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Guaiazulene: a new treatment option for recalcitrant diaper dermatitis in NICU patients

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***Aim*: Based on a maternal observation, we aimed to evaluate the treatment effectiveness of guaiazulene (GA) containing local pomade in the high-risk neonates with recalcitrant diaper dermatitis (RDD). *Methods*: We included 30 NICU patients of RDD, with level II-III aged between 22 and 67 days. Study group patients ($n = 20$) were treated with GA containing local pomade (0.05 g/100 g). Control group consisted of patients who had extended antifungal treatment. A visual scale was used to assess the response to treatment at the end of a week. Scoring was done at the beginning of the treatment, on the first, third and seventh days. *Results*: Statistically significant differences in visual scores were determined between the two groups at the initial and following days of the treatment. In study group, improvements at the first and third days of the treatment were better than those of control group. Additionally, complete recovery rate in study group was better than that in controls. *Conclusion*: Having beneficial but no adverse effects, GA containing local pomade provided rapid recovery in risky neonates with RDD, who required rapid improvement.**

Keywords: Diaper dermatitis, guaiazulene, newborn

Introduction

Diaper dermatitis (DD) or napkin dermatitis is defined as an eczematization of the areas covered by diaper. It is most likely irritant contact dermatitis, a nonimmunologic reaction triggered by irritants present in the area covered by diaper [1,2]. Since change of physiology in the diaper area is the main reason for DD, it is still the most common dermatologic problem in infants [2]. In neonatal intensive care units (NICU), the routine skin care of diapered area includes wiping and diapering. Today, NICUs are filled by risky preterm babies. These babies have large amounts of immunocompromise features. Additionally, the use of broad-spectrum antibiotics and invasive medical devices increases the tendency to abnormal colonization on the skin and mucosa. This unique population is also at risk of recurrent and/or recalcitrant diaper dermatitis (RDD). There are a small number of studies on treatment of recalcitrant diaper dermatitis in risky neonates who are followed up in NICUs.

Guaiazulene (GA) containing topical herbal pomade is mainly used for the prevention and treatment of nipple cracks in nursing mothers [3,4]. Guaiazulene, also known as "Azulon" or "Isopropyl-1,4-dimethylazulene", is a dark blue crystalline hydrocarbon, which is a derivative of azulene. Guaiazulene or guaiac(um) is obtained mainly from the oil of *guaiacum officinale* tree seen in northern coast of South America and the Caribbean, and chamomile oil [5,6]. Different pharmaceutical forms of GA were used over the centuries for treatment of various diseases due to their various beneficial effects, such as anti-inflammatory, antiseptic, antibacterial, epithelializing, antioxidant, antitumor, immunemodulatory, antifungal, expectorant, diaphoretic, diuretic, laxative and an acrid stimulant properties [5,7–9]. Guaiazulene was approved by FDA as a cosmetic colorants additive, and is used in many cosmetic products and toothpaste [10].

A mother, who was using GA containing local pomade for her nipple cracks, reported us a quick improvement in DD in her baby after using this local preparate. Upon this, we aimed to perform controlled prospective study of effects of GA on recalcitrant diaper dermatitis in risky infants.

Material and methods

Infants with RDD from the NICU (level II and level III) of the Erciyes University Gevher Nesibe Hospital were recruited from May 2009 to January 2011. The majority of NICU patients were admitted for prematurity and associated problems. Parents agreed and provided written informed consent. This study was approved by the ethics committee of the institute.

In our neonatology unit, diapers are checked every 3 h (eight times) a day and those contaminated with urine or feces are immediately replaced. Commercial pH-buffered wipes are used for cleaning the skin of the diapered region. Also, all of the fed newborns by oral and oro-gastric tube are given p.o. nystatin 100.000 IU t.i.d. for invasive fungal infection prophylaxis during hospital stay in our unit [11]. Barrier effective creams including zinc-oxide and petrolatum were locally applied three times a day as the initial treatment modality of DD in our unit. In cases of DD lasting more than a week, a local antifungal agent was added to the initial treatment for a week. Recalcitrant DD was determined as diaper dermatitis which lasted more than two weeks despite the overall treatments.

Subjects with RDD were included into the study or control groups randomly. All infants used the same products for routine skin care (diapers, wipes, bathing) throughout the study. In control group, the same treatment including a barrier effective creams plus local antifungal agent was continued for one more week. In study group, the GA (Garmastan® pomade, 0.05 g/100 g,

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Med Ilac, Istanbul, Turkey) was applied three times per day by NICU nurses. No other topical product was used during the study in both groups.

A five-point visual scale was used to evaluate the severity of dermatitis and response to the treatment (none = 0; mild erythema = 1; moderate erythema = 2; moderate erythema plus maceration = 3; and severe erythema plus pustules or ulceration = 4) [12]. Scoring was made by two blinded research staffs on the first, third and seventh days. Administrations of the local agents were discontinued after 48 h in cases whose rash score became zero. Disappearance of severe or moderate rash was considered a positive therapeutic effect. Any new sign or symptom that occurred during therapy was recorded as an adverse effect in study group.

Inclusion criteria were defined as birth before 38 gestational weeks by Ballard scores, clinical stability, ability to obtain more than 50% of the daily calories needed by oral or oro-gastric tube feeding, being younger than 10 weeks, and failure to improve of DD with initial and extended treatments in a total of more than two weeks. The exclusion criteria were defined as being older than 38 weeks of gestation at birth and older than 10 postnatal weeks of age at the presentation, clinical instability, acute rash (existing less than a week and respond to initial and/or extended treatment within two weeks) and receiving phototherapy.

Wilcoxon signed ranks test was used for the comparison of rash scores during the study and Mann–Whitney *U*-test was used for determining the differences within the groups with $p < 0.05$ assumed to be significant.

Table I. Demographic characteristics of the study population.

	Control	Study	*p*
Number of infants	10	20	
Gender (M/F)	6/4 (60%/40%)	14/6 (70%/30%)	
Gestational age at birth (week)			
Mean ± SD	33.80 ± 1.93	33.20 ± 2.96	0.86
Median (range)	33.5 (31–37)	32 (28–37)	
Birth weight (g)			
Mean ± SD	2023 ± 700	2114 ± 931	0.60
Median (range)	1770 (1230–3300)	1735(900–4060)	
Treatment beginning day (day)			
Mean ± SD	34.5 ± 4.74	34.3 ± 10.26	0.48
Median (range)	33.5 (28–41)	33. 0 (22–67)	

Results

During the study period lasted a year 30 infants who filled the inclusion criteria were enrolled the study. Twenty of them were included the study group and control group were consisted of remaining 10 of them. Demographic characteristics of the study population were shown at Table I. Difference of the birth weight and gestational ages of both groups was not statistically significant.

Average day of the starting extended treatment was 34.5 ± 4.7 (median: 33.5 range: 28–41) days in control group. Average initial day of the GA treatment was 34.3 ± 10.2 (median: 33, range: 22–67) days in study group. Difference of the average-initial day of the treatment was not statistical significant within groups (Table I).

In control group, the mean rash score was 3.3 ± 0.67 at the beginning, same scores continued at the first day (3.3 ± 0.67, $p = 1.0$) and began to decline after the third day (2.9 ± 0.73, $p = 0.46$). At the end of first week, mean rash score was 2.50 ± 0.52 ($p = 0.46$) and moderate erythema with and without maceration was continued in all patients (Figure 1).

In study group, mean rash score was 3.50 ± 0.76 and decreasing to 2.25 ± 0.96 ($p < 0.001$) and 1.1 ± 1.02 ($p < 0.001$) at the treatment day 1 and 3, respectively. At the end of the week, the mean total score was 0.2 ± 0.41 ($p = 0.001$), and four of the 20 patients (20%) had mild DD. In these patients, lesions completely recovered with

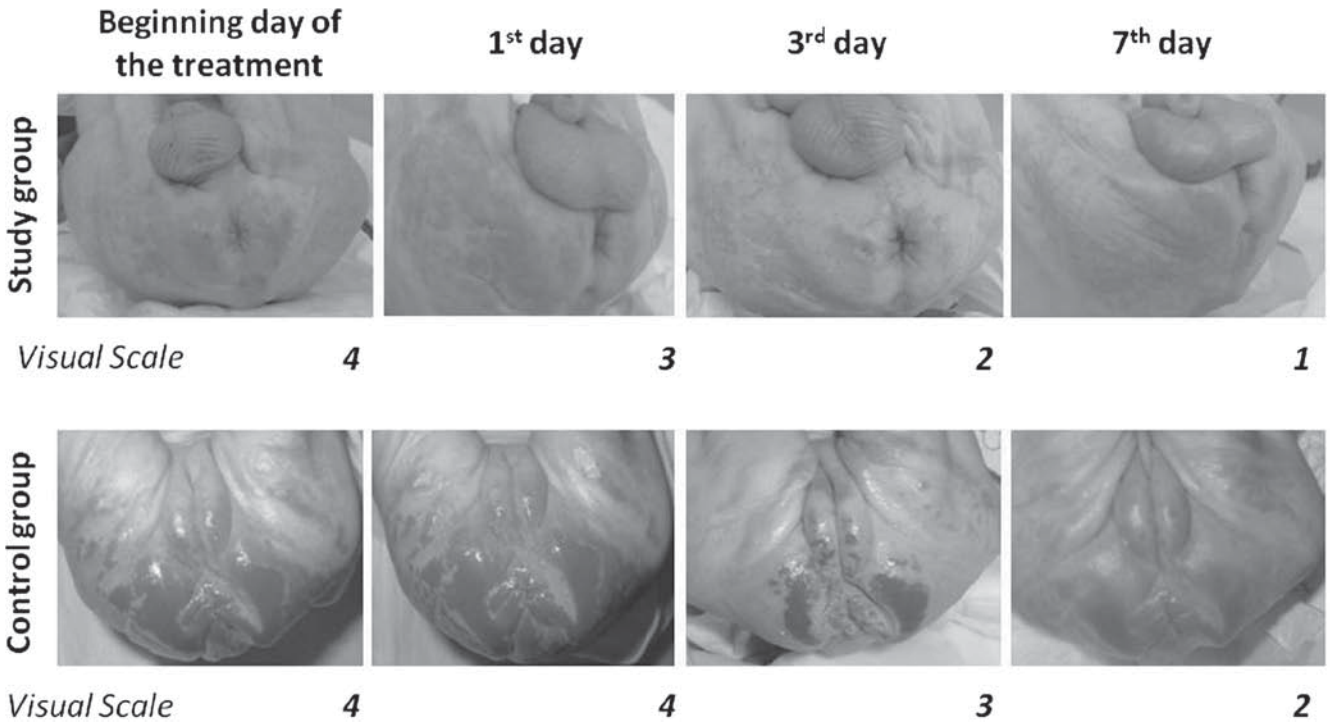


Figure 1. A comparative example of the patients with recalcitrant diaper dermatitis in study and control groups.

treatment of 10 days on average. The remaining 16 (80%) patients improved completely within a week (Graph 1).

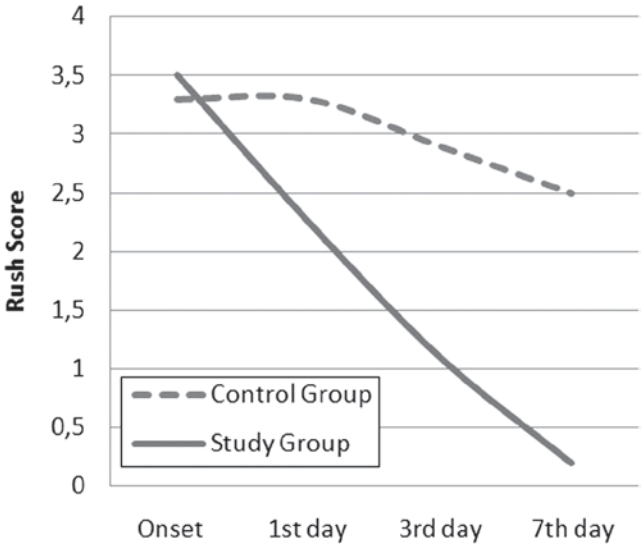
Difference of the treatment beginning days and initial rash scores of the groups was not significant. However, difference of the rash scores of following days of both groups was statistically significant (Table II).

No local or systemic side effects were detected in any patient during local GA application.

Discussion

The present study showed that remedial effects of GA containing local drug are better and faster than extended routine treatment on recalcitrant DD in risky newborns who are desired quick healing. Its beneficial effects are more prominent than routine treatment in the first days of treatment.

Overhydration, skin irritants (e.g. urine, feces, associated enzymes and bile salts), locally increased temperature, obstruction of the surface skin, mechanical friction (skin-diaper and skin-skin), increased skin pH (prolonged exposure to urine and feces), use of broad-spectrum antibiotics (abnormal colonization), gestational age (inherent stratum corneum barrier maturation), diet (fecal composition), fluid content of diet (urinary frequency), and underlying medical conditions are the factors causing DD through disruption of the stratum corneum lipids in the diapered region of skin [13–15]. NICU patients, particularly premature infants, show various immune deficiencies. Also, they have abnormal skin and mucosal flora due to employed invasive medical devices, nonphysiological nutrition form (oro-gastric gavage), use of broad-spectrum antibiotics, and damaged skin/mucosal integrity. When skins with the immature structure and insufficient barrier function are covered with diapers, defective structure and function of stratum corneum deteriorate [13,16,17]. Routine care of NICU patients should include diaper skin care as well as whole skin. Unless there is any skin problem, skin care of diaper region consists of wiping and changing diaper after every contamination with feces or urine [16]. Diapers should be changed frequently to keep skin dry and to reduce skin contact of the diaper area with urine and especially feces [18–21]. This local remedies, balances the skin's hydration, and prevents contact with skin irritants [18–22]. In our unit, commercial diapers are used and checked every three hours and those contaminated with urine or feces are immediately replaced. Commercial pH-buffered wipes were used for cleaning the soiled with feces diaper area.



Graph 1. Mean rash scores of the groups. In study group, improvement of the lesions was better than control group. Better curative effect of the GA was apparent from the first day to the end of the treatment.

Topical use of barrier effective creams such as zinc-oxide or petrolatum are useful for DD [13,17,18]. Nonresponsive cases to treatment for DD longer than two weeks are considered to be recalcitrant. In this situation, adding to the treatment a locally antifungal agent recommended. Also, nonpotent corticosteroids are used in treatment for suppressing the inflammation in severe inflamed cases [13,17,18]. *Candida albicans* is often isolated by 80% in diaper area rash, which lasts more than three days [23–25]. Superficial fungal infections can be treated with topical nystatin, miconazole, clotrimazole, and ciclopirox [13,15,17,21,23–25]. In our patients, who did not improve after initial treatment, a local antifungal agent was added to the treatment. However, recovery rate in control group was worse than study group (Graph 1).

Recalcitrant and recurrent DD are frequently seen in those with thrush, although oral antifungal medications probably have a limited role in the treatment of candidal DD [13,17,21,24]. In our unit, we gave p.o. nystatin 100.000 IU t.i.d. to all of the fed newborns for prophylaxis of the invasive fungal infection during hospital stay [11]. Hence, we applied all known treatment modalities to patients with RDD.

Guaiazulene is a member of the azulene group drugs, which has been used for centuries in various diseases. Currently, it is used as a colorant in cosmetic products, and as antioxidants in canned foods. Beneficial features of GA in clinical practices are its anti-inflammatory, epithelializing, antioxidant, antiseptic, antifungal, antitumoral, antiulcer and immune modulator properties [9,11,22,26–28]. Anti-inflammatory effect suppresses by inhibiting of lipid peroxidation COX-2 [8,9,26,27]. It is used in conjunctival injuries [29], skin damage resulting from UV exposure [30], atopic dermatitis [22], gingival, mucosal diseases of mouth and after oral surgery [18,31,32] due to its epithelializing effect. Additionally, it is used in water-soluble mucosa-adhesive polymer films, which are used in acute radiation-induced oral mucositis due to epithelializing,, antifungal and antibacterial characteristics [31–34]. It has antibacterial effects against to *S. aureus, S. fecalis, E. coli, P. aureginosa, H. pylori*, and other enterobacterial agents [6,8,33]. It has also a potent effect to *C. albicans* [7,27,34]. Guaiazulene may be useful in DD by reducing inflammation, balancing the hydration, and improving

Table II. Clinical effects of the topical treatments on patients with diaper dermatitis.

	The age at the onset of treatment		Rash scores							
			At the onset		1st day		3rd day		7th day	
Groups	Control	Study	Control	Study	Control	Study	Control	Study	Control	Study
Mean ± SD	34.5 ± 4.74	34.3 ± 10.26	3.3 ± 0.68	3.5 ± 0.76	3.3 ± 0.68	2.25 ± 0.97	2.9 ± 0.74	1.10 ± 1.02	2.5 ± 0.53	0.2 ± 0.41
Median (range)	33.5 (28 to 41)	33 (22 to 67)	3.0 (2 to 4)	4 (2 to 4)	3 (2 to 4)	2 (1 to 4)	3 (2 to 4)	1 (0 to 3)	2.50 (2 to 3)	0 (0 to 1)
p value	0.50		0.40		0.007		<0.001		<0.001	

the surface epithelium of stratum corneum layer. Also, it is useful in nipple cracks probably with a similar mechanism. Our study could be demonstrated that GA was effective to RDD, and provided a rapid improvement. Its effects on the first and third treatment days were more pronounced than controls (Graph 1). Additionally, completely cure rates were significantly higher than the control group at the end of the first week of treatment.

Today, while increased *in vitro* studies on cytotoxic and photoreactivity features of GA, no known severe side effects of local use of GA have been reported [7,10] except allergic contact chielitis in users of GA containing toothpaste [30]. GA and azulene derivatives have been reported to be cytotoxic against normal human cells and human tumor cells [35]; moreover, azulene caused DNA damage in human Jurkat T-cells [36]. The photoreactivity of GA can cause photosensitization when it is photoexposed after application on the skin [37]. Since it is photolable, GA may degrade and lose the some effects or can create irritants in the applied skin region under a normal level of light [29]. However, a recent study resulted in findings suggesting that light decrease the GA cytotoxicity on human (gingival) cells resulted from accelerating the apoptotic mechanism by degraded [37]. Despite the all controversial knowledge on the photoreactivity of GA, light related side effects are not expected in the diaper area which is protected from light. We also did not see any systemic and/or local side effects.

There are some limitations in our study. The study and control population was small due to scarcity of the newborns with recalcitrant DD who followed-up in our NICU We attribute the scarcity of the incidence of dermatitis in our unit to routine maintenance as well as oral nystatin prophylaxis in all fed newborns in our units. Diaper-free periods as a treatment for DD are not proper for NICU patients because of facilitating environmental bacterial contamination with feces and urine.

Recalcitrant diaper dermatitis in hospitalized high risky premature infants by remedies is difficult. Our data indicate that GA, by various beneficial effects on diaper skin area, may be a useful agent in cases with RDD. However, further studies will be needed to prove its safety and effectivity in neonates.

Declaration of Interest: The authors report no conflicts of interest.

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