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Comparison of the therapeutic effects of Nystatin, Clotrimazole and Mupirocin in infants with diaper dermatitis: A randomized, controlled trial

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ABSTRACT

Diaper dermatitis is a common cutaneous disorder in neonates and infants, which is caused by chemical irritants, maceration, zinc deficiency and microorganisms. This study aimed to compare the therapeutic effects of three commercial products (Nystatin, Clotrimazole and Mupirocin) in infants suffering from diaper dermititis. This single-center, randomized controlled study was carried out in Iran. A total of 112 infants were included in this trial and assigned to 3 experimental groups (Clotrimazole, Nystatin and Mupirocin) and 1 control group (zinc oxide). Survey participants underwent a designed treatment programs for 7 days. Total symptom score after 7 days (TSS-7) and beginning of recovery were assessed as efficacy parameters. All statistical analyses were conducted using Statistical Package for Social Sciences (SPSS), version 19. Although the severity of diaper dermatitis was significantly decreased in all groups by the end of trial (P <0.001), the reduction rate was found to be considerably greater in the Clotrimazole (2.54±0.58 to 0.75±0.65) and Mupir ocin (2.17±0.71 to 1.00±0.91), respectively. In add ition, time required for first response was significantly lower in Mupirocin, in comparison with the other medications. Clotrimazole and Mupirocin were superior to others with respect to reduction of symptom score and time of recovery, respectively. Therefore, it is important to determine the etiology of skin distruption and priorities of treatment to apply the best therapeutical approach.

Keywords: Diaper dermatitis, Clotrimazole, Nystatin, Mupirocin

INTRODUCTION

Diaper dermatitis is the most common cutaneous eruptions of infancy caused by several conditions, such as zinc deficiency, chemical irritants (urine, faeces), prolonged exposure to moisture, friction and yeasts. Increased skin pH and maceration due to the production of ammonia from stool and urine lead to over hydration of stratum corneum[1]. This can lead to impaired epidermal barrier function which makes the stratum corneum more susceptible totrauma, bacterial and viral infections[2]. Therefore, a wide spectrum of microorganisms can be diagnosed from the diaper area, especially *Candida albicans.* Candidiosis can be observed in 70–80% of all infants, mainly as secondary infection. In some cases, it may be considered the primary cause of disease due to the formation of digestive enzymes[3].

Prevalence of diaper dermatitis is highest among infants aged 6–12 months, since fecal enzymes are present in low levels during the first few months of life. However, some negative side effects may continue till diapers are not further used, including erythema, papules, and irritation[4]. Thus, effective therapeutic agents for diaper dermatitis are directed both at eliminating predisposing factors and reducing adverse effects[5]. Regular cleansing of the exposed skin, frequent diaper changes and administration of corticosteroids, zinc oxide, vitamins A and D and fluid absorbing ointments are recommended as a base-line therapy[6]. However, the main treatment is topical antimicrobial agents, including Nystatin, Clotrimazole and Mupirocin which are frequently applied by clinicians[7]. Mupirocin (Bactroban) is a unique therapeutic agent due to its mechanism of action. It reversibly inhibits iso-leucyl transfer RNA-synthetase, thereby preventing protein synthesis[8]. In contrast, Clotrimazole interferes in the biosynthesis of sterols (eg. ergosterol, a major component of the cell membrane) required for cell membrane production[9]. Similarly, Nystatin binds to ergosterol and forms pores in the membrane[10].

Although many infants may benefit from these products, there is a lack of randomized experiments about the efficacy of the topical antimicrobial agents in diaper dermatitis. Initial survey that compared the efficacy of and clinical outcome of 2% mupirocin and nystatin as treatment regimens in diaper candidosis, indicated that mupirocin produced a greater zone of inhibition than nystatin[11]. In addition, Hoeger et al. carried out a randomized, evaluator-blinded, controlled trial to compare the efficacy and safety of clotrimazole and nystatin in infants with diaper dermatitis. They conclude that despite both treatments were safe and well-tolerated, Clotrimazole is superior to Nystatin with respect to development in efficacy parameter including total symptom score after 7 days (TSS7) and global assessment (GA) of clinical response[12].

In sum, therapy with topical agents for most mild to moderate *Candidiosis* is commonly successful. Relapses and complications, however, are frequent and the management of severe infections remain problematic[13, 14]. In these circumstances, appropriate investigations are required to select the best therapeutic approach. Thus, the present randomized trial aimed to comparethe therapeutic efficacies of three commercial products (Nystatin, Clotrimazole and Mupirocin) in infants suffering from diaper dermititis.

MATERIALS AND METHODS

Study design

This single-center, randomized controlled study was carried out in Iran, in 2015. The parents were informed about the target of present investigation and after obtaining informed consent and institutional review board approval, they were randomly assigned to 4 groups (3 experimental groups and 1 control group).Blinding was not possibleas the commercially available tubes differed in consistency and appearance. Ethical approval was not required, since all of the medications were common methods of treatment and their safety was confirmed by previous studies and relevant centers.

Participants and eligibility criteria

To be eligible for recruitment, all patients were clinically examined by a specialist and a complete history was taken from subjects regarding age, gender, history of infectious disease, type of diaper and daily frequencies of diaperchange and washing diaper area. Children were eligible for the trial if they had a clinical diagnosis of diaper dermatitis with a total symptom score (TSS) of at least 1 (aged between 4 months and 2 years). TSS was determined by five symptoms: erythema, maceration, desquamation, oedema and papules. Severity of eachsymptom was scored on a 4-point Likert scale as follows: 0 = normal,1 = mild, 2 = moderate, 3 = severe according to Hoeger et al.[12].Exclusion criteria were chronic diaper dermatitis persisting for longer than6 weeks, hypersensitivity to the study medications, congenital immunodeficiency, lost of follow up, concomitant skin diseases, including allergic contact and perianal streptococcal dermatitis, psoriasis and anogenital warts. In addition, infants were excluded from the trial if they received corticosteroids or any immunosuppressive therapy within the past 2 weeks. Use of systemic or topical anti-inflammatory therapy, antimycotical drugs, and antibiotics or any other medication against the symptoms of diaper dermatitis were not allowed during the investigation period.

Interventions

The planned study duration was 7 days and the participants underwent a total of three scanning sessions in this period. Parents were instructed to treat the diaper area only with the administered topical antimicrobial agent after washing with lukewarm water and drying the area. We have contacted to the parents via phone numbers to determine the beginning of recovery. Patients in each group were treated with the oitments as follows: Clotrimazole,

two times a day, zinc oxide, three times a day and Nystatin and Mupirocin, four times a day. All medications were administered in the dose of fingertip unit (FTU), *i.e.* the amount of topical drug that is squeezed out from a standard tube on the fingertip of patient. Additional instructions were given to the parents for reapplying the medication accordingly, when the ointment was removed during diaper change. Follow-up visits (sessions 2 and 3) were scheduled for days 3 and 7, respectively. Based on the examinations in 4th day of investigation, the treatment was stopped for children who had completely recovered by that time. However, it was continued to the 7th day for the patients who were not received complete health.

Study Outcomes

Total symptom score after 7 days (TSS-7) and beginning of recovery were assessed as efficacy parameters. Rate of recovery was graded using a 4-point Likert scale (from 0 to 4) for each symptom, as mentioned above. The zero score was representative of complete health, while 1–3 scores were indicative of partial recovery and symptom-scores of 3 and more were defined as unsuccessful treatment.

Statistical analyses

All statistical analyses were conducted using Statistical Package for Social Sciences (SPSS), version 19. The data are expressed as means±standard deviation and number (%).Group comparisons were made using Mann-Whitney *U* test, Student's *t*-test, or one-way analysis of variance (ANOVA) and chisquare test. A *P*-value of less than 0.05 was considered to be statistically significant in this trial.

RESULTS

Baseline characteristics

A total of 112 children were randomized to one of the treatments, while 17 patients were excluded during the research period according to the exclusion criteria. Among this population (95 children), fourthy-eight (50.5%) of subjects were female and 47 (49.5%) were male and the mean age of patients was 6.26±5.96months, ranging from 1 day to 2 years. The children were distributed almost equally in the intervention groups (Zinc oxide: 22n, Clotrimazole: 28n, Nystatin: 27n and Mupirocin: 18n).As shown in table 1, there was no statistically significant difference between the groups, regarding demographic and baseline characteristics including severity of symptoms, beginning of recovery, daily frequencies of diaper change, gender, and age. There was not any side effect from either of the medications.

Table 1.Demographic and baseline characteristics of the study population

Parameters	Zinc oxide	Clotrimazole	Nystatin	Mupirocin	P value
Age	5.77±6.22	6.79±5.14	6.93±6.36	6.28±6.42	P>0.05
Diaper changing	3.19±1.99	2.57±1.40	2.85±1.13	3.17±1.98	P>0.05
Severity	2.32±0.78	2.54±0.58	2.37±0.63	2.17±0.71	P>0.05
Gender					
Male	11(50%)	13(46.43%)	14(51.85%)	9(50%)	P>0.05
Female	11(50%)	15(53.57%)	13(48.15%)	9(50%)	
Types of coverage					
Diaper	21(95.45%)	26(92.86%)	26(96.3%)	16(88.89%)	P>0.05
Napkin	1(4.55%)	2(7.14%)	1(3.7%)	2(11.11%)	

Efficacy parameters

The efficacy parameters were the beginning day of recovery and also improvment in the TSS score after 7 days of treatment. Despite the severity of diaper dermatitis was markedly decreased in all groups by the end of trial ($P < 0.001$), the reduction rate was observed to be considerably greater in the Clotrimazole and Mupirocin, respectively. The respective decreases were 2.32±0.78 to 1.68±0.99 in Zinc oxide group, 2.54±0.58 to 0.75±0.65 in Clotrimazole group, 2.37±0.63 to 1.44±1.05 in Nystatin group and 2.17±0.71 to 1.00±0.91 in Mupirocin group (Tables 1 and 2). On the other side, time required for first response was significantly lower in Mupirocin, in comparison with the other medications (Table 2).

Table 2. Beginning of recovery and severity of diaper dermatitis after treatment in study groups

Parameters	Zinc oxide	Clotrimazole	Nystatin	Mupirocin	P value
Beginning of recovery	2.80±0.63	2.78±0.75	2.88±1.22	2.50±0.65	P<0.05
Severity	1.68±0.99	0.75±0.65	1.44±1.05	1.00±0.91	P<0.05

In another comparison, the prevalence of diaper dermatitis severity in all groups were assessed before and after treatments (Table 3). It can be observed that Clotrimazole and Mupirocin are more efficient in reduction of severity of diaper dermatitis, in compare with zinc oxide and Nystatin, since the disturbution of severity scores were shifted to the lower levels. Among investigated demographic parameters, frequency of diaper changing and washing the area are negatively associated with the improvment of cutaneous eruptions (P<0.05).

Table 3. Severity of diaper dermatitis before and after treatment

Degree of severity	Zinc oxide	Clotrimazole	Nystatin	Mupirocin
Before treatment				
0	0(0%)	0(0%)	0(0%)	0(0%)
1	4(18.18%)	1(3.57%)	2(7.41%)	3(16.67%)
2	7(31.82%)	11(39.29%)	13(48.15%)	9(50%)
3	11(50%)	16(57.14%)	12(44.44%)	6(33.33%)
4	0(0%)	0(0%)	0(0%)	0(0%)
After treatment				
0	1(4.54%)	9(32.14%)	5(18.52%)	6(33.33%)
1	11(50%)	18(64.29%)	11(40.74%)	7(38.89%)
2	5(22.74%)	0(0%)	5(18.52%)	4(22.22%)
3	4(18.18%)	1(3.57%)	6(22.22%)	1(5.56%)
4	1(4.54%)	0(0%)	0(0%)	0(0%)

DISCUSSION

The diaper environment is well-suited to causing skin irritations due to increased moisture of the stratum corneum. In addition, lipases and proteases within feces cause skin irritation. High pH environment of the diaper (attributed to urease in stool or bathing products) also increase the activities of these enzymes[15]. Thus, allowing the child time outside of the diaper provides the most efficacious therapeutic intervention. However, since diaper use is largely unavoidable, barrier ointments and pastes are often the first line treatments[16]. At first, a study indicated benefits of continuous topical administration of petrolatum and zinc oxide used by clinicians and parents[17]. Considering these findings and substantial experience of physicans and parents, medications containing these substances have been employed for decades as first line therapy. The efficacy of zinc oxide was confirmed by this study, as control group. However, Zinc oxide pastes are difficult to wash off and may not be effective for moderate-to-severe diaper dermatitis and may have adverse effects at high concentrations[18]. As a result, in recent years, combination creams containing triamcinolone, nystatin, clotrimazole and betamethasone have gained popularity as a topical therapy, despite a lack of investigations addressing the efficacy and safety of such use. Based on several evidences, the inappropriate use of topical corticosteroids in the diaper dermatitis can lead to Cushing's syndrome, systemic absorption, skin atrophy, and growth delay[19, 20]. On the other side, some experiments reported low potencynonfluorinated topical corticosteroids as safe and effective therapies in the diaper area[21].In present randomized, evaluator-blind, controlled trial, we compared three of the most commonly administered agents in diaper dermatitis, nystatin, mupirocin, and clotrimazole. Clinical cure rates (total symptom score after 7 days of treatment) were significantly higher with clotrimazole and mupirocin than with nystatin and zinc oxide (control group). Our findings are in line with another prospective, randomized controlled study conducted by Hoeger et al. Based on their reports, clotrimazole ointment was found to be significantly more effective than the nystatin and zinc oxide [12]. Although there is a lack of surveys about the treatment of diaper dermatitis by mupirocin, in coincidence with our results, in cases of mild localized staphylococcal infection, mupirocin administered twice daily has been used effectively[22].

Cutaneous superinfection and extent of colonization by microorganisms such as Candida sp. in diaper dermatitis is highly associated with the severity of disease. These findings stress the importance of time in terms of pathophysiological implication of diaper dermatitis[23]. However, as our knowledge, this is the first research investigating the efficacy of drugs by time. Indeed, the other efficacy parameter of this trial was the beginning day of recovery. This measure was significantly shorter in mupirocin than the other medications. Therefore, it is suggested to consider this item as an efficacy parameter for further studies.

In agree with present trial, Borkowski documented that frequent diaper changes and cleaning of the diaper area as often as every two hours, reduce the exposure to irritants in stool and urine[24]. It may be due to maintaining skin integrity by allowing the skin to contact the air and have an opportunity to dry and respite from the forces of the irritants and diaper.

Findings of this survey should be reported with caution, since present study has several limitations including short course of treatment, nonblinding condition, and single center design. Therefore, it is suggested to consider these items in further investigations. In conclusion, clotrimazole and mupirocin were superior to nystatin and zinc oxide with respect to reduction of symptom score and time of recovery, respectively. Therefore, it is important to determine the condition and etiology of skin distruption, to apply the best therapeutical approach. The treatments were safe and well tolerated and any of patients did not demonstrated side effects of administrated medications.

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Declaration of interest
The authors report no conflicts of interest.

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