented high antioxidant activities of *Prunus amygdalus*.²¹

The principle ingredients of *Vitex negundo* are flavone vitexcarpin,²² negundins A and B, diasyringaresinol, lyoniresinol, vitrofolal E and F,²³ 6-phenyldihydronaphthalene-type lignan, vitedoin A, phenyl-naphthalene-type lignan alkaloid, vitedoamine A, and trinorlabdane-type diterpene, and vitedoin.²⁴ *Vitex negundo* has anti-inflammatory, free radical scavenging, analgesic, antihistaminic, and antibacterial activities. Chawla et al. reported the anti-inflammatory activity of *Vitex negundo*.²⁵ Munasinghe et al. demonstrated the free radical scavenging activity of *Vitex negundo*.²⁶ Dharmasiri et al. confirmed the anti-inflammatory, analgesic and antihistamine properties of *Vitex negundo*.²⁷ Perumal et al. reported the potent antibacterial activity of *Vitex negundo* against *Escherichia coli*, *Klebsiella aerogenes*, *Proteus vulgaris*, and *Pseudomonas aerogenes*.²⁸

The principal constituents of *Rubia cordifolia* are purpurin, munjistin, purpuroxanthin, pseudo-purpurin and rubiadin,^{28,29} anthraquinones (cordifoliol and cordifodiol)³⁰ and a naphthoic ester (rubialactone).³¹ *Rubia cordifolia* has antioxidant antibacterial and anti-inflammatory activities. Tripathi et al. demonstrated the antioxidant activity of *Rubia cordifolia*, which inhibited lipid peroxidation in a dose dependent manner.³² Cai et al. demonstrated the antioxidant activity of hydroxyanthraquinones from *Rubia cordifolia*.³³ Qiao et al. demonstrated the antibacterial activity of the constituents in *Rubia cordifolia*.³⁴ Jain et al. demonstrated the anti-inflammatory activity of the constituents of *Rubia cordifolia*.³⁵

Conclusion

Infantile irritant diaper dermatitis is an inflammation of the infantile skin covering the groin, lower stomach, upper thighs and buttocks. Infantile irritant diaper dermatitis may become difficult to treat, if the area becomes infected or the infant develops allergy to medications applied to the area. This study was conducted to evaluate the efficacy and safety of "Diaper Rash Cream" in the management of IIDD.

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The positive benefits observed in this study might be due to the synergistic action of the active ingredients of the formulation viz. anti-inflammatory activities (of *Aloe vera*, *Vitex negundo*, and *Rubia cordifolia*), antibacterial activities (of zinc calx, *Aloe vera*, *Vitex negundo*, and *Rubia cordifolia*), wound healing activities (of *Aloe vera*), and antioxidant activities (of *Vitex negundo*, *Prunus amygdalus* and *Rubia cordifolia*). Therefore, it can be concluded that "Diaper Rash Cream" is effective and safe in the management of IIDD.

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<p>Functional Somatic Syndromes are illnesses characterized by symptoms that, as yet, have no clear pathophysiology. These include chronic fatigue syndrome, fibromyalgia, Gulf War illness, irritable bowel syndrome, and premenstrual dysphoria. Although the clinical manifestations of these illnesses are not identical, they have in common increased sensitivity to pain, sleep disturbances, difficulty with concentration, and labile mood.</p> <p style="text-align: right;">(NEJM – December 23, 2004)</p>	<p>The Australian government is proposing that by mid 2005 every packet of cigarettes and tobacco sold there will feature graphic images of smoking related diseases over half the front and rear panels.</p> <p>The proposals warnings covering half each pack in January 2001, and Brazil, which introduced similar images in February 2002.</p> <p style="text-align: right;">(BMJ – May 2004)</p>
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