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REVIEW ARTICLE

The use of moist exposed burn ointment (MEBO) for the treatment of burn wounds: a systematic review

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ABSTRACT

Moist exposed burn ointment (MEBO) is an oil-based herbal paste, purported to be efficacious in managing burn wounds and more commonly used in Asia and the Middle East. A PRISMA-compliant systematic review was performed to analyse the evidence for the use of MEBO on burn wounds. Wound healing rate was the primary outcome of interest. PubMed-listed randomised controlled trials (RCTs) comparing the efficacy of MEBO with placebo, standard care or other therapies in the treatment of partial thickness burns in adults and children were eligible for inclusion (November 2019). Six RCTs were eligible. The majority of trials comparing wound healing between MEBO and SSD favoured MEBO (two of three). There may be improved healing in MEBO-treated wounds vs. those treated with povidone-iodine + bepanthenol cream. There was no difference between MEBO and Acquacel Ag, but *Helix Aspersa* had faster healing rates than MEBO. However, all evidence was from moderately to poorly reported trials with a high risk of bias, thereby limiting the strength of this evidence. In conclusion, the evidence for MEBO in English-language literature was poor and inconsistent with respect to wound healing rate and analgesis compared to 1% SSD, Acquacel Ag, *Helix aspersa* cream and povidone-iodine + bepanthenol cream. Blinded RCTs comparing MEBO to both placebo and other common topical treatments may further improve the confidence in concluding their analysis. There is some evidence that MEBO is as safe as its comparators as shown by the low complication rate.

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Introduction

There are several nonsurgical treatment options for superficial and partial thickness burns. They include inorganic and biosynthetic dressings, topical treatments such as silver sulfadiazine (SSD) and alternative/complementary therapies such as honey. The evidence for many of these treatments, however, remains weak. A 2013 Cochrane review by Wasiak et al., assessing the efficacy of a range of dressings for treating burn wounds could not draw firm conclusions due to a lack of adequately powered high-quality comparactive trials [1]. Similarly, the 2013 Cochrane review by Hoogewerf et al. also failed to draw conclusions on topical treatments for facial burns owing to a paucity of high-quality evidence [2]. The optimal treatment options for superficial and partial thickness burns remains controversial and subject to active investigation.

Moist exposed burn ointment (MEBO) or moist exposed burn treatment/therapy (MEBT), an oil-based herbal paste, was developed in 1989 in Beijing. It remains a popular topical treatment for burn wound treatment especially in Asia and the Middle East. The main ingredient in MEBO is beta-sitosterol, a plant-derived sterol with reportedly anti-inflammatory and antipyretic properties [3–5]. The oily component of MEBO is thought to improve wound moisture retention. Given the recognised importance of moisture in wound healing [6–8], the hypothesis that MEBO positively affects wound healing appears intuitive. Numerous anecdotal reports [9,10], animal studies [11,12] and non-comparative reports [13,14], concluded that MEBO was efficacious in treating burns and other wound types. Several more reports have been published in Chinese literature with authors supporting the use of MEBO for treating a wide range of ailments [15]. Ang et al. noted that some hospitals in China have reported survival rates reaching 90% in patients receiving MEBO following burn injuries covering 40–80% of their total body surface area (TBSA) [16]. These claims, including those that MEBO prevents shock in burned patients [17] if confirmed would make this herbal paste an important addition to burn management algorithms.

Despite these claims, it has been noted there is a paucity of scientifically rigorous studies assessing MEBO's efficacy for treating burn wounds [16]. The Cochrane review by Wasiak et al. [1] did not include an assessment of the efficacy of MEBO although one nonrandomised comparative study of MEBO vs. Aquacel Ag by Mabrouk et al. [18] was listed as awaiting assessment. Hoogewerf et al.'s Cochrane review included one study comparing MEBO with silver sulfadiazine (SSD) for routine care of facial burns [19], however noting the small sample size and absence of intention to treat analysis as barriers to forming evidence-based conclusions [2]. Similarly, the Cochrane review by Norman et al. [20] concluded there was only low/very low-grade evidence relating to the effect of MEBO on the incidence of infection and wound healing time due to study imprecision and reporting inconsistency in the included trials [21,22]. No systematic reviews of studies assessing MEBO have been published to date.

For these reasons, this systematic review was performed to collate and analyse the evidence for the use of MEBO from English-

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Figure 1. PRISMA flow chart.

language literature. The clinical question, with reference to PICOS, was as follows:

- Participants: Patients with burn wounds,
- Intervention: Treatment of burn wounds with MEBO,
- Comparisons: Comparison to either standard of care or placebo,
- Outcomes: Effect on wound healing measures.
- Study design: Comparative studies.

Methods

A systematic review was performed following PRISMA guidelines. The review protocol was not published or registered prospectively on a registry.

Inclusion and exclusion criteria

Randomised controlled trials (RCTs) comparing the efficacy of MEBO with placebo, standard wound care or other therapies in treating superficial and partial-thickness burn wounds in adults and children were eligible. Non-comparative studies, retrospective studies, reviews, animal studies, expert opinion articles and preliminary reports were excluded. Economic analyses were only included if they also investigated clinical outcomes.

Outcome measures

The primary outcome of interest was the effect of MEBO on wound healing. Therefore, time to wound healing, wound healing rate, transepidermal water loss (TEWL) and reduction in wound surface area were considered primary outcome measures. Secondary outcomes of interest were post-dressing pain reduction, complications and wound infections.

Search strategy

The EMBASE and MEDLINE databases were searched from inception to November 2019 using the term: (MEBO OR MEBT OR 'moist exposed burn therapy' OR 'moist exposed burn treatment' OR 'moist exposed burn ointment').ti,ab. The search was duplicate-filtered and limited to human studies reported in English.

Study selection

Two authors independently assessed titles and abstracts for relevance and verified by a third.

Data extraction

Data extraction was performed by one author and independently verified by two others. Data extracted from each study included bibliometric indices (authorship, year of publication, the country in which study was conducted and type of study), anatomical area, TBSA, population characteristics and outcomes.

Assessment of the risk of bias in included studies

The risk of selection, performance, detection, attrition, reporting and other biases in each study was assessed using the Cochrane Collaboration's risk of bias assessment tool (RevMan version 5.2.11, Cochrane Collaboration) [23].

Descriptive statistics were used to synthesise data.

Results

Search results

The search results are summarised in Figure 1. Eight articles remained after applying the exclusion criteria [16,17,19,22,24–27]. However, since three of these articles all reported data from a single RCT by Ang et al. [16,19,27], their data were pooled and were treated as one article. A similar approach was taken by Dat et al. in a Cochrane review of studies of Aloe vera for treating acute and chronic wounds [28]. Therefore, the eight eligible articles represent data from six RCTs.

Characteristics of included studies

All studies provided level 3 evidence on the Oxford scale. The included RCTs (578 patients) were undertaken in Greece [22,26], Germany [17], Singapore [16,19,27] and Egypt [24,25] between 2002 and 2011 (Table 1). Tsoutsos [26], Hindy [24] and their respective teams included only patients with facial burns whilst Allam et al. [25] included only patients with hand burns. The remaining studies did not specify the affected anatomical region [16,17,19,22,27]. Only two trials included patients with non-thermal burns although the aetiology remains unclear [17,25].

The depths of burns in the patients included in the trials were deep partial thickness (DPT) [26], superficial partial thickness (SPT)

Table 1. Summary of eligible studies.

First author, year (Country of origin)	Number of participants (Male:Female) (Extent of burn)	Burn thickness	Burn aetiology	Anatomical region	Mean age in years (range)	Study design	Comparison(s)	Outcome (measure)	Result	
									MEBO	Comparison
Hirsh, 2008 (Germany)	40 adults (M25:F15) (<20% TBSA)	Partial thickness	Thermal	Not specified	41.15 (20–65)	RCT	MEBO vs. 1% SSD ($n = 20$ each)	Day 12 Wound healing (mean *TEWL):*	11	7
								Day 0 Inflammation (WCC and CRP):	NR	NR
								Day 8 inflammation (WCC and CRP):	NR	NR
								Pain (mean VAS score D1):	5	5
								Pain (mean VAS score D12):	3.8	3.5
								Adverse effects:	0	0
Hindy, 2009 (Egypt)	60 patients (<25% TBSA in >12-years-old, <15% TBSA in <12-years-old)	Superficial partial thickness	Thermal	Facial	NR	RCT	Aquacel Ag (I) vs. MEBO (II) vs. saline (III) ($n = 20$ each)	Mean time to complete healing (II vs I vs III):	10.35 ± 2.8	10.05 ± 2.3, 12.05 ± 2.4*¥
								Pain (mean VAS score D1 & D2):	3.1 ± 1.9	NR
								Itching (proportion itch-free) (%):	65	25, 10*¥
								Adverse effects:	NR	NR
Ang, 2002 (Singapore)	115 patients (<40% TBSA)	Partial thickness	Thermal	Not specified	22	RCT	MEBO ($n = 57$) vs. 1% SSD ($n = 58$).	Wound healing rate (days to 75% healing):	17	20
								Pain (mean week 1 post-dressing verbal numerical rating scale):	2.9	3.5*
								MRSA infection rate (%):	37.4	38.5
								Adverse effects	NR	NR
Allam, 2007 (Egypt)	106 patients (<25% TBSA)	Partial thickness	Thermal	Hand	NR	RCT	MEBO vs. 1% SSD cream and a polyethylene bags ($n = 53$ each)	Mean days to healing (superficial partial thickness)	10.48 ± 2.66	14.53 ± 3.83*
								Mean days to healing (deep partial thickness)	30.50 ± 5.10	36.60 ± 5.08*
								Pain Score 0 (%):	35.85	33.96
								Pain Score 1 (%):	47.17	41.51
								Pain Score 2 (%):	16.98	24.53
								Pain Score 3 (%)	0	0
								Adverse effects	NR	NR
Carayanni, 2011 (Greece)	211 adults (<15% TBSA)	Partial thickness	Thermal	Not specified	42.68 (18–75)	RCT	MEBO ($n = 104$:*50 deep partial and 54 superficial partial*) vs. Povidone iodine + bepanthenol cream ($n = 107$: *52 deep partial and 55 superficial partial*)	Time to wound healing (days to 50% reduction in TEWL for superficial partial thickness burns)	8.7	10.75*
								Reduction in admission for deep partial thickness burns (days)	3.02	2.79
								Pain (mean morning VAS on day 2)	3	4.2
								Pain (mean evening VAS on day 2)	3.8	4.7
								Adverse effects (allergic reactions, (%)	10.6	7.5
								Wound infection rate (%)	5.8	7.5
Tsoutsos, 2009 (Greece)	46 adults (extent not reported)	Deep partial thickness	Not specified	Facial	(20–70)	RCT	*Helix aspersa* extract (Elicina cream) (27) vs. MEBO ($n = 16$)	Days to full epithelialisation (photographic assessment)	15 ± 3	11 ± 2*
								Days to eschar detachment	11 ± 2	9 ± 2*
								D4 pre-intervention pain score (VAS)	6.50 ± 0.89	6.22 ± 1.25
								D4 30 mins post-intervention pain score (VAS)	4.50 ± 0.52	3.52 ± 0.80*
								Adverse effects (allergic reactions)	0	0

Abbreviations. CRP: C-reactive protein; MEBO: moist exposed burn ointment; SSD: silver sulfadiazine; TBSA: total body surface area; TEWL: transepidermal water loss ;VAS: visual analog scale; WCC: white cell count.

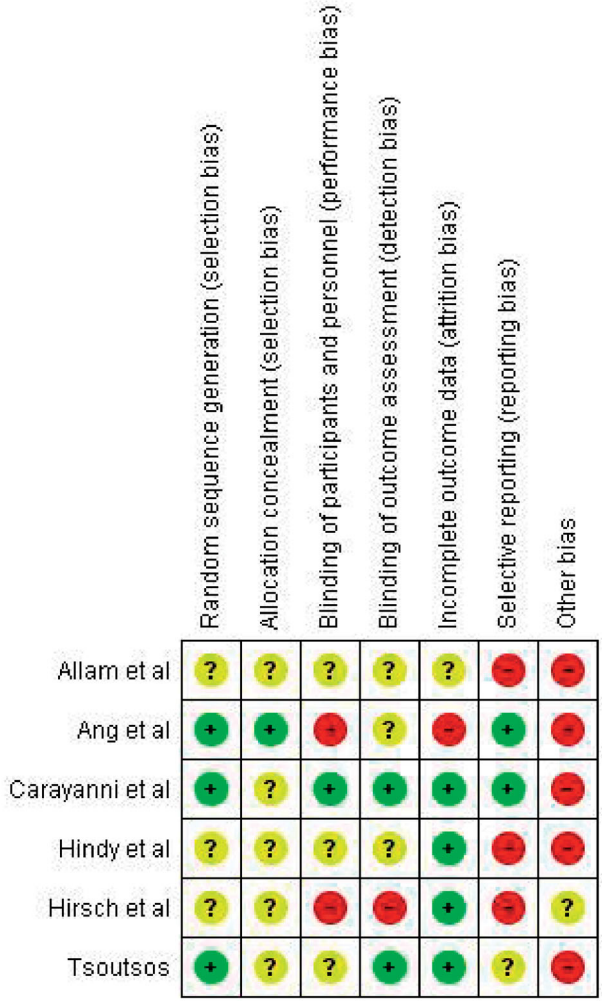

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

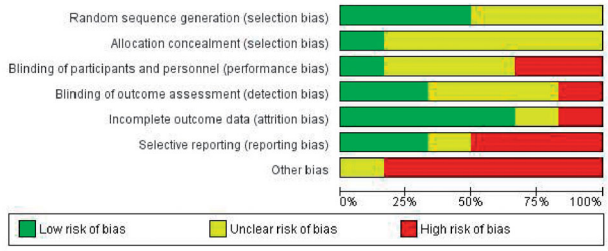

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

[24] and two studies included patients with both SPT and DPT burns [22,25]. Two trials included patients with partial-thickness burns but did not specify whether these were SPT or DPT [16,17,19,27]. Only Ang et al. [16,19,27] detailed the method used to determine burn depth.

Three studies compared MEBO with 1% SSD cream [16,17,19,25,27]. Others compared with sodium carboxymethylcellulose silver (Aquacel Ag) [24], povidene iodine plus bepanthenol cream [22] and *Helix aspersa* extract (Elicina cream) [26]. Only Hindy [24] included a negative control group (saline-soaked gauze dressing).

Characteristics of studies excluded after reading full-texts

Two studies were excluded after reading full-texts: an economic analysis that did not assess efficacy [29] and a nonrandomised study [18].

Risk of bias in included studies

Figures 2 and 3 summarise and illustrate the authors' risk of bias assessment. The trials by Hirsch [17], Hindy [24], Allam [25] and their respective colleagues had the highest or unknown risk of bias across all domains (Figure 2). The studies by Ang [16,19,27] and Tsoutsos' [26] teams had a lower risk of bias whilst Carayanni et al. [22] was judged least likely to be biased.

Three trials had a low risk of selection bias owing to detailed random sequence generation [16,19,22,26,27]. Although the remaining three trials all randomised patients into study arms, their procedures were unclear [17,24,25]. Only Ang et al. [16,19,27] detailed allocation concealment making it unclear whether the remaining five trials [17,22,24–26] adequately concealed allocation. Across most trials, the risk of selection bias is unclear (Figure 3).

None of the trials had a low risk of performance bias although there was insufficient information in three of the trials [24–26] to allow an assessment. The remaining three trials were at high risk of performance bias due to the non-blinding of patients and some study personnel [16,17,19,22,27].

Three trials [16,19,22,26,27] were at low at risk of detection bias because outcome-assessors were either blinded or non-blinding was unlikely to have affected outcome measurement. Two trials [24,25] had an unclear risk of bias whilst one had a high risk of detection bias [17].

Four trials had low risk [17,22,24,26], one was at high risk [16,19,27] and the remaining trial had an unclear risk of attrition bias [25].

Only two trials had a low risk of reporting bias [16,19,22,27]. Three trials had a high risk of reporting bias [17,24,25] and the risk in the remaining trial was unclear [26].

Effects of interventions

Meta-analysis was precluded by the heterogeneous reporting of outcomes; poor definition of the study population (i.e. not separating SPT and DPT burns); missing data and poor reporting (Table 1). A narrative synthesis was performed.

Measures of wound healing (primary outcome)

Both Ang [16,19,27], Allam [25] et al. observed faster healing in patients treated with MEBO compared to SSD. The mean number of days to 75% wound healing recorded by Ang et al. for the MEBO and SSD groups were 17 and 20 respectively [16,19,27]. In Allam et al's study [25], patients with SPT burns healed faster compared to when treated with MEBO compared to SSD (10.5 ± 2.7 versus 4.5 ± 3.8 days) ($p < 0.05$). Similarly, patients with DPT burns treated with MEBO healed faster (30.5 ± 5.1 vs. 36.6 ± 5.1 days) ($p < 0.05$). Hirsch et al. measured day 12 TEWL and markers of inflammation such as CRP and leukocyte count as markers of wound healing [17] comparing MEBO with SSD. The finding that patients treated with MEBO had greater loss of water transepidermally (11 vs. 7) suggests that these wounds healed slower than those treated with SSD. However, the levels of other markers were not reported.

Patients treated with *Helix aspersa* cream by Tsoutsos et al. healed significantly faster compared to MEBO, as assessed on photographs by blinded assessors (11 ± 2 vs. 15.3 days) [26]. This

planimetric finding was corroborated by another from the same study showing that eschar detachment was faster in patients treated with *Helix aspersa* cream [26].

Hindy found no difference in the healing times of MEBO and Aquacel Ag (10.35 ± 2.8 vs. 10.05 ± 2.3 days) [24]. Compared to povidone-iodine + bepanthenol cream, patients treated with MEBO healed faster as shown by faster 50% TEWL reduction (8.7 vs. 10.75 days) [22].

In summary, more trials comparing wound healing between MEBO and SSD favoured MEBO. There may be improved healing in MEBO-treated wounds vs. those treated with povidone-iodine + bepanthenol cream. There was no difference between MEBO and Acquacel Ag, but *Helix Aspersa* had faster healing rates than MEBO.

Pain and itch

Two studies found no difference in the analgesic effects of MEBO and SSD. Hirsch et al. found no statistically significant difference in mean visual analogue scale (VAS) scores between the MEBO and SSD groups on both days 1 and 12 (both mean 5 on day 1 then 3.8 and 3.5, respectively on day 12) [17]. Similarly, Allam et al. found no statistically significant difference in pain scores between MEBO and SSD [25]. One study found a statistically significant difference in pain profiles between MEBO and SSD [16,19,27]. MEBO patients rated their pain as less than that of the SSD group after one week (2.9 vs 3.5 mean post-dressing verbal numerical pain rating (VNPR) score). However, the MEBO group had a higher mean VNPR on admission (5.09 vs. 4.72) (*p-value unreported*) which may partially explain the pain score differences. Furthermore, by the third week, there were no longer any differences in analgesic effect.

In Hindy's study, the MEBO group rated their pain as significantly less than that of the Aquacel Ag and saline control groups during the first 48 h [24]. However, although the mean VAS score for the MEBO group was 3.1 ± 1.9, those of the Aquacel Ag and saline control groups were not reported. MEBO also had a greater ichthyotic effect than Acquacel Ag as shown greater proportions itch-free patients in the MEBO group compared to the Aquacel Ag and saline control groups (65 vs. 25% and 10%, respectively) [24]

There was no difference in the analgesic properties of MEBO and povidone-iodine + bepanthenol cream (mean morning VAS scores: 3.0 vs. 4.2, respectively, mean evening VAS scores: 3.8 vs. 4.7 respectively) [22].

Tsoutsos et al. found that pain scores were significantly improved with *Helix Aspersa* compared to MEBO (4.50 ± 0.52 vs. 3.52 ± 0.80) [26]. In this trial, mean VAS scores were similar between the MEBO and *Helix aspersa* groups before dressings were applied (6.50 ± 0.89 vs. 6.22 ± 1.25).

In summary, there was no difference in the analgesic effects of MEBO and SSD. It is unclear whether MEBO has superior analgesic effects to Acquacel Ag, *Helix Aspersa* and povidone-iodine + bepanthenol cream.

Incidence of adverse effects

The incidence of adverse effects was very low in all studies and for all interventions. One MEBO vs. SSD RCT reported no adverse outcomes for either intervention but the other two RCTs did not report their incidence of adverse effects [16,19,25,27]. There was no difference in allergy rates between MEBO and either *Helix aspersa* [26] or povidone-iodine + bepanthenol creams [22]. The respective rates of adverse effects of MEBO and Aquacel Ag were not reported in the sole trial comparing the two [24]

Only two trials reported the incidence of wound infections [16,19,22,27]. There was no difference in the incidence of methicillin-resistant *Staphylococcus aureus* infections between the MEBO and SSD groups in one trial (37.4 vs. 38.5%, respectively) [16,19,27]. Similarly, no statistically significant difference was seen in the incidence of Staphylococcus and Pseudomonas infections in groups receiving either MEBO or povidone-iodine + bepanthenol creams (5.8 vs. 7.5%, respectively) [22].

In summary, the incidences of adverse reactions and wound infections were low and no statistically significant differences were noted between MEBO and any of the comparators.

Discussion

There has been a suggestion that there are "double standards" in assessing complementary and alternative therapies in medicine [30]. It is therefore crucial that these treatments are subjected to the same scientifically rigorous analysis as used for 'traditional' treatments. As such, this systematic review was performed with the aim of pooling data relating to the efficacy of MEBO for the treatment of burn wounds. Such a synthesis for the first time allows both surgeons and patients to appraise collated and synthesised evidence of MEBO and several comparators and is therefore crucial to cost-effectiveness calculations by these groups. Data from six RCTs, all level 3 evidence, mostly poorly reported, were eligible for inclusion. The heterogeneity of study methods, comparators and outcome measures precluded meta-analysis. Even the three studies comparing MEBO to 1% SSD were sufficiently heterogeneous to preclude meta-analysis of only these studies.

The results of this review should be interpreted with the following caveats in mind. There were varying anatomical locations and not all papers specified. The appropriateness of 1% SSD as a comparator or standard treatment is debatable since SSD has been shown to be consistently associated with poorer healing outcomes compared to treatments such as skin substitutes, silver-containing dressings and silicon-coated dressings [1]. Other factors precluding meta-analysis included variability in outcome measurement. Surrogates included time to complete wound healing [24–26], TEWL [17], time to 75% healing [16,19,27] and 50% reduction in TEWL [26].

MEBO effect on wound healing

The results do not consistently favour MEBO or any of its comparators. Of the three studies comparing the wound healing properties of SSD with MEBO, two favoured MEBO [16,25] whilst one favoured SSD [17]. One of the favourable studies was poorly reported, exposing it to significant biases [25]. The small improvement in the other favourable study was not statistically significant [16,19,27]. This small and statistically insignificant benefit should be interpreted in the context of moderate risk of bias due to issues with blinding and failure to analyse on an intention to treat basis.

Wound healing was also reportedly improved in MEBO compared to Acquacel Ag [24] and povidone-iodine + bepanthenol cream groups [22]. The results in the Acquacel Ag trial were at risk of bias due to poor reporting [24]. The highest quality study used an indirect surrogate measure, that is, reduction in TEWL to suggest faster healing in SPT but not DPT burns [22]. This trial by

Carayanni et al. was at risk of intrinsic bias as it was funded by a manufacturer of MEBO [31].

Patients receiving *Helix aspersa* cream healed faster than those receiving MEBO [26]. This study by Tsoutsos et al. [26] was at moderate risk of bias and also compared MEBO to a treatment that is not standard of care. Due to these quality issues, these results should, therefore, be interpreted with caution. At present, poor evidence shows no difference in wound healing properties.

MEBO effect on secondary outcomes

Similar caution should be exercised in interpreting the effects of the interventions on secondary outcomes. In summary, there was no difference in pain profiles in two [17,25] of three trials comparing MEBO with SSD and in one trial comparing MEBO with povidone-iodine + bepanthenol cream [22]. One 3-week trial found that MEBO had better analgesis than SSD but only in the first week [16,19,27]. *Helix aspersa* cream had a greater analgesic effect than MEBO [26].

The claim that MEBO was more analgesic than Acquacel Ag could not be verified since pre-treatment VAS scores were not reported [24]. Furthermore, the Acquacel Ag trial was either inadequately randomised, poorly reported or both. The identity of outcome assessors and blinding protocols were also not specified.

Wound infection and adverse effects rates were similarly low in both MEBO and comparator groups in all studies. However, none of the studies reported adverse events according to item 19 of the CONSORT scale which advises recording adverse events with reference to standardised criteria.

Limitations

This systematic review was conducted following PRISMA guidelines. However, some limitations remain. The methodological flaws of the eligible studies and their effect on this review's conclusions have been extensively described above. This abundance of preclinical evidence of efficacy would suggest a likely positive clinical efficacy. However, the evidence was not high quality enough to definitively answer this question. Furthermore, there was a selection bias towards trials indexed on MEDLINE and EMBASE, arguably the two preeminent general healthcare databases. Several case reports written in unscientific formats and listed on the manufacturer's website were excluded as they were largely anecdotal [15]. Papers were limited to English-language publications. Attempts were made to contact all authors for clarification of missing data required but only one author responded.

Conclusions

The evidence for MEBO in English-language literature was poor and inconsistent with respect to wound healing rate and analgesis compared to 1% SSD, Acquacel Ag, *Helix aspersa* cream and povidone-iodine + bepanthenol cream. Blinded RCTs comparing MEBO to both placebo and other common topical treatments such as paraffin wax, which may also provide a moist and exposed environment, may further improve the confidence in concluding their analysis. There is good evidence that MEBO is as safe as its comparators as shown by the low complication rate.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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