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The Effectivity of pH 4 Emulsion on Skin Barrier Function in The Elderly: A Systematic review and meta-analysis

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ABSTRACT

Background: The pH of the skin surface is elevated in the elderly therefore it may cause impaired barrier function manifest as various cutaneous abnormalities, including xerosis, pruritus, dermatitis, and skin infections. Consequently, skin care products for the elderly should contain moisturizing ingredients which are formulated to normalize the skin surface pH. Application of pH 4 emulsion is potentially beneficial to improve barrier function in the elderly and promoting skin health. We aimed to determine the difference of effectiveness of pH 4 emulsion compared to identical non pH 4 emulsion on decreasing TEWL in the elderly. A systematic review and meta-analysis was performed of randomized clinical trials assessing the effects of pH 4 emulsion on skin barrier function in the elderly.

Methods: Medline Pubmed, Scopus, ProQuest, Cochrane library, ClinicalTrials.gov, the reference list, conference proceedings, researchers in the field of eligible studies were searched. Four studies (n=98 subjects) were included in qualitative analysis of which two studies (n=45 subjects) were included in the meta-analysis. The mean age of the participants was 71.1 years old.

Interventions use the application of pH 4 water in oil emulsion (n=2) and pH 4 oil in water emulsion (n=2). Duration of intervention (24 hours-7 weeks) and outcomes of interest varied among included studies.

Results: Pooling of data using random-effects model found lower TEWL score in the pH 4 emulsion than in non pH 4

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emulsion, with no significant difference (overall effect mean difference -0.068, 95% confidence interval -0.485 – 0.348, p = 0.11, I^2=60.1, two RCTs). In addition to that, the qualitative analysis found that the application of pH 4 emulsion increased stratum corneum hydration, decreased skin surface roughness and scaliness, decreased DASI, and improved ICLL length and lamellar organization.

Conclusion: The meta-analysis result of the mean differences of TEWL scores lowering effect between pH 4 emulsion and non pH 4 emulsion is statistically inconclusive. This is despite the observation that the pH 4 emulsion appears to be more effective comparatively. The qualitative analysis found that the application of pH 4 emulsion had improved skin barrier function in the elderly. Larger scale, well-designed RCTs assessing the effects of pH 4 emulsion on skin barrier function in the elderly, are still needed.

Keywords: pH 4 emulsion; Skin barrier elderly

Abbreviations:
TEWL: Trans Epidermal Water Loss
RCT: Randomized Controlled Trial
DASI: Dry skin Area and Severity Index
ICLL: Intercelullar Lipid Lamellae
Mesh: Medical subject headings
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis
TEM: Transmission Electron Microscopy
HPTLC: High Performance Thin Layer Chromatographic

Introductions

According to United Nations World Population Ageing, the population above 60 years old is referred to as the old age or elderly population. [1] With advances in medical and healthcare technology, human lifespans are increasing and the study predicts that the elderly population will exceed the number of young populations by 2050. [1]

Aging skin displays structural and functional skin barrier changes. [2] Stratum corneum plays a role as the epidermal skin barrier, “brick and mortar” model, to prevent insensible water loss from the skin surface (TEWL), prevent the entry of external molecules and microorganisms. According to the “brick and mortar” concept, the corneocytes act as “the bricks” surrounded by intercellular lipid lamellae (“the mortar”) and attached by corneodesmosome (“the rivets”). [3]

The normal skin surface pH is slightly acidic, ranging from 4.5 -5.3. [4] This acidic pH of the skin maintains functions of the skin such as cohesion of stratum corneum, epidermal barrier homeostasis, and antimicrobial defense. In elderly people, however, the skin surface pH becomes less acidic, ranging from 5.0-6.0. [5] It may cause impaired barrier function to manifest as a variety of cutaneous abnormalities, including xerosis, pruritus, dermatitis, and skin infections. TEWL measurement is very important and is commonly used as an instrument to measure the effect of various cosmetic products and the skin barrier function.

Evidence suggests the importance of skin

emolliating and moisturizing in elderly skin to maintain healthy skin in elderly people. Because of the importance of skin surface pH regulation, skin care products for the elderly should contain moisturizing ingredients which are also formulated to normalize the skin surface pH. [6] Several studies suggested acidifying aged skin with an acidic pH to improve skin health in the elderly. [7]

There has never been systematic reviews and meta-analysis assessing the effects of pH 4 emulsion on skin barrier function in the elderly. Therefore, we conducted a systematic review and meta-analysis evaluating the efficacy of the application of pH 4 emulsion on skin barrier function in the elderly. TEWL measurement was chosen to determine skin barrier function improvement.

Methods

Literature Search

The following databases were searched until the time of data analysis: Medline Pubmed, Scopus, ProQuest, Cochrane library, ClinicalTrials.gov. The reference list, conference proceedings, researchers in the field of eligible studies were searched to identify additional studies.

The following Mesh terms were used for searching: “pH emulsion” AND “skin barrier elderly”. A literature search was performed by three reviewers independently using PRISMA flow diagram 2009. [8] Differences in opinion were resolved between all reviewers to reach consensus.

Inclusion criteria were: clinical trials with/without randomization from 2011 until 2020, participants mean age ≥ 60 years, intervention: pH 4 emulsion application to the elderly skin, participants did not have any dermatitis or skin inflammation at the test area, participants did not have systemic diseases, outcomes: TEWL score. Studies were excluded if they: were written neither in Indonesian nor English, were case report, serial case, letter, literature review.

Study Selection

Three reviewers conducted the study selection independently. Duplicate articles were removed. Title and abstract review, full-text review were assessed for eligibility using the predefined inclusion and exclusion criteria. Differences in opinion were resolved between all reviewers to reach a consensus.

Data extraction

Data extraction was performed independently by three reviewers using The Cochrane Collaboration data collection form for RCTs only. [9] Differences in opinion during data extraction were resolved between all reviewers and consensus was reached.

Assessment of risk of bias

Risk-of-bias assessment was performed independently by three reviewers using The Cochrane Collaboration data collection form for RCTs only [9] and The Cochrane Collaboration’s tool for assessing the risk of bias in randomized trials. [10]

Data synthesis

Meta-analysis difference in weighted mean was conducted using Comprehensive Meta-Analysis: A Computer Program for Meta-Analysis, version 3.3. Where data was not available to enable pooling, a descriptive synthesis was performed.

Results

Initial database searches identified 50 non-duplicate records. 44 were excluded during the title/abstract review, 2 were excluded during the full-text review. Four studies were included in this review, of which 2 studies were included for meta-analysis. Figure 1 gives details of the study selection process.

Study Characteristics

The characteristics of included studies are given in Table 1

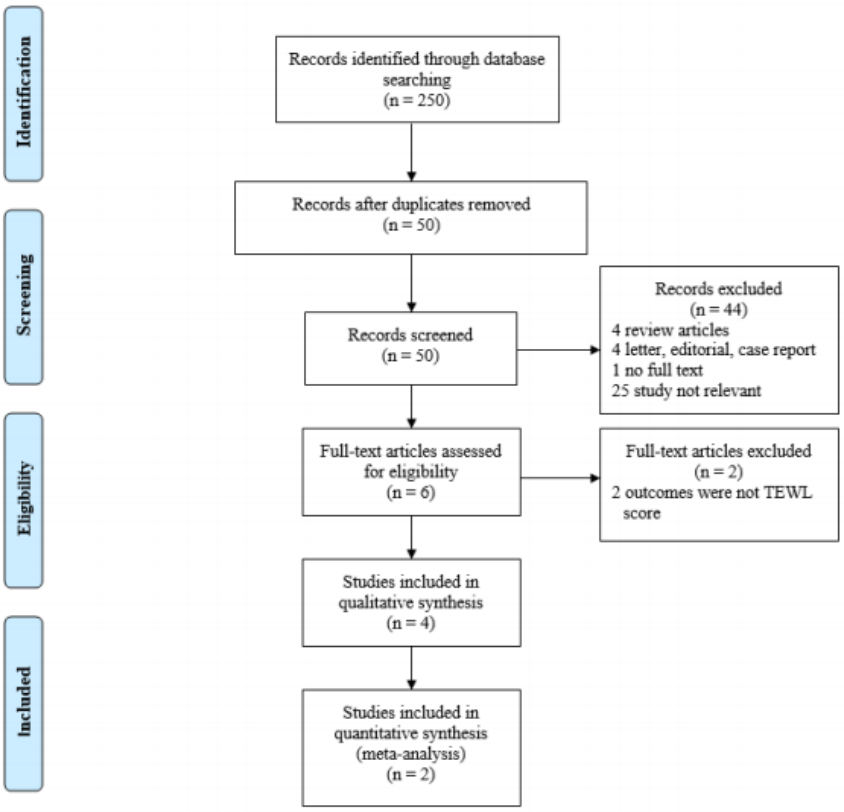

Figure 1. PRISMA flow diagram

Table 1. Characteristics of included studies

Study	Mean age	N recruited/ analyzed	Intervention Group	Comparison Group	Duration of Intervention	*Outcome*
Fischer *et al* 2018[11] (a)	67.1 years	28/26	Twice daily application of pH 4 water in oil emulsion (contained glycolic acid and ammonia) on the forearm	Twice daily application of pH 5.8 Water in oil emulsion (identical but did not contain glycolic acid and ammonia) on the forearm	4 weeks	TEWL (Tewameter® TM300); Skin roughness and skin scaliness (Visioscan® VC 98)
(b)	64.5 years	10/10	Application of 1 mL acetone, 10 minutes later followed by application of pH 4 water in oil emulsion (contained glycolic acid or ammonia) on the forearm	Application of 1 mL acetone, 10 minutes later followed by application of pH 5.8 water in oil emulsion (identical but did not contain glycolic acid and ammonia) on the forearm, application of 1 mL acetone without emulsion	24 hours	TEWL (Tewameter® TM300); Skin-surface pH (skin-pH-Meter® PH905)
Blaak *et al* 2015[12]	87 years	26/20	Twice daily application of pH 4 oil in water emulsion on the body	Twice daily application of pH 6 oil in water emulsion (identical) on the body	7 weeks	TEWL (TEWL DermaLab®); DASI; Skin surface pH (skin-pH-Meter® P905); Stratum Corneum hydration (Corneometer ® CM 825); Micro-biological assessment (microbial culture)

Study	Mean age	N recruited/ analyzed	Intervention Group	Comparison Group	Duration of Intervention	*Outcome*
Kilic *et al* 2019[7]	63.4 years	20/19	Twice daily application of pH 4 water in oil emulsion (contained glycolic acid and ammonia) on the forearm	Twice daily application of pH 5.8 water in oil emulsion (identical but did not contain glycolic acid and ammonia) on the forearm, pH 4 control untreated and pH 5.8 control untreated.	4 weeks	TEWL (Tewameter®) ; Skin surface pH (Skin pH meter pH 900 PC); Stratum corneum hydration (Corneometer ®); ICLL length (TEM CM 10); Number of lipid content (HPTLC)
Blaak *et al* 2017[13]	73.5 years	23/23	Twice daily application of pH 4 oil in water emulsion on the forearm	Untreated	3 weeks	TEWL (*DermaLab apparatus*); Stratum Corneum hydration (*Corneometer ® CM 825 apparatus*); Skin surface pH (*PH900 PC skin pH meter*); ICLL length (TEM); Number of lipid content (HPTLC)

All included studies were conducted in Germany (n=4) between 2015 until 2019. The total sample size was 98 elderly people with a mean age of 71.1 years.

1. Fischer et al 2018 [11] conducted 2 studies

(a) 26 participants were analyzed. The pH 4 water in oil emulsion was applied to the intervention areas twice daily on the forearm and the pH 5.8 water in oil emulsion was applied to the comparison areas twice daily on the forearm. TEWL and skin-surface roughness and scaliness were assessed before and after 4 weeks (in mean±SD). Both formulations reduced the TEWL score. The pH 4 emulsion led to a significant decrease of TEWL score (day 0 and day 28; 6.68± 2.14gr/h/m^2 and 6.29±1.33 gr/h/m^2) compared to the 5.8 pH emulsion (day 0 and day 28; 6.34±1,48 gr/h/m^2 and 6.54±1.32 gr/h/m^2). Both formulations also reduced the skin-surface roughness and skin scaliness, but the pH 4 emulsion led to a significant decrease of skin scaliness (day 0 and day 28; 0.92±0.51 and 0.55±0.20, p<0.01).

(b) 10 participants were analyzed. The intervention areas were applied of 1 mL acetone, 10 minutes later followed by application of pH 4 water in oil emulsion on the forearm and the comparison areas were applied of 1 mL acetone, 10 minutes later followed by application of pH 5.8 water in oil emulsion on the forearm, application of 1 mL acetone without emulsion. TEWL and skin-surface pH were assessed before the emulsion was applied and after 24 hours (in mean±SD). The pH 4 emulsion led to significant decrease of TEWL score (10 mins after acetone and 24 hours; 7.59±1.36gr/h/m^2 and 6.4±0.98 gr/h/m^2, p<0.01), while the pH 5.8 emulsion (10 mins after acetone and 24 hours; 7.44± 1.07gr/h/m^2 and6.72±0.66 gr/h/m^2) and acetone only (10 mins after acetone and 24 hours; 7.79±0.98gr/h/m^2 and 7.35±1.04 gr/h/m^2). In addition to that, the pH 4 emulsion also reduced the skin surface pH (10 mins after acetone and 24 hours; 5.84±0.35 and 5.66±0.44), while the pH 5.8 emulsion and acetone only did not result in significantly lower pH. The authors concluded that application of the pH 4 emulsion resulted in significantly decreased skin surface pH,

improved skin barrier function, and reduced skin-surface roughness and scaliness compared to the application of the pH 5.8 emulsion.

2. Blaak et al 2015 [12] conducted a study on 20 participants. The intervention group (n=12) applied pH 4 water in oil emulsion twice daily on the body and the comparison group (n=8) applied pH 5.8 water in oil emulsion. TEWL, DASI, skin-surface pH, stratum corneum hydration, and a microbiological assessment were assessed before and after 7 weeks (in graphic and median). Significantly reduced DASI in the intervention group (before and after; 230 and 30, p=0.002) and comparison group (before and after; 285 and 70, p=0.036). After treatment, the skin-surface pH decreased specifically in the intervention group (before and after; 5.55 and 5.2, p=0.003), while the comparison group remained at baseline level (before and after; 5.75 and 5.5, p=0.527). Furthermore, a significant increase in stratum corneum hydration was only seen in the intervention group (32.1 AU and 36.1 AU, p=0.005). Evaluation of TEWL showed no significant differences between groups. The TEWL in intervention group (before and after; 4.25 gr/h/m^2 and 4.6 gr/h/m^2, p=0.305) and in the comparison group (before and after; 4.65 gr/h/m^2 and 4.5 gr/h/m^2, p=0.270). The microbiological analysis is not as clear as the other outcomes. It revealed an increase in cell count in both groups. It should be carefully interpreted, and more research is needed. The authors concluded that application of the pH 4 emulsion for 7 weeks resulted in significantly improved skin barrier function compared to the application of the pH 5.8 emulsion.

3. Kilic et al 2019 [7] conducted a study on 19 participants. The pH 4 water in oil emulsion was applied to the intervention areas twice daily on the forearm and the pH 5.8 water in oil emulsion was applied to the comparison group areas, control pH 4 untreated, control pH 5.8 untreated. TEWL, skin-surface pH, stratum corneum hydration, ICLL length, and the number of lipid content were assessed before and after 4 weeks (in mean±SD). A slight increase in mean TEWL was observed in both pH 4 emulsion (day 1 and day 29; 7.82±2.87gr/h/m^2 and 9.24±2.76 gr/h/m^2, p<0.05) and pH 5.8 emulsion (day 1 and day 29; 7.56±2.52gr/h/m^2 and 8.54±2.1 gr/h/m^2, p<0.05). The pH 4 emulsion also reduced the skin surface pH (day 1 and day 29; 5.08±0.51 and 4.62±0,5, p<0.001), while the pH 5.8 emulsion, control pH 4, and control pH 5.8 did not result in significantly lower pH. The pH 4 emulsion resulted in significantly higher skin hydration (day 1 and day 29; 34.52±5.83 AU and 37.82±5.57 AU, p<0.05) compared to pH 5.8 emulsion (p=0.031). In addition to that, analysis of TEM showed anincreased mean length of ICLL in both emulsions, but significantly higher in pH 4 emulsion (p=0.002). The pH 4 emulsion also resulted in higher number of lipid content (day 1 and day 29; 17.7±2.77 µg/slide and 26.72±3.52 µg/slide, p<0.001) compared to pH 5.8 emulsion (day 1 and day 29; 17.22±2.25 µg/slide and 22.07±2.64 µg/slide, p<0.001). (p=0.003). The authors concluded that application of the pH 4 emulsion can reacidify the skin in the elderly and resulted in significantly improved skin barrier function compared to the application of the pH 5.8 emulsion.

4. Blaak et al 2017 [13] conducted a study on 23 participants. The pH 4 oil in water emulsion was applied to the intervention areas twice daily on the forearm, while the comparison areas were left untreated. TEWL, skin-surface pH, stratum corneum hydration, ICLL length, and the number of lipid content were assessed before and after 3 weeks (in graphic and mean). The

result, presented in charts, showed that the TEWL was significantly decreased in the intervention area compared to the comparison area (p=0.003), and stratum corneum hydration was increased compared to the comparison areas (p < 0.01). For the measurements of skin surface pH, there was no real change. Analysis of TEM showed an increased length of ICLL in the intervention area (day 1 and day 22; 103.79± nm/1000nm^2 and 220.22± nm/1000nm^2, p=0.019) and decreased length of ICLL in comparison areas. (day 1 and day 22; 103.79± nm/1000nm^2 and 87.21± nm/1000nm^2, p<0.002). The pH 4 emulsion also resulted in an increased number of lipid content (day 1 and day 22; 27.51± ng/carrier and 38.08± ng/carrier) while the comparison area resulted in a decreased number of lipid content (day 1and day 22; 27.51± ng/carrier and 21.9± ng/carrier). The authors concluded that the application of the pH 4 emulsion can improve skin barrier function in the elderly.

Risk of Bias in included studies

Based on data on the characteristics of the study, the research articles that will be included in the meta-analysis are 2 studies, Fischer et al 2018 (a) and Kilic et al 2019 which reported the mean TEWL pre and post-treatment data in pH 4 emulsion and non pH 4 emulsion.

Risk of bias of the two studies included in the meta-analysis was performed using The Cochrane Collaboration data collection form for RCTs only [9] and The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. [10]

The two studies had a low risk of bias in the majority of the domains, but the risk of bias for the domains allocation concealment and blinding of participants were high in Fischer et al 2018, due to the nature of the intervention, and the risk of bias for the domain allocation concealment was unclear in Blaak et al 2015, because it was not mentioned in the research article. Overall, the quality of the included studies was high. Details of the assessment are given in Table 2.

Table 2. Risk of bias of included studies in the meta-analysis

Study	Random Sequence Generation	Allocation Concealment	Blinding of participants	*Blinding of outcome assessment*	Incomplete Data *outcome*	Selective Reporting	Other Bias
Fischer *et al* 2018[11] (a)	Low	high	high	low	low	low	low
Kilic *et al* 2019[7]	low	Unclear	low	low	low	low	low

Meta-analysis

Meta-analysis weighted mean difference of TEWL score between pH 4 emulsion group compared to non pH 4 emulsion found lower TEWL score in the pH 4 emulsion group than in non pH 4 emulsion group, with no significant difference (overall effect mean difference -0.068, 95% confidence interval -0.485 to 0.348, p = 0.11, I^2=60.1, two RCTs). (Figure 2)

The insignificant result might be due to the heterogeneity of the studies included and the limited number of studies.

Discussion

This is a systematic review and meta-analysis evaluating the efficacy of the application of pH 4 emulsion on lowering TEWL scores in the elderly. The quality of studies included was high.

Skin care products for the elderly should contain moisturizing ingredients. However, due to the elevated skin surface pH in the elderly and its

importance in maintaining skin barrier function, moisturizing products should also be formulated to normalize the skin surface pH. TEWL is a common parameter that is used for measuring the effect of cosmetic products and skin barrier function.

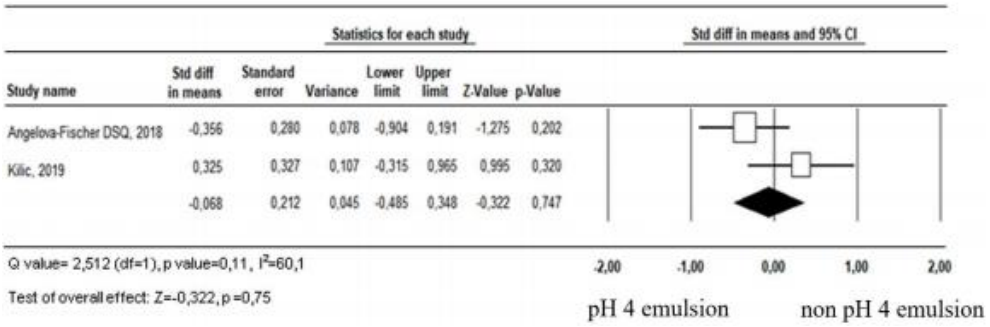

Figure 2. Forest Plot mean difference of TEWL score lowering effect of pH 4 emulsion versus non pH 4 emulsion

The analysis showed that both applications of pH 4 emulsion and non pH 4 emulsions had a lowering TEWL score effect compared to the control group. These data support the study of Moncrieff et al [14] that skin moisturizing is important to maintain normal skin barrier function.

The pooling of data using a random effects model found a lower TEWL score in the pH 4 emulsion than in the non pH 4 emulsion, with no significant difference. RCTs assessing the effects of pH 4 emulsion on TEWL and other skin barrier parameters in the elderly are still needed. In addition to the TEWL score, the studies also reported other important outcomes including skin roughness and skin scaliness (Fischer et al 2018 (a)) and DASI (Blaak et al 2015), stratum corneum hydration (Blaak et al 2015, Blaak et al 2017, and Kilic et al 2019), ICLL length and lamellar organization (Blaak et al 2017 and Kilic et al 2019). The data showed that application of pH 4 emulsion have a positive effect on those outcomes, support the literature that the pH of skin surface plays important role in desquamation process [2], synthesis of the intercellular lipid lamellar, and hydration of stratum corneum. [15,16]

Conclusion

The meta-analysis of the mean difference of TEWL score lowering effect of pH 4 emulsion versus non pH 4 emulsion result is statistically inconclusive. This is despite the observation that the pH 4 emulsion appears to be more effective comparatively.

The qualitative analysis found that the application of pH 4 emulsion had improved skin barrier function in the elderly. A larger scale, well-designed RCTs assessing the effects of pH 4 emulsion on skin barrier function in the elderly are still needed.

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Conflict of Interest

There is no conflict of interest

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