

Sunflower seed oil for skin barrier repair in newborns: A systematic review and meta-analysis with biophysical parameters

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Abstract

Background The skin barrier in newborns is immature, and moisturizers may help repair the barrier. The recommended skincare products for newborns are those containing fewer ingredients. Hence, natural oil-like sunflower seed oil (SSO), free of chemical ingredients, is a cost-effective option. The aim of this study was thus to assess the efficacy of topical SSO to improve skin barriers in newborns.

Methods Online searching in Pubmed-MEDLINE, Scopus, EBSCO, Cambridge Core, ProQuest, Cochrane library, ClinicalTrials.gov, and Google Scholar databases found five relevant articles included in a systematic review (n=1,272 subjects), from which three articles are used in meta-analysis (n=908 subject).

Results A meta-analysis showed that following a topical application of SSO, transepidermal water loss (TEWL) tended to lower than other moisturizers (standardized mean difference [SMD] -0.11, confidence interval [CI] 95%, -0.23 to 0.11, p=0.07, I²=0%), and it was not comparable to no moisturizer (SMD 0.09, CI 95%, -0.19 to 0.38, p=0.52, I²=0%). The stratum corneum hydration (SCH) was comparable to other moisturizers (SMD 0.03, CI 95%, -0.20 to 0.26, p=0.81, I²=0%), but it was significantly higher than no moisturizer (SMD 0.77, CI 95%, 0.48 to 1.06, p<0.00001, I²=0%). Qualitative analysis showed that SSO may reduce neonatal skin condition score.

Conclusion A meta-analysis showed that topical application of SSO may act as a moisturizer and improve skin hydration, but it may not repair the barrier. SCH indicates that it increased significantly, which means the hydration improved. The TEWL analysis did not show supportive results for SSO compared to either other moisturizers or control; however, the qualitative analysis did show that SSO had a positive effect on the clinical condition.

Key words

Sunflower seed oil, skin barrier, newborn.

Introduction

The skin barrier of newborns is immature. Thus, higher water absorption and desorption rate exhibit impairment of barrier function.¹ Mathanda et al. found that *transepidermal water loss* (TEWL) is higher in newborns than in adults and increased in younger gestational age.² Newborns have a thinner epidermal layer, as

well as poor integrity, that contains fewer keratinocytes, and hence it produces less

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antimicrobial peptide and natural moisturizing factor. Skin pH in newborns is also higher than in adults. Those differences lead to the malfunction of the newborn skin barrier.¹

The skin barrier is immature, especially during the first week of life, and is considered one of the *port d'entrée* for microorganisms, which then cause infection and sepsis in newborns.^{3,6} Infection and sepsis cause high rates of morbidity, mortality and increase the risk of birth defects.^{3,4} In addition, they are the cause of death in newborns, with a total of 74,759 cases in the world in 2019. In Indonesia, these infections and sepsis were the cause of death in 6,913 cases, which is 5.56% of total newborn deaths.⁵

Skincare recommendation in newborns includes maintaining the skin barrier function. Clinical trials have shown that the use of moisturizers can help repair the skin barrier in newborns.^{7,8} However, it should be noted that newborns have a higher risk of systemic toxicity caused by topical agents due to the disruption of the barrier itself and the body-to-surface area ratio compared to the larger body mass. Immature metabolism, excretion, distribution, and protein binding in infants also increase the risk of toxicity. It is estimated that newborn skin is exposed to 10 different skincare products in the neonatal period with 50 different chemicals. Not only can this trigger irritation, but it can also increase the risk of allergic contact dermatitis in infants.⁹ Thus, baby skincare products containing the fewest of basic ingredients are recommended. Currently, there are many hypoallergenic baby skincare products on the market, but they still have too many types of basic ingredients. The use of natural ingredients is a solution in choosing a skincare regimen, in this case, moisturizer, for newborns.

Although not all-natural oils have a good effect,

natural oil is one of the most widely used and easily available moisturizing ingredients.¹⁰ The ratio of oleic to linoleic acid in natural oils is thought to determine its function in repairing the skin barrier. Therefore, a positive effect is associated with a higher ratio of linoleic to low oleic acid.^{10,11} One of the natural oils with high levels of linoleic acid is sunflower seed oil (SSO).¹² The other SSO advantages are availability and cost-effectiveness, especially in lower-middle-income countries, such as Indonesia.

An objective assessment that is often used to assess the condition of the skin barrier is the measurement of TEWL. The TEWL is used to measure the evaporation of water from the skin. Stratum corneum hydration (SCH) is also assessed as another parameter by evaluating the water content in SK.¹³⁻¹⁵ This study aimed to assess the efficacy of SSO as a skin barrier in neonates, using TEWL and SCH as the main parameters. Other parameters found in the included studies were also assessed and used as considerations. Topical SSO is expected to be effective, and clinicians can consider its topical application as a cost-effective alternative therapy in managing skin barrier repair, especially in newborns.

Methods

This study was a systematic review and meta-analysis, and it followed the Cochrane handbook¹⁶ and PRISMA statement¹⁷ as guidelines. Pubmed-MEDLINE, Scopus, EBSCO, Cambridge Core, ProQuest, Cochrane library, ClinicalTrials.gov, and Google Scholar were searched. Furthermore, reference lists of relevant publications and relevant literature reviews were searched to identify other eligible studies. Three reviewers conducted the literature search independently. The following terms were used for searching in PubMed-MEDLINE and

Cochrane: (("sunflower oil"[MeSH Terms]) AND "topical administration"[MeSH Terms]) AND "infant, newborn"[MeSH Terms]. Similar terms were used to search other databases. Cross references of relevant studies were examined to identify any additional studies.

Study Selection and Data Extraction: Studies were selected based on the 2009 PRISMA flowchart.¹⁷ Abstracts of the citations obtained from the initial broad search were screened independently by three reviewers to identify potentially eligible studies. Full-text articles of these studies were then assessed for eligibility by them independently using the predefined eligibility criteria. Multiple publications from the same studies were included only if any additional information was available; otherwise, they were considered duplicates, and information was used only once.

Eligibility criteria include clinical trials with newborn participants (in their first <96 hours of life), using SSO as an interventional arm. The primary outcomes for this study were TEWL and SCH. Data extraction was performed independently by three reviewers using The Cochrane Collaboration data collection form for RCTs only.¹⁸ Any disagreements in the paper selection and data extraction were resolved by consensus.

Statistical Analysis: The meta-analysis was performed using the weighted mean of mean differences between the treatment and control groups. The Review Manager, Version 5.4.1, was used in the analysis. The I^2 was used to calculate the heterogeneity of each outcome. If heterogeneity could not be found, data were analyzed using the fixed-effects meta-analysis. However, if heterogeneity was found ($I^2 > 50\%$), random effect analyses were used. When data were not available to enable pooling, a descriptive synthesis was performed.

Assessment of risk of bias: The quality of evidence of each study was assessed using the Cochrane Risk of Bias Tool for Randomized Controlled Trials.¹⁹

GRADE Evidence: The key information concerning the quality of evidence was assessed as per GRADE guidelines.²⁰ All authors discussed and agreed with the GRADE allocation.

Result

Initial searching from databases yielded 119 studies. After excluding duplicates, 14 relevant article titles were obtained. Their abstracts were then reviewed so that eight articles were excluded: one review article, five research articles not within the topic of this meta-analysis, and two observational studies. Six full articles were assessed for eligibility, and one of them was excluded because it was a duplication (thesis) of another article (journal). Five research articles were used in qualitative and quantitative studies to assess the effectiveness of SSO on the skin barrier conditions of newborns.^{6,21-24} Selection process is presented in Error! Reference source not found..

The total number of participants was 1272 newborns. The characteristic of included studies is presented in **Table 1**. Kanti et al., 2017 conducted a study on 50 term newborns and found that the SSO application three times a week for five weeks tended to decrease TEWL and significantly increase SCH. Comparable results were found in the baby lotion (L) group. This study had other relevant outcomes. Skin pH decreased significantly in both groups. Changes in sebum levels in this study were not significant in both treatment groups. Clinical skin condition assessed by the neonatal skin condition score (NSCS) showed a decrease, indicating improvement. However, skin topography

assessed by surface evaluation of living skin did

Table 1 Characteristics of included studies.

No	Authors, Year	Country	Sample Size	Population	Study Arms			Frequency	Duration
					Interventional Arm		Cont rol		
					1st	2nd			
1	Kanti et al., 2017	Germany	50	aterm	sunflower seed oil	baby lotion	no	Three times a week	Five weeks
2	Cooke et al., 2016	United Kingdom	115	aterm	sunflower seed oil	olive oil	yes	twice a day	Four weeks
3	Summers et al., 2019	Nepal	995	aterm and preterm	sunflower seed oil	mustard oil	no	±4 times a day	Four weeks
4	Caglar et al., 2020	Turkey	90	preterm	sunflower seed oil	almond oil	yes	Four times a day	Five days
5	Kanti et al., 2014	Germany	22	preterm	sunflower seed oil	no	yes	Every 3–4 hours	Ten days

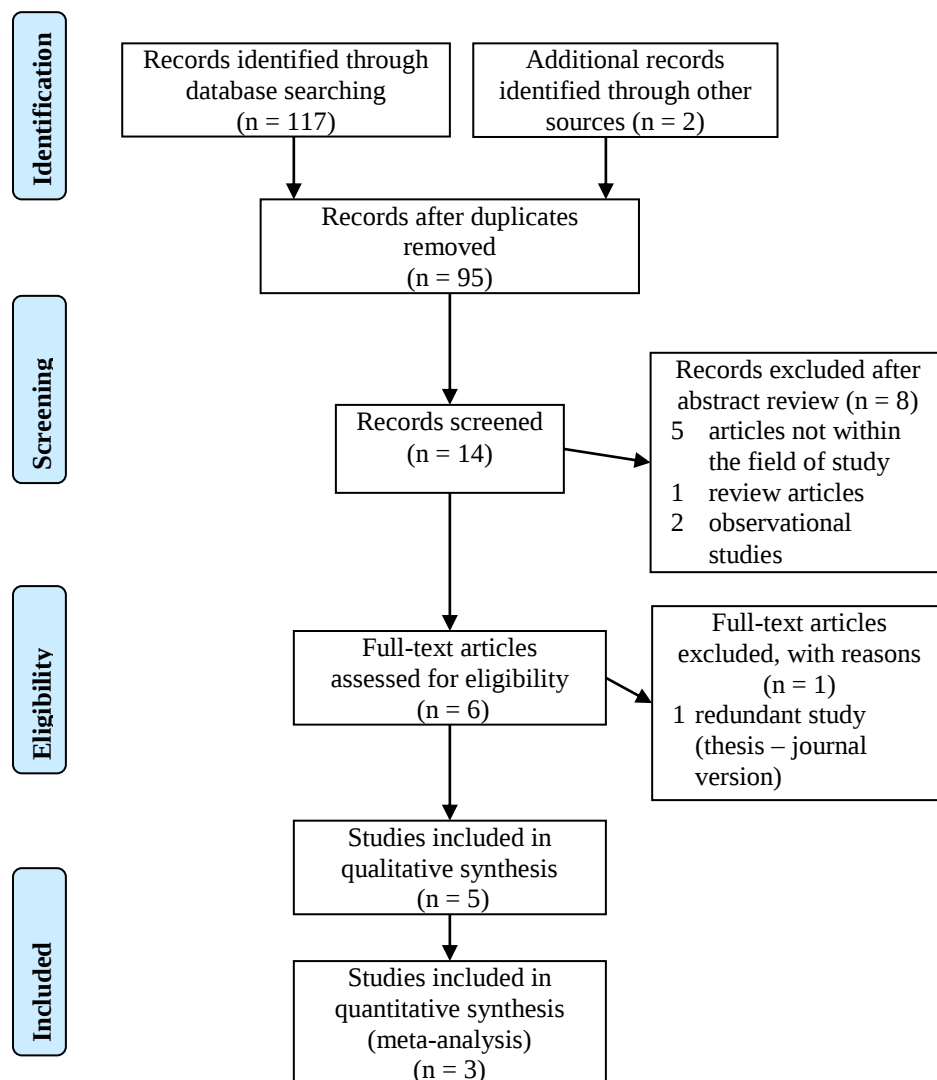


Figure 1 Flow diagram of study selection process following the PRISMA statement¹⁷.

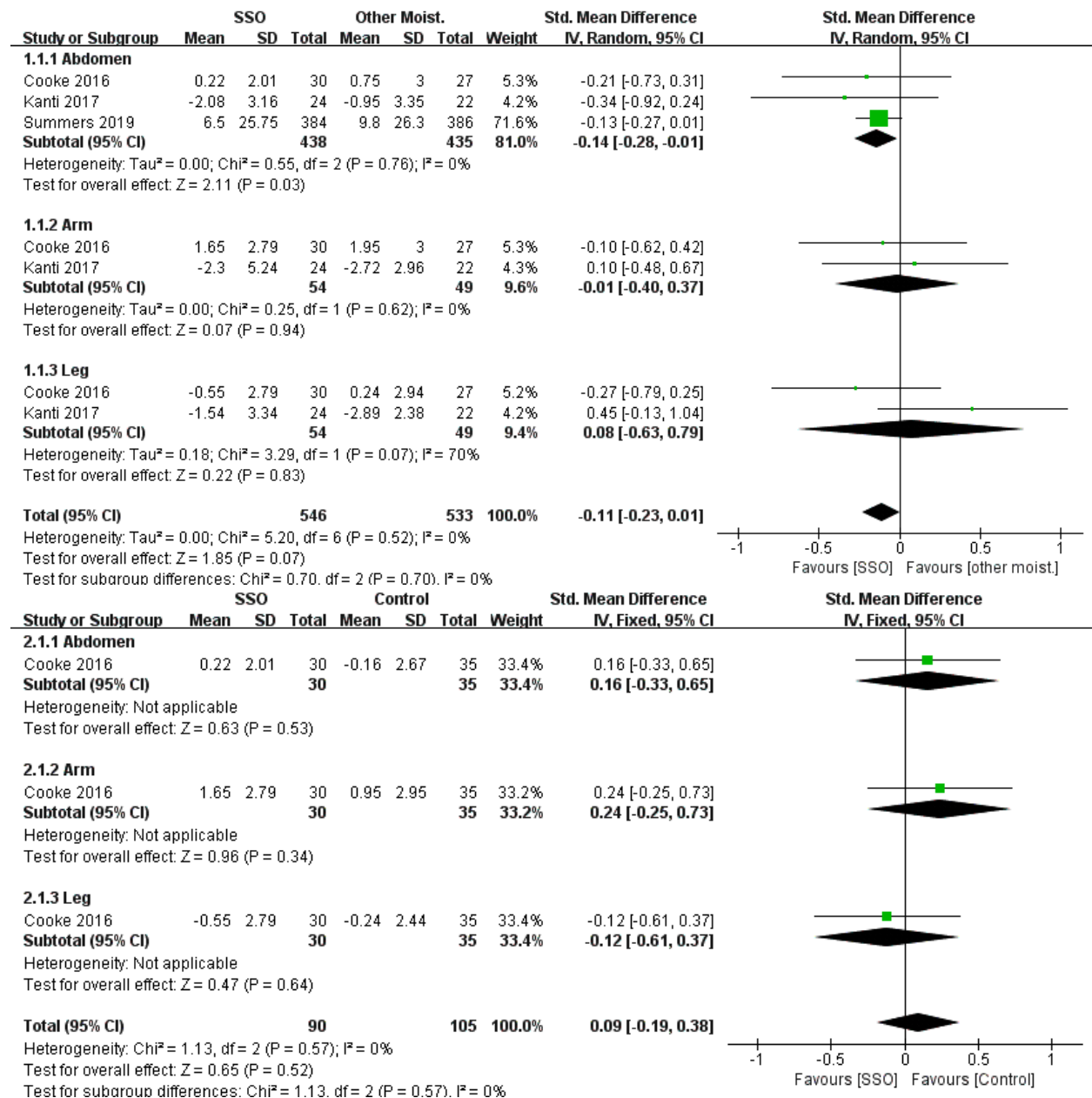


Figure 1 Meta-analysis of TEWL in newborn following SSO application compared to other moisturizers and control

not show significant changes in both treatment groups.

Cooke et al. (2016) included 115 term newborns in their study. An SSO application twice a day

for four weeks did not provide a significant change in TEWL, but it caused a significant increase in SCH. The increase in SCH was higher in the SSO group and the olive oil group than the control group (C), which was not

applied to any emollient. However, there was no significant difference in pH reduction between

the three groups. Another outcome of this study was lipid formation as assessed by ATR-FTIR

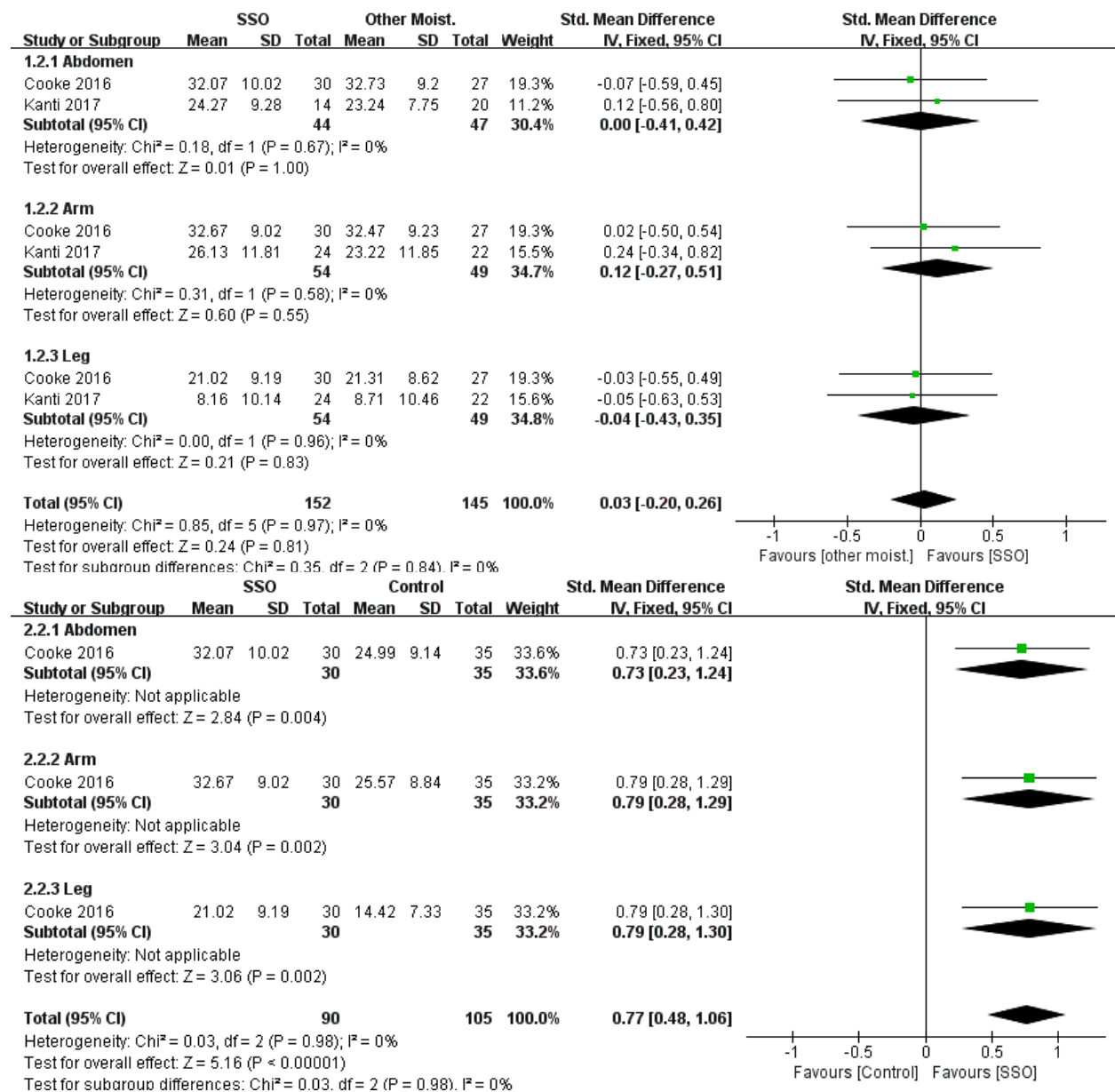


Figure 2 Meta-analysis of SCH in newborn following SSO application compared to other moisturizers and control

spectroscopy. Lipid formation was increased in all three groups, but this increase was lower in both treatment groups than in group C. Clinical skin condition assessed by the NSCS modification showed improved results in all three groups.

Summers et al. (2019) conducted a study on 995, both preterm and term newborns. SSO application about four times a day for four weeks increased TEWL significantly and decreased pH significantly in this study. An increase in TEWL also occurred in the comparison group using mustard oil. However,

the TEWL measurement in this study was carried out at home with relative humidity conditions that tend to be high for TEWL

measurement. Thus, this increase in TEWL may be due to sweat gland maturation. The decrease in pH was equal at the end of the study between

Table 2 Risk of bias of included studies

	Random Sequence Generation	Allocation Concealment	Selective Reporting	Other Bias	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	AHRQ Standard
Kanti et al. (2017)	?	?	+	+	?	?	-	Poor
Cooke et al. (2016)	+	+	+	+	+	+	-	Fair
Summers et al. (2019)	+	+	+	-	-	-	+	Poor
Caglar et al. (2020)	+	+	+	+	+	+	+	Good
Kanti et al. (2014)	?	?	+	+	?	?	+	Poor

the two groups, but the decrease in pH was faster in the SSO group. SK protein showed a decrease in both groups indicating an adaptation process in desquamation in normal newborns. The clinical condition of the skin appeared to worsen for erythema and rash until Day 14, but it decreased at the end of the study.

Caglar et al. (2020) conducted a study on 90 healthy premature newborns and found that water concentration in stratum corneum increased significantly after SSO application four times a day for five days compared to the control group (C). A similar result was obtained after the *almond oil* (AO) application. The NSCS remained low in SSO and AO groups but increased in C. Kanti et al. (2014) included 22 term newborns, finding that when SSO was given every 3-4 hours for ten days, TEWL increased and SCH decreased significantly until Day 11. After ten days, SSO was discontinued, and TEWL decreased again, and SCH increased

on Day 21. Meanwhile, in the control group, both TEWL and SCH values remained stable. The pH values tend to be stable in both groups. Sebum levels tended to be low or undetectable at baseline until the end of the study in both groups. The NSCS assessment in this study remained low with SSO application, whereas it increased in control groups.

Meta-analysis was carried out following the studies by Kanti et al. (2017), Cooke et al. (2016), and Summers et al. (2019). The SCH, mentioned in Caglar et al. (2020), was the percentage of water concentration, not in arbitrary units. While the research of Kanti et al. (2014) was only provided in a boxplot. Meta-analysis showed that after topical application of SSO, TEWL tended to lower than other moisturizers (standardized mean difference [SMD] -0.11, confidence interval [CI] 95%, -0.23 to 0.01, $p=0.07$, $I^2=0\%$, 3 RCTs with three anatomic region subgroups), and it was

comparable to no moisturizer (SMD 0.09, CI 95%, -0.19 to 0.38, $p=0.52$, $I^2=0\%$, three anatomic region subgroups) (**Figure 1**). The SCH was comparable to other moisturizers (SMD 0.03, CI 95%, -0.20 to 0.26, $p=0.81$, $I^2=0\%$, three RCTs with three anatomic region subgroups), but significantly higher than no moisturizer (SMD 0.77, CI 95%, 0.48 to 1.06, $p<0.00001$, $I^2=0\%$, three anatomic region subgroups) (**Figure 2**). Qualitative analysis showed that the SSO application could reduce the neonatal skin condition score, as mentioned above.

Kanti et al. (2014; 2017) did not provide important information such as random sequence generation, allocation concealment, and blinding. Furthermore, Kanti et al. (2017) stated missing data for SCH parameter for abdomen, and Cooke et al. (2016) has imbalanced drop out in study groups; thus risk of bias for incomplete outcome data was high for those studies. Summers et al. (2019) stated that they could not blind the personnel due to the different color and smells of the oil they used. They also measured TEWL at home with high relative humidity, contributing to the high risk of other biases. Risk of bias of included studies listed in **Table 2**.

The quality of evidence of meta-analysis was assessed using GRADE. The TEWL outcome that compared SSO to other moisturizers was downgraded for imprecision due to wide CIs in each studies. The TEWL outcome that compared SSO to no moisturizer (control) group was downgraded for the same reason. The SCH outcome that compared SSO to either other moisturizers or control was downgraded for the risk of bias, due to incomplete data in one RCT. The GRADE assessment of meta-analysis is presented in Error! Reference source not found..

Discussion

TEWL and SCH are objective measurements that assess the skin barrier, but ambient conditions may confound the result due to sweating. Ambient conditions suggested by the European Group of Efficacy Measurement of Cosmetics and other Topical Products (EEMCO) are to set the examination room with limited circulation at a temperature of 20°C – $22^{\circ}\text{C} \pm 1^{\circ}\text{C}$ with a relative humidity of $<60\%$.¹⁴ Other literature mentions that humidity levels $<10\%$ can cause moisture loss in SK.²⁵ In Summers et al. (2019), 45.6% of visits were carried out in humidity $>80\%$ with a mean relative humidity of $75.1\% \pm 13.2\%$, while two other studies included a meta-analysis in optimal humidity.

The temperature setting in all of the studies was not categorized as optimal temperature for measurement. This is understandable considering the condition of neonates who easily fall into hypothermic conditions, especially if the room temperature is $<20^{\circ}\text{C}$.²⁶ The recommended room temperature for newborns according to the World Health Organization is 25°C , and according to the International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations, it is 23°C – 25°C for term infants and $>25^{\circ}\text{C}$ for premature infants.^{27–29} With these recommendations for neonates, room temperature ranged 20°C – $22^{\circ}\text{C} \pm 1^{\circ}\text{C}$ for measurement of skin biophysical parameters is difficult to achieve. However, to be more accurate, a minimal perspiration effect should be achieved in the measurement by setting the temperature to be the minimum temperature that the infant can tolerate with uniformly conditioned relative humidity, within 10% – 60% .

Considering the improvement of the barrier, the expected result is a decrease in TEWL and an increase in SCH. The quantitative analysis found that TEWL decreased lower than other

moisturizers tested, but not significantly, and it was comparable with the control group. The SCH was comparable to other moisturizers, and it increased significantly higher than the control. Possible explanations for this condition are the improvement of the barrier accompanied by increased activity of sweat glands, hydrated skin due to the temporary effects of using moisturizers, eroded skin, acute dermatitis, and atrophic epidermis.¹⁴ The last three possibilities can be ruled out because no clinical condition was found. Erythema was found in Summers et al. (2019), but it did not correlate with an increase in TEWL because TEWL in this study was increased until the end of the observation, whereas erythema improved after Day 14. The quality of evidence shows that further research may have a significant impact on the possible effects and could change the likelihood.²⁰

The temporary hydrating effect of using moisturizers may have contributed to this finding. Several studies have distanced the treatment by measurement, and this is intended to avoid results that only describe the temporary effect of the remaining moisturizer applied. Kanti et al. (2017) gave a period of 12 hours, while Kanti et al. (2014) gave 3–4 hours from the last moisturizer and/or bath to measure skin function parameters. Caglar et al. (2020) discontinued the use of moisturizer 6 hours before the last measurement. According to the literature, after 8 hours, only 50% of the moisturizer remains on the surface of the skin.¹¹ In these studies, the measurement distance was still too close to the application of moisturizer, except in the study by Kanti et al. (2017).

Increased activity of sweat glands is also still possible to cause this condition because as previously mentioned, sweat glands are active only after birth.⁹ This process is also influenced by environmental adaptation, environmental temperature, humidity conditions, and different

skin morphology and physiology in newborns.^{14,30} The control group was expected to provide a proper comparison, was only obtained in 1 RCT with a relatively small number of participants. Thus, it is difficult to conclude that this sweat gland maturation does not cause unexpected TEWL value.

The majority of subjects in the studies were in a reasonably good clinical skin condition at baseline, and only a few of them showed mild to moderate dry skin, scaling, or rash. The research of Kanti et al. (2017) and Cooke et al. (2016), who used term infants as research subjects, showed a decrease in score after treatment, which means an improvement in skin condition in all groups, including the control group in Cooke et al. (2016). Research by Caglar et al. (2020) and Kanti et al. (2014), who used premature infants as research subjects, showed a significant increase in the control group but not in the treatment group using natural oils. This indicates that the application of natural oils may provide a protective effect in premature infants, while it does not show any difference in term infants.

However, this study had some limitations. Research article examining the effectiveness of SSO for skin barrier repair was still limited. One study had to be excluded because the authors only provided the data in boxplot and did not respond to correspondence. There were also differences in the ambient conditions of the included studies that did not meet the measurement standards; hence, it could be biased.

In conclusion, the SSO application may improve skin hydration. The SCH indicated that hydration increased significantly. However, decrease in TEWL following SSO application

was not statistically significant than other moisturizers tested. There was also a minimal difference when SSO was compared with control. Hence, SSO may act as a moisturizer, but it may not repair the skin barrier. Sweat glands maturation may also confound the result due to assessment in unoptimized ambiance. However, the qualitative analysis showed that SSO administration also positively affected the clinical skin conditions. The GRADE assessment suggests that further research is required to conclude the effectiveness of SSO and other moisturizers applications as barrier repair. Further studies with TEWL measurement under adjusted ambiance temperature and humidity may help to minimize the confounding factor. A control group with a more significant number of participants will also be of benefit.

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