

Role of menthol in treatment of candidial napkin dermatitis

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Background: The antibacterial, antifungal and probable anti-inflammatory effects of menthol were evaluated in the treatment of napkin dermatitis (ND).

Methods: A pilot clinical trial was conducted in Iran at the Tehran University of Medical Sciences. Eligible neonates with a diagnosis of candidial ND who did not require critical care or systematic antifungal and anti-inflammatory drugs were included in the study. Overall, 84 patients were randomly allocated into two groups: menthol group ($n=42$) receiving standard therapy (topical clotrimazole) plus menthol drops applied topically and control group ($n=42$) receiving standard therapy plus a placebo. Thirty-five neonates in each group finished the course of study and were analyzed for skin rash using Munz and Concannon rash scoring methods before therapy and on the 1st, 3rd, 5th and 7th day after the treatments.

Results: Demographic data and the baseline total skin rash score were not significantly different between the menthol and control groups. The total course of therapy for complete healing was found to be shorter in the menthol group (4.3 ± 1.6 vs. 6.9 ± 1.8 days, $P=0.0001$) and erythema and pustules had a significant ($P=0.0001$) relief in this group. During the study no severe adverse effects of the drug were observed.

Conclusion: Topical application of menthol may be effective in treatment of candidial ND.

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Key words: clinical trial; menthol; napkin dermatitis

Introduction

Napkin dermatitis (ND) (commonly known as diaper rash or nappy rash) is a common disorder in neonates and infants, which is caused by activating factors including contacts, chemical stimulants and/or poor hygiene^[1] as well as predisposing factors such as skin humidity, high skin pH^[2] and infections.^[3] A wide spectrum of gram positive (including *Staphylococcus aureus*) and gram negative bacteria can be isolated from the napkin area in the presence or absence of ND, and the role of bacterial infections is not well defined pathophysiologically. In most ND patients after 72 hours of infection, *Candida albicans* can be isolated from their skin.^[4] In some patients, Candidiosis may be a secondary infection, and in others it may be considered the primary cause of ND due to the production of a protease that may digest the stratum corneum of skin and in turn it may weaken its normal barrier defense system.^[5] Other infectious microorganisms that might be involved in ND are *Streptococci*, *Herpes virus*, *Dermatophytes*, and *Cytomegalovirus*.^[1] Frequent use of topical corticosteroids, soaps, preservatives, napkin tissues, aromatics and topical antibiotics may also play an accentuating role in the course of therapy.^[3] Several agents and their combinations are used for the management of ND including lesion protectants (e.g., zinc oxide, Lanolin, Aquaphore[®]), light and weak corticosteroids (e.g., hydrocortisone 0.5%), antifungals (e.g., nystatin, clotrimazole) and even cholestyramine and sucralfate.^[6,7] Napkin dermatitis is treated successfully outside the hospital setting and is not a common clinical problem in secondary care.^[8] Young parents are familiar with topical corticosteroids in the treatment of ND because these agents alleviate skin lesions of their newborns promptly. With regard to the skin texture of newborn babies, the transdermal absorption of corticosteroids may be high and dangerous

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even if the agents are weak and of low potency.

Herbal medicine is nowadays widely used around the world, and Iran has an ancient history of traditional herbal medicine. Traditionally, concentrated water of *Mentha* was used in Iran as an antipruritic to relieve some gastrointestinal symptoms.^[9] Menthol is a monocyclic monoterpene which is the main compound in the essential oil of *Mentha piperita*.^[10] The major herbal source for natural menthol is *Mentha arvensis*. It is routinely used as a cooling, anesthetic, antipruritic and antiseptic agent in many pharmaceutical formulations, toothpastes and gums.^[11] The antibacterial effect of Aetheroleum *Mentha piperita* against gram positive (e.g., *Staphylococci*) and gram negative bacteria (e.g., *Escherichia coli*) is described elsewhere.^[12] The essential oil of *Mentha piperita* is considered to have inhibitory effects on growth of *Candida albicans*.^[13,14]

Multi-potential pharmacologic effects (antipruritic, antibacterial, anticandidal properties) of menthol makes it an useful medication for the treatment of ND. If menthol could control the candidal and bacterial infections while relieving pruritus, the inflammatory process might be controlled more effectively. This pilot study was to evaluate the clinical use of adding a topical menthol preparation to the standard therapy with clotrimazole in the management of ND.

Methods

This pilot study was conducted in the Department of Neonatology at Valiasr General Teaching Hospital Affiliated to Tehran University of Medical Sciences from March 2004 to July 2006. Eligible patients were neonates aged less than 28 days with candidal napkin dermatitis diagnosed clinically and laboratorily, who were given critical care (ventilators or urine bag) but no systematic antifungal and anti-inflammatory medication (amphotericin B or corticosteroids) nor topical drug (cod liver oil or antibiotics). The neonates were tested for skin allergy to the topical formulation of menthol on the back side of their arm and calf. Absence of erythema, pruritus and inflammation for at least 24 hours were considered no hypersensitivity to menthol. Excluded were neonates who were discharged from the hospital before the 7th day of therapy, who had any critical conditions which required additional systematic or topical therapy or with life-threatening condition. Neonates with relieving signs and symptoms of ND before the 7th day of therapy were not excluded.

Before and during the treatment, the status of the disease and lesions was scored using Munz^[15] and Concannon's method.^[16] The total skin surface of the neonates was divided into 11 parts, and erythema, papules, pustules, scratches and wounds were

monitored before and on the 1st, 3rd, 5th, 7th day after treatment.

Menthol[®] drop (Poursina Pharmaceutical Company, Tehran, Iran; which consists of menthol 5%, ethanol (96°) 25%, and poly ethylene glycol(400) 75%), and a generic formulation of clotrimazole 2% (Parsdarou Pharmaceutical Company, Tehran, Iran) were used as active drugs. The placebo was a drop with the same appearance, packaging and formulation constituents but no menthol provided by the Poursina Pharmaceutical Company. Menthol[®] drop (or placebo drop) was applied to eligible patients (1 drop/cm² on affected area) twice daily and after 10 minutes clotrimazole was routinely applied.

The parents of eligible neonates were informed of the study by one of the investigators, and a written informed consent was signed by the parents. The consent form was in accordance with the *Declaration of Helsinki II* and the *Tehran Declaration for Ethics in Human Researches*.^[17] The study protocol was approved by the Isfahan University of Medical Sciences Board of Human Studies (Registration No.83441).

Statistical analysis was performed with SPSS for Windows (version 11.0; SPSS Inc., Chicago, IL) by the Chi-square test, Mann-Whitney *U* test, Student's *t* test and paired tests. *P* values less than 0.05 were considered statistically significant.

Results

One hundred and six neonates were screened for study entry, of whom 13 did not meet the inclusion criteria and the parents of 9 neonates refused to participate in. The remaining 84 neonates were randomly allocated to the menthol (*n*=42) and control (*n*=42) groups. Six neonates in the menthol group and 4 in the control group discontinued the intervention because they needed other topical drug therapies. The clinical data were incomplete for 1 neonate in the menthol group and 3 in the control group. Therefore, 70 neonates (35 in each group) with fully completed rash score records were statistically analyzed, who completed the 7 days course of study or were healed clinically before the end of the study.

Sex distribution was not statistically different between the menthol and control groups, with a male to female ratio of 15:20 vs. 18:17 (*P*=0.632). Both gestational age (34.1±3.3 vs. 32.8±3.8 weeks, *P*=0.096) and actual body weight (2546±917 vs. 2134±871 g, *P*=0.057) were not statistically different between the menthol and control groups. Before the course of therapy (day 0), the mean ± SEM of total rash score of patients in the menthol and control groups was not significantly different (26.9±3.1 vs. 28.1±2.7, *P*=0.826 by Student's *t* test). After the administration of the drugs

on the 1st day, the total rash score in the two groups was clinically improved (19.0 ± 2.6 vs. 25.1 ± 2.3 , $P=0.062$ by Student's *t* test). On the 3rd, 5th and 7th day of therapy the total rash score was both clinically and statistically significant between the menthol and control groups (8.9 ± 2.1 vs. 12.8 ± 2.0 , $P=0.030$; 3.1 ± 1.0 vs. 4.6 ± 0.9 , $P=0.034$; and 0.0 ± 0.0 vs. 2.5 ± 1.2 , $P=0.049$ respectively by the Mann-Whitney *U* test). The course of complete healing was shorter in the menthol than in the control group (4.3 ± 1.6 vs. 6.9 ± 1.8 days, $P=0.0001$). Erythema and pustules were significantly relieved in the menthol group ($P=0.0001$).

Discussion

Skin occlusion by napkin and urine residuals and stool in the napkin area can cause dermatologic changes of ND, which may be aggravated by infection of *Candida albicans*.^[18] Contact of ammonia under nylon may not cause the signs of dermatitis,^[14] but 10^5 of *Candida albicans* on skin may result in clinical signs of ND.^[12] Fungus can be isolated from the affected skin and stools of neonates for a rate of 41% and 39% respectively.^[13,19] In another study, erythema, papules and pustules in the groin and perineal area were considered causes of candidial ND because the fungus could be isolated from the affected skin in 80% of these cases.^[20] There was a positive correlation between the severity of candidiosis and ND.^[21] Other sources of infections (e.g., gram negative and/or gram positive bacteria) may be considered if erythema lasts for at least 72 hours.^[2,15,16] Topical antifungals and corticosteroids or their combination are commonly used for the treatment of ND^[22] but the safety of these agents is not well determined.^[14,18]

Menthol has multiple pharmacologic effects, including antibacterial effects against gram positive (e.g., *Staphylococci*) and gram negative (e.g., *Escherichia coli*) bacteria, as well as antifungal effect against *Candida albicans*.^[8] Its *in vitro* activity against *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Enterococcus faecalis*, *Trichophyton* and *Aspergillus sp.* is also obvious.^[8] The antifungal effect of menthol has also been confirmed using agar diffusion cutting plug technique.^[13,14] Menthol is also used as a topical analgesic in the temporal areas because of its neurophysiologic and psychologic musculoskeletal relaxing effect.^[8] The anesthetic and antipruritic effects of menthol can be attributed to its fast sodium channel blocking effect.^[6] If a drug has antibacterial and antifungal effects, it could play a unique role in pharmacotherapy of ND.^[23,24] Adding menthol to the standard therapy of ND is useful to its well-known permeation enhancer effect, which is further enhanced in an alcoholic base.^[10] The antifungal effect of clotrimazole

can be augmented as seen in the present study.

In the present study, the total rash score of neonates on the 3rd, 5th and 7th day of therapy was significantly different between the two groups, which indicates the additional beneficial effect of menthol. The number of pustules and the area of erythema were significantly reduced in the menthol group compared with those in the control group, suggesting a probable anti-inflammatory effect of menthol.

Breathable napkins reduce the growth of *Candida albicans* by lowering warmth and moisture in the napkin area, which are essential to the growth of the fungus, and also reduce the level of CO₂ at the skin surface.^[25] In the present study we used breath superabsorbent napkin in both groups.

The present study focused on the safety of topical application of menthol and its dermal direct absorption. Menthol is used ubiquitously as antipruritic, antiseptic, analgesic, and cooling formulations.^[10] It is used as a topical formulation on skin.

In conclusion, this pilot study suggests that topical application of menthol may play a role in the treatment of candidial ND. Further studies are required to identify the proper concentration of the drug and suitable dosage. Toxicological study of topical use of menthol on bare skin of neonates are needed.

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Competing interest: None declared.

Contributors: Sabzghabae AM developed and wrote the protocol, and was responsible for data analysis, and interpretation of results. Nili F performed all physical examinations, protocol review of the study and clinical coordination. Eizadi-Mood N was responsible for data analysis, interpretation of results and scientific editing of the manuscript. Anvari M was responsible for data collecting. All authors have read and approved the content of the manuscript.

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