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ORIGINAL ARTICLE

Comparison the effects of topical application of olive and calendula ointments on Children's diaper dermatitis: A triple-blind randomized clinical trial

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Abstract

This study compares the effective of of topical application of olive and calendula ointments on childrens' diaper dermatitis (DD). This triple-blind clinical trial was conducted on 73 healthy children under the age of 2 years with non-severe and not infected DD, referred to a pediatric healthcare center in Tabriz, Iran. The children were assigned to 1.5% olive ointment (n = 37) and 1.5% calendula ointment (n = 39) using a random block method with the ratio of 2:2. The severity of DD in both groups was measured and compared on a six-point scale on days 0 (before the intervention) and 3, 5, and 7 after interventions. The findings releaved there was not significant stastistical difference between the olive oil and calendula groups in terms of severity of DD in the third, fifth and seventh days. No adverse effect was reported from either of the medications in this study. The external validity and consequently the ability to generalize the findings may be diminished as this study was conducted at a single site. Owing to olive ointment and calendula ointment providing the same results in the healing of DD, olive ointment can be used as an alternative case to DD.

KEYWORDS

calendula, diaper dermatitis, olive, traditional agents

1 | INTRODUCTION

Diaper dermatitis (DD) is the most common type of skin inflammation in infants (Ravanfar, Wallace, & Pace, 2012). It is also one of the most common skin diseases in infants and children, and most children experience it at least once (Blume-Peytavi et al., 2016). The global prevalence of DD is between 7 and 35%. In some studies, it is reported to be up to 50% (Hockenberry & Wilson, 2014). DD accounts for 25% of the causes for referral to a pediatrician and physicians (Hockenberry & Wilson, 2014). This disorder usually starts from 3 to 12 weeks and reaches the peak at the age of 6–12 months (Uber et al., 2015).

DD causes behavioral disorders, such as restlessness, crying, irritability, impaired sleep patterns, and nutrition in children and anxiety among parents (Stamatas & Tierney, 2014). It may be initially associated with localized asymptomatic erythema (Hockenberry & Wilson, 2014) and may be involved by secondary infection with normal and opportunistic flora, such as Streptococcus and fungus (Visscher, 2009).

Several therapies for DD in children have been developed. These treatments include chemical and alternative therapeutic and traditional treatments. The Chemical treatments include zinc oxide, vaseline lotion (Xhauflaire-Uhoda, Henry, Piérard-Franchimont, & Piérard, 2009), petrolatum, talcum powder, ointment vitamin A-D (Li, Zhu, & Dai, 2012), in cases of involving the bacterial and fungal infections, topical antifungals, such as clotrimazole, miconazole, nystatin (Fernandes, Machado, & Oliveira, 2009), and corticosteroids, such as betamethasone and triamcinolone are considered (Ference & Last, 2009). Other suitable alternative and herbal therapies include lanolin, calendula (Li et al., 2012), *Aloe vera* (Panahi et al., 2012), bentonite (clay shampoo) (Adib-Hajbaghery, Mahmoudi, & Mashaiekhi, 2014), breast milk (Farahani, Ghobadzadeh, & Yousefi, 2013), honey, olive oil, and beeswax (El Sakka, Abdulrhman, Iman, & Shehata, 2013). Each of these drugs has side effects and may lead to allergies (Stamatas & Tierney, 2014) and drug resistance to some antibiotics and respiratory complications (Sinniah, 2011). Long-term use of corticosteroids may also be associated with adverse effects, such as epidermal atrophy,

hypothalamic–pituitary–adrenal (HPA) axis suppression, Cushing's syndrome, growth interruption (Emdadi & Bazmamon, 2004), and granulomas of infancy (Al-Faraidy & Al-Natour, 2010).

Calendula is a one of common herbal remedy used for DD (Noonan, Quigley, & Curley, 2006). In some study has revealed that Calendula can cause dermatitis by itself (Bolognia, Jorizzo, & Schaffer, 2012). Therefore, strategies to avoid the negative consequences of topical administered medication were needed.

Olive oil has a long history of use as a pharmaceutical and home remedy for minor ailments such as burns (Zahmatkesh & Manesh., 2015), cord separation and skin disorders (Erenel et al., 2010). In addition, it is a natural and nongreasy lubricant (Waterman & Lockwood, 2007). Active components of olive oil include oleic acid, phenolic constituents and squalene. The most important and highly existing phenolic constituents include hydroxytyrosol, tyrosol and oleuropein, which have antioxidant and anti-inflammatory functions (Cicerale, Lucas, & Keast, 2012). The components of squalene in olive oil include vitamins K, D, and E, beta-carotene and Ubiquinol-10, which have antioxidant properties (Lopez et al., 2014). Many evidences indicate the anti-inflammatory and protective effects of olive oil in treatment of DD without significant side effects (Dokmanović et al., 2015; El Sakka, Abdulrhman, Iman, & Shehata, 2013; Khadem-Haghighian, Koushan, & Asgarzade, 2012; Kiechl-Kohlendorfer, Berger, & Inzinger, 2008). In a study conducted by Webb et al. (2008) indicated the olive-based emulsion was well tolerated in critically ill neonates. Olive oil is used as an oily base in many moisturizing and curing creams in children's products (Zahmatkesh & Manesh, 2015). Furthermore, It is suggested that Olive oil can be effective in the treatment of seborrheic dermatitis, acne, psoriasis, and atopic dermatitis (Cui, Xin, Yin, Zhang, & Han, 2015). Nevertheless, there is some studies indicate that topical oils includes olive oil on baby skin may damage the skin barrier and lead to childhood atopic eczema (Danby et al., 2013). The use of oily ingredients, including olive oil considerd to have a little sesitizing or irritant potential especially on patients with atopic dermatitis and other chronic eczematous disorder (Kränke, Komericki, & Aberer, 1997). By contrast some studies reveald the benefits of the vegetable oils may be due to fatty acid effects on the lipid structures of the cutaneous barrier (Darmstad & Dinulus, 2000; Darmstadt et al., 2002). A theory suggests that fatty acids from the oils are absorbed in the blood and thus modulate the barrier function and other aspects of the immune function from other entrance gates of the pathogen agents (Sarkar, Podder, Gokhale, Jagadeesan, & Garg, 2017).

A search of the literature found no study that assessed and compared the effect of olive ointment with other DD care preparations. The current study compared the effective of olive ointment and calendula ointment on children's DD.

2 | METHODS

2.1 | Design

This was a triple-blind randomized clinical trial with a control group. The subjects of this study were children with DD that were referred to a pediatric healthcare center in Tabriz, Iran from May first to the end of July 2017. The sampling method was simple random and it was performed until the required number of subjects were acquired. After obtaining institutional review board approval and informed consent, children who met the entry criteria were randomly (using a permuted-block randomization method) assigned to either the olive ointment or the calendula ointment group (made by pharmacy department of Shahid Beheshti in Tehran, Iran). The planned study duration was 10 days. Children in each group were treated with the respective topical after diaper changing per day for a period of 7 days. To determine irritant reaction, an appropriate amount of respective ointment was applied to the skin of the arm of the baby (1.1 cm) and then was examined after 20 minutes. In the absence of skin reaction, parents were given instructional materials on how to care for the diaper area properly and treat with the medication. The medication containers (30 g tubes of 1.5% olive ointment and 1.5% calendula ointment) were coded by the pharmacist after the preparation in the pharmacy department of Shahid Beheshti University of Medical Sciences. The mothers, the investigator, and the assessor as well as the statistician were blinded.

The study was approved by the university ethics committee (Iran University of Medical Sciences, Tehran, Iran) and complied with the Helsinki Declaration. Moreover, the children's parents involved in the study were fully informed of the care process of the and provided signed consent preceding the study.

2.2 | Participants

Inclusion criteria were: being full-term at birth, age 0–24 months, no history of drug or food allergy, non-use of immunosuppressive drugs or antibiotics, and absence of known underlying diseases. No need for special treatments, no hospitalization, no bacterial and fungal inflammation, having less than a score of 5 (≤4) based on the six-point scale. Exclusion criteria during the study were the use of other medications to treat DD, urinary tract infection, skin allergy in the place of dermatitis and failure to respond to treatment within the first 3 days or worsening the severity of DD.

2.3 | Dermatitis area care

In both groups, the hygiene advice was to use a slightly larger diaper to minimize friction, wash the baby after each change of diaper, to not use a napkin or scented soap, to dry the site with the least friction, change the diapers on time, and not cover the area for a few hours a day. This was communicated to the mothers using face-to-face methods and an educational pamphlet. They were also advised to inform the researcher if they had an exacerbation of inflammation or a desire to use another medication. The incidence of side effects and adverse reactions were recorded at the end of the week by the researcher, who was blinded to the group assignment. To reduce interference factors, diapers with a same brand were prescribed by the pediatrician. Most of the subjects had the same brands of diapers (Figure 1).

2.4 | Assessmnt of trial variables

The variables of this study were measured as follows:

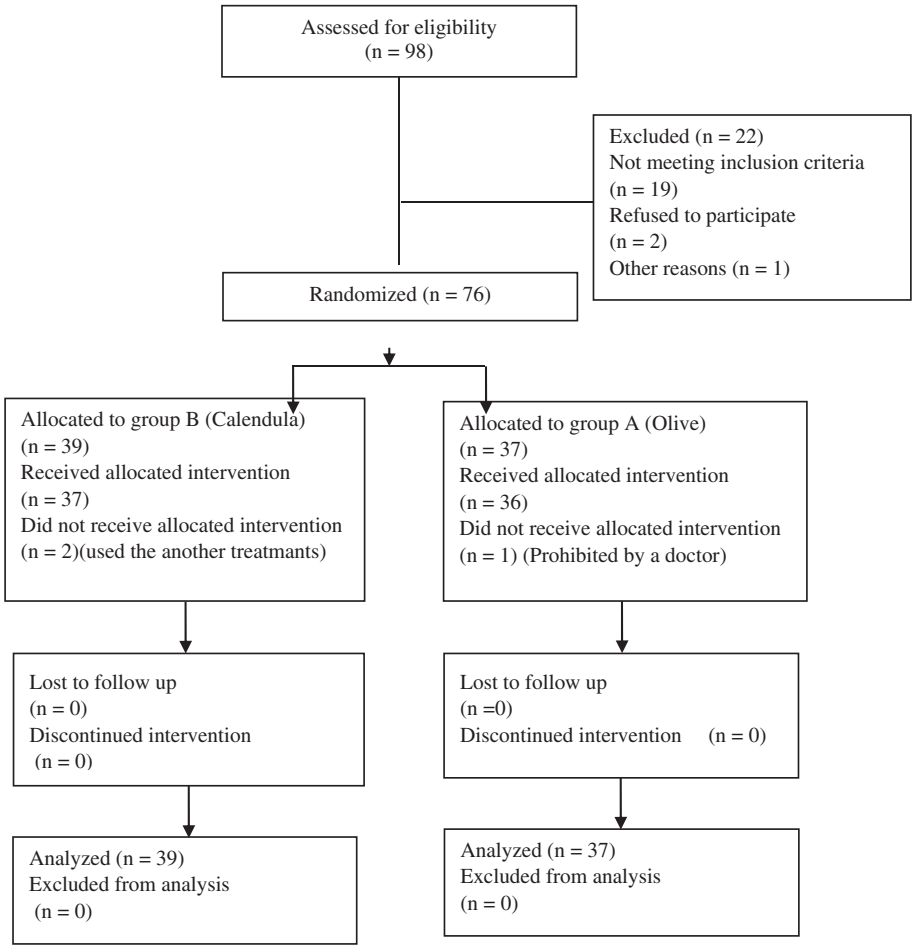

FIGURE 1 The enrollment of participants into two groups of olive oil ointment and calendula ointment

2.4.1 | Demographic characteristics form

This tool included questions about age, gender and ethnicity of the children, and was completed after receiving the written consent from their parents.

2.4.2 | Daily care form

This form included questions such as the time the children spent without a diaper, the numbers of diapers being changed, the frequency of the use of ointment the duration of dermatitis and side effects caused by taking medications. At the beginning of the study, it was presented to mothers and they were asked to complete this form on a daily basis and bring them to the hospital and deliver them to the researcher at the end of the seventh day of intervention.

2.4.3 | Measurement of the severity of diaper dermatitis as primary outcome

In order to measure the severety of dermatitis, a six-point scale (Al-Faraidy & Al-Natour, 2010; Baharestani & Ratliff, 2007; El Sakka et al., 2013; Ravanfar et al., 2012) was used on days 0, 3, 5, and 7 of the intervention. The degree of DD based on this scale was as follows: 0 (no erythema), 1 (slight, diffused, or partial erythema), 2 (completely visible erythema), 3 (severe erythema without deep infiltration), 4 (severe erythema with deep infiltration), 5 (severe erythema with deep infiltration and vesiculation or epidermal defects).

In both groups, the method of measuring the severity of DD using a six-point scale was taught to the mothers using colored images. The researcher assessed the rate of recovery and adherence to the treatment via the telephone, on the third and fifth days of the intervention. The severity of DD in children on day 0 (the time when the mother and child are present in the hospital) and the day 7 (the time of referral to the hospital) was evaluated by the researcher using this scale. It is worth mentioning, the researcher at days 3 and 5 contacted the mothers with visual communication devices in diagnosis assistance. This scale was valid and reliable and was used in numerous studies. In the present study, its reliability was confirmed by the *inter-observer agreement* method between researcher (ZSH) and a pediatrician who was familiar with the study scale (SHO) who were with the Kappa coefficient of 0.9. The effective of the treatment was determined by complete healing in the dermatitis area and getting score 0 based on the scale. The interventions in both groups were continued for 7 days.

2.5 | Sample size

The sample size was determined to be 76 children according to $\alpha = 0.05$, $\beta = 0.2$, $d = 0.5$, the standard deviation reported by a previous study ($\delta 1 = 0.68$, $\delta 2 = 0.73$) (El Sakka et al., 2013), and 20%

possibility of dropouts (n = 38 samples in each control and experiment groups).

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 \left(\delta_1^2 + \delta_2^2\right)}{d^2} = \frac{(1.96 + 0.84)^2((0.68)^2 + (0.73)^2}{(0.5)^2} = \frac{7.8}{0.25} = 32$$

2.6 | Statistical analysis

The differences between the topical application of 1.5% Olive ointment and 1.5% Calendula ointment were assessed using the chi-squared test on nominal and ordinal data and using the independent samples t-test for quantitative data. The DD scores from the baseline were ordinal data. These were analyzed by performing the Mann–Whitney U test to compare groups at each reference time. We calculated a post hoc pairwise comparison with the Wilcoxon signed-rank test when $p < .05$ was in the analysis of variance. Statistical analyses were performed using SPSS version 20 software. $p < .05$ was considered statistically significant for analyses.

2.7 | Findings

In this study, 76 children participated as follows: olive ointment 1.5% (n = 37) and calendula ointment 1.5% (n = 39). During the study, two children from the group of calendula ointment due to another treatment and one child from the olive ointment group were prohibited by the physician to continue the given medication. Nevertheless, these children were still checked on throughout the study until the end of study. There was no significant difference between the topical application of the Olive ointment and Calendula ointment groups in any of the demographic or baseline characteristics (Table 1).

According to the results of this study, no statistically significant difference was found between the groups in terms of the severity of DD on the day 0 (before the intervention). The initial signs of healing inflammation began in both groups after first day of intervention. According to the results of the Mann–Whitney U test, no statistically significant differences were found between the groups in improving the DD on days 0, 3, 5, and 7 of the intervention ($p > .05$; Table 2; Figure 2).

3 | DISCUSSION

The present study was the first research to campare the effects of olive ointment and calendula ointment on DD in children. Evidence from the present study showed that olive ointment was effective in healing DD as much as calendula ointment. The severity of dermatitis on days 0, 3, 5, and 7 was similar between the groups. No similar study founded in the literature research to assess the effects of olive oil alone or compared with other medications on the treatment of DD in children. Therefore, there is no source for comparison. Nevertheless, we used the most relevant studies to compare their findings with those of the present study.

Kiechl-Kohlendorfer et al. (2008) investigated the effect of olive-lanolin oil on skin integrity of preterm infants and the results were compared with Bepanten and control groups. Olive-lanolin oil caused no side effect and resulted in less inflammation than those treated with Bepanthen cream. Also, both groups (Olive-lanolin oil and Bepanthen cream) showed lower inflammations compared with the control group ($p < .001$; Kiechl-Kohlendorfer et al., 2008).

El-Sakka et al. (2013) compared the effect of olive oil, honey and wax with nystatin on DD in infants. While there was no statistically significant difference in the score of symptoms in the groups before the intervention, mixture of olive oil, honey and wax were more effective than nystatin on day 5 (p = .04) and on day 10 (p = .001) of the intervention. The reason behind the superiority of this mixture could be attributed to either interactions of the three agents or the simultaneous positive effects of the three agents on the inflammation(El Sakka et al., 2013).

Cui et al. (2015) studied the local effect of olive oil on the prevention of radio dermatitis in patients with nasopharyngeal carcinoma in the acute clinical phase. Similar to the findings of the present study, it confirmed the preventive and therapeutic effect of olive on skin inflammation. Finally, it was found that mild inflammatory reactions due to irradiation (grades I and II) occurred in 93.6% of the intervention group and 72.3% of the control group. Severe dermatitis during the radiotherapy and chemotherapy in the intervention group was significantly less than that in the control group ($p < .001$). In this study, olive oil was used as a prophylaxis, which was definitely an oily and effective ingredient for relieving inflammation. The positive effect of olive oil as an oily and effective ingredient, in comparison with control group where no effective material was used, is justified (Cui et al., 2015).

Also, the of Oğuz, Işık, Güngör, Şeker, and Ogretmen's (2014) study on the protective effect of olive oil for sore nipples during nursing practice. 56 persons participated in the study. At the end of the study, 50 (89.2%) patients were more satisfied with the use of olive oil than lanolin oil and 6 (10.8%) were satisfied with the use of lanolin oil. Also, 37 (66.1%) patients in the olive oil group and 26 (46.4%) patients in the lanolin oil groups did not report any pain(Oğuz et al., 2014).

By contrast, there is some study that challenged the usefulness of topical oil on skin. Cooke et al. (2016) assessed the feasibility of topical oils on baby skin in terms of development to childhood atopic eczema by a controlled, assessor-blinded study. 115 healthy neonate srandomly assigned into three groups of olive oil, sunflower oil, and no oil. The results reveald significantly improved hydration but significantly less improvement in lipid lamellae structure in both oil group compared to the no oil group. The study suggests being cautious about the use of oils on neonatal skin (Cooke et al., 2016). Another study by Danby et al. (2013) conducted to ascertain the effect of olive oil and sunflower seed oil on the biophysical properties of the skin. Finally, the results showed in contrast to sunflower seed oil, topical treatment with olive oil significantly damages the skin barrier (Danby et al., 2013). Kränke et al. (1997) performed a study to evaluate allergic reaction regarding to olive oil by "positive" patch test. 100 objects (77 woman and 23 men) enrolled and assessed. At the end of study, five patients (two men) showed "positive" test reaction. Finaly only one patient could be classified probably allergic. The study considered

TABLE 1 Demographics and baseline characteristics of study participants and comparisons between olive oil ointment 1.5% and calendula ointment groups 1.5%

	Olive oil ointment group (n = 36)		Calendula ointment group (n = 37)		p value[a]
Gender, *n* (%)					.197
Male	15	41.7	21	56.8	
Female	21	58.3	16	43.2	
Age (month), mean (SD)	7.56 ± 5.27		7.2 ± 4.3		.745
Ethnicity, *n* (%)					.199
Turk	35	97.2	32	86/5	
Non - Turk	1	2.8	5	13.5	
The time without diaper per day, mean (SD)	1.19 ± 1.26		1.06 ± 1.27		.67
The numbers of diaper change per day, mean (SD)	5.58 ± 1.84		6.13 ± 0.91		.214
The times of ointment consumption per day, *n* (%)					.337
Less than 4 times	22	61.1	20	54.1	
4–5 times	9	25	4	10.8	
More than 5 times	5	13.9	13	35.1	

[a] $p < .05$ is significant.

that olive oil not suitable to applied in patient with atopic eczema and venous disorders. Even though the olive oil appears weak reaction factor (Kränke et al., 1997).

The current study showed olive oil can be effective as much as calendula oil. Although the study concludes that inflammation could be reduced by olive oil that have antioxidant and anti-inflammatory activities due to active ingredients such as oleic acid, phenolic constituents, and squalene (Lopez et al., 2014; Waterman & Lockwood, 2007), the review did not find any evidence to assess antimicrobial and antifungal effect of olive oil on DD infected by secondary infection.

In the low-income countries the policy of diaper area care needs to be consider. In some of the Asian developing countries olive oil as a readily available, anti inflammatory, and antioxidant agent, is traditionally used for topical DD treatment by some people. However, firm conclusions regarding the effect of topical applications of olive oil on DD await large, welldesigned, and sufficiently powered investigations.

3.1 | Limitation and strength

This study was conducted at a single site. For this reason, the external validity and consequently the generalizability of the findings can be reduced, and the replication of this study with a larger data set isessential. It is worth to mention that the significant limitation in this study was assessing DD severity by those mothers who had not enough knowledge about six-point scale. Also it was not possible to accurately control the type and numbers of diapers used by mothers,

TABLE 2 Comparison of the degree of diaper dermatitis between the groups on days 0, 3, 5, and 7

Group	Severity of diaper rash[a]	Olive oil ointment group (n = 36)		Calendula ointment group (n = 37)		p value Mann–Whitney U test
		n	%	*n*	%	
Day 0	Degree1	10	27.8	10	27	**p = .764**
	Degree2	10	27.8	13	35.1	
	Degree3	13	36.1	11	29.7	
	Degree4	3	8.3	3	8.1	
	$\overline{X} \pm SD$	2.25 ± 0.98		2.18 ± 0.92		
Day 3	Degree0	28	77.8	26	70.3	**p = .413**
	Degree1	6	16.7	7	18.9	
	Degree3	2	5.6	2	5.4	
	Degree4	0	0	2	5.4	
	$\overline{X} \pm SD$	0.28 ± 0.57		0.47 ± 0.92		
Day 5	Degree0	35	97.2	33	89.2	**p = .17**
	Degree1	1	2.8	2	5.4	
	Degree2	0	0	2	5.4	
	$\overline{X} \pm SD$	0.02 ± 0.16		0.15 ± 0.49		
Day 7	Degree0	37	100	36	100	**p > .999**
	$\overline{X} \pm SD$	0 ± 0		0 ± 0		

[a] Severity of diaper rash defined according to the six-point scale: 0 (no erythema), 1 (slight, diffused, or partial erythema), 2 (completely visible erythema), 3 (severe erythema without deep infiltration), 4 (severe erythema with deep infiltration).

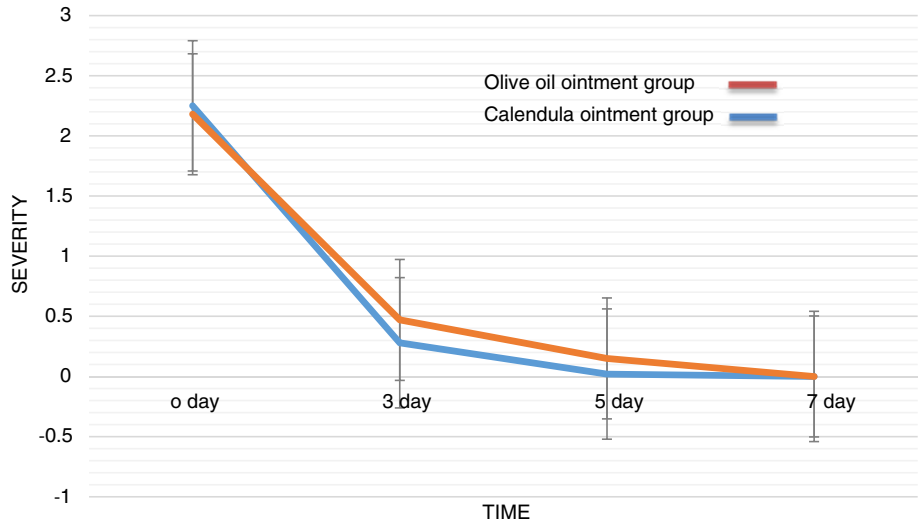

FIGURE 2 Comparison the severity of diaper dermatitis between the groups on days 0, 3, 5, and 7

because of phone interviews. However to reduce interference factors, diapers with a same brand were prescribed by the pediatrician. Most of the subjects had the same brands of diapers. It was tried to reduce the limitations using pamphlets and instructional images.

Since the farmaceutical forms (ointment) and base formulations (beewax and lanolin) of both medications (olive and calendula ointment) are the same, it is possible to minimize the interference factor and causes more balance between groups. In addition, excludig a score of 5 based on the six-point scale, in contrary with some other similar studies in DD, contributed to more concentration on only uninfected DD.

4 | CONCLUSION

In the current study, the severeity of DD in children was measured on days: 0 (one day before the beginning of the intervention) and 3, 5, and 7 days after the intervention in two groups to compare the effect of ointments in inflammation over time. According to the results of this study (Tables 1–2), no statistically significant difference was found between the groups of olive ointment and calendula ointment in terms of the severeity of DD on the days 0 (before the intervention) and 3, 5, and 7 days after the intervention. No adverse side-effects were observed in participants. Although the olive ointment was not more effective than calendula ointment in the treatment of DD, due to the same effect, it can be used as an alternative treatment. Given the availability of olive oil, it can serve people with poor economic status and lack of access to health facilities specially in Mediterranean areas and can reduce the need for chemical treatments.

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