Efficacy and feasibility of amniotic membrane for the treatment of burn wounds: A meta-analysis

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BACKGROUND: Burns cause a huge economic burden to society, and the wounds can be very difficult to manage. Clinical experience suggests that amniotic membrane (AM) is an economical and effective biological dressing for burns. However, few systematic reviews or meta-analyses have been published on such use. We aimed to evaluate the role of AM dressings in burn wounds.

METHODS: A systematic search of the PubMed, Cochrane, Embase, and Web of Science databases was conducted in March 2020. The search was conducted to identify randomized control trials that compared selected features of AM with those of other dressings, such as silver sulfadiazine, polyurethane membrane, and honey. For skin-grafted wounds, we compared AM-covered skin grafts and traditional staple-fixed skin grafts. Outcomes of interest for the efficacy analysis included wound infection, pain, itching, scarring, and healing time. The number of adverse events in each treatment group, the rate of withdrawal because of adverse effects, the cost of treatment, and patient acceptability were assessed for the feasibility analysis.

RESULTS: Eleven randomized controlled trials with 816 participants total were identified in our review. Amniotic membrane treatment was more effective than conventional methods, silver sulfadiazine, and polyurethane membrane in treating burn wounds, but AM appears to be less effective than honey. No reports of AM-related disease transmission or adverse reactions were described in the included articles.

CONCLUSION: Amniotic membrane has beneficial effects in treating burn wounds; however, the evidence needs to be strengthened by further robust randomized controlled trials. (*J Trauma Acute Care Surg.* 2021;90: 744–755. Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Systematic Review/Meta-analysis, level III.

KEY WORDS: Amniotic membrane; burn wounds; meta-analysis.

Burns, with their high morbidity and mortality, are a major public health concern.[1,2] Burn treatment consumes large amounts of medical resources and causes a huge economic burden to society.[2,3] Burn wounds are very traumatic and difficult to manage, often because of complications from the initial skin loss, such as pain and itching.[4] In addition, hypertrophic scars induced by burns can cause physical and psychological trauma to the patient, which may reduce the patient's self-esteem and affect the patient's quality of life.[5] Finding a suitable dressing for the burn wound remains a major problem. While achieving the primary goal of wound healing, reducing the cost of burn treatment is also an important goal.

Amniotic membrane (AM), formed from fetal ectoderm, is a thin and pliable membrane (about 20- to 50-μm thick).[6–8] It was first proposed as a biological skin substitute in 1910, and its first use as a dressing for burn wounds was reported in 1913.[9–11] Amnion has the advantage of being transparent, thin, light-weight, elastic, adhesive, semipermeable, and easily moldable; furthermore, it has low immunogenicity.[6,8,10] It can alleviate pain, reduce inflammation, control water loss, prevent bacterial colonization, prevent scarring, and promote epithelialization and wound healing.[7,8,10,12,13]

Clinical experience suggests that AM is an economical and effective biological dressing for superficial second-degree burns, and it can also be used as an adjunct to meshed autograft or as a temporary dressing for recently excised wounds before auto grafting.[6] However, few systematic reviews or meta-analyses have been published addressing the effectiveness and safety of human AM for the treatment of burn wounds. Hence, this meta-analysis was conducted to systematically evaluate the role of AM dressings in burn wounds, based on scientific evidence.

PATIENTS AND METHODS

Data Sources and Search Strategy

PubMed, Cochrane, Embase, and Web of Science databases from inception to March 2020 were searched by using terms such as "amnion" and "burn" to identify available data sources. Both free-text words and Medical Subject Headings were used to search PubMed and Cochrane. Only free-text words were used to search Embase and Web of Science because of a limitation of their interface. The details of the search strategies are presented in Supplemental Digital Content (Supplemental Table, http://links.lww.com/TA/B862). Only articles in English were included. To avoid omitting relevant randomized

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controlled trials (RCTs), conference summaries and reference lists of all identified records were also scanned.

Selection of Studies

Inclusion criteria were as follows: (1) RCTs evaluating AM for the treatment of burns irrespective of the degree of burn; (2) RCTs comparing AM with placebo, each other, or other treatment options; and (3) RCTs reporting complete efficacy outcome(s). When multiple publications from the same cohort reported different outcomes in a mutually exclusive way, all reports meeting the inclusion criteria were included.

Exclusion criteria were as follows: (1) Nonburn wounds such as the skin graft donor sites; (2) animal trials, case reports, dissertations, reviews, or duplicate secondary analyses; (3) papers that were unavailable in English; and (4) studies that were unable to extract any related outcome data.

Outcome Measures

For the efficacy analyses, outcomes included wound infection, pain, itching, scarring, and healing time. For feasibility analysis, we assessed the number of adverse events in each treatment group, the rate of withdrawal because of side effects, the cost of treatment, and patient acceptability.

Data Extraction and Quality Assessment

Two reviewers independently verified all potentially suitable trials through screening of the titles and abstracts of each report. Potential trials were then retrieved in full and verified for eligibility. Data extracted from the identified trials included the key characteristics of the studies, therapy design, and outcomes. The methodological quality of studies was assessed by the "risk of bias" assessment tool developed by the Cochrane Collaboration.[14] Any discrepancy was resolved by discussion or following arbitration by a third reviewer, if necessary.

Statistical Analysis

The results were extracted as either continuous or dichotomous variables, depending on how they were reported in the study. All statistical analyses were conducted using Review Manager (RevMan), version 5.3 computer program (Cochrane, London, England). Standardized mean differences (SMDs) or mean differences (MDs) with 95% confidence intervals (CIs) were calculated for continuous outcomes; risk ratios (RRs) with 95% CIs were calculated for dichotomous outcomes. Heterogeneity was evaluated using the I^2 statistic. With substantial heterogeneity for outcome data ($I^2 > 50\%$ or $p < 0.10$), a random-effects model was chosen to calculate pooled estimates. Otherwise, a fixed-effect model was used. Funnel plot regression was used to examine the publication bias. Subgroup analyses were performed according to the type of treatment in the control group. Statistical significance was defined as $p < 0.05$ unless otherwise stated. Throughout the process, we complied with PRISMA's reporting requirements (http://links.lww.com/TA/B861).

RESULTS

Study Selection and Characteristics

The initial database search identified 455 potentially relevant studies. After removing duplicates, there were 311 records. Of those, 258 were excluded based on the title and abstract; 53 full reports were then further reviewed for eligibility. Finally, 11 studies met the inclusion criteria and were identified for further data extraction (Fig. 1). Eight trials focused on acute burn wounds,[4,6,8,9,12,15–17] and the other three, on skin-grafted burn wounds.[3,5,18] For acute burn wounds, three articles compared AM with conventional methods,[8,9,15] three with silver sulfadiazine,[4,12,16] one with honey,[17] and one with polyurethane membrane.[6] For skin-grafted wounds, a comparison was made between AM-covered skin grafts and traditional staple-fixed skin grafts. Table 1 summarizes the general characteristics of the included reports, which were published between 1985 and 2017. All of these were unicentric trials. Sample sizes ranged from 15 to 211 participants, 816 participants in total. Mohammadi et al.[5] was the follow-up report of Mohammadi et al.[18] on the same cohort; therefore, the population was counted only once. The mean age of the participants was 18.8 years (range, 1 day to 62 years); 57% of the subjects were male. The characteristics of AM used in the included trials are described in Table 2.

Efficacy Outcomes

Acute Burn Wounds

Wound Infection

Bacterial invasion inhibits wound healing.[15] Six studies reported bacterial infection.[6,8,9,15–17] Pooled analyses showed that the bacterial invasion rate of burn patients treated with AM was lower than that of patients treated with conventional methods (RR, 0.51; 95% CI, 0.28–0.92; $p = 0.03$) or silver sulfadiazine (RR, 0.73; 95% CI, 0.53–1.00; $p = 0.05$), comparable with those treated with polyurethane membrane (RR, 0.33; 95% CI, 0.04–2.97; $p = 0.33$), but higher than those treated with honey (RR, 4.05; 95% CI, 1.51–10.85; $p = 0.005$) (Fig. 2).

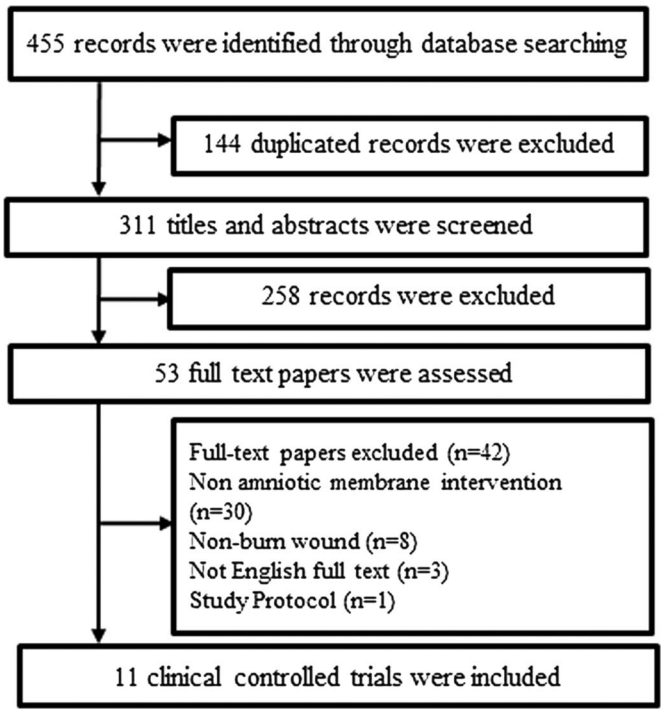

Figure 1. Flowchart of study selection.

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TABLE 1. Clinical Characteristics of Included Trials

Study	Study Design	Country	Patients	Age (Mean or/and Range), y	Female, %	Burn Type	Burn Wounds Type	Burn Size (%TBSA)	Severity of Burns	Intervention	Intervention vs. Placebo, n	Dressing Change	Healing Time	Adverse Events
Sharma et al. (1985)[15]	Controlled trial	India	Inpatient	6–50	67	NR	Acute	<20%: 2 20–40%: 12 >40%: 1	2nd degree	Fresh AM vs. conventional methods; half covered AM vs. half uncovered	5 vs. 5; 5 vs. 5	NR	NR	NR
Subrahmanyam (1994)[17]	Randomized, controlled trial	India	Inpatient	Mean, 24.85	33	Scald, 18 vs. 25; flame, 4 vs. 12; contact burn, 2 vs. 3	Acute (≤6 h)	10–40% (19.4% vs. 18.5%)	Partial skin thickness	Fresh AM vs. honey-impregnated gauze	24 vs. 40	NR	17.5 ± 9.08 vs. 24 ± 9.4	NR
Andonovska et al. (2008)[8]	Randomized, controlled trial	Macedonia	Inpatient	NR	NR	Hot water, 11 vs. 9; hot fluids, 3 vs. 5; flame, 9 vs. 5; electricity, 5 vs. 6; chemical, 2 vs. 2; other: 0 vs. 3	Acute (<24 h)	<10%: 7 vs. 13 10–20%: 12 vs. 10 20–30%: 5 vs. 3 30–40%: 3 vs. 2 40–50%: 2 vs. 1 >50%: 1 vs. 1	Dermal and subdermal burns	AM vs. standard methods (exposition, occlusive dressing and initial expansion with skin transplantation)	30 vs. 30	NR	NR	NR
Branski et al. (2008)[9]	Randomized, single-blind, controlled trial	United States	Acute stay and tub room daily visits	1–16 (mean, 7)	29	Scald, 23 vs. 22; flame, 30 vs. 27	Acute (mean, 1 day)	<40% (12 ± 7 vs. 11 ± 6%)	Partial-thickness burns	Facial amnion with antimicrobial ointment vs. facial antimicrobial ointment alone	53 vs. 49	0.5 ± 2 vs. 6 ± 3	6 ± 2 vs. 8 ± 2	NR
Mohammadi et al. (2009a)[12]	Randomized, single-blind, controlled trial	Iran	Outpatient	18.21 (mean)	42	Scald, 57 vs. 59; flame, 34 vs. 31; flash, 10 vs. 13; contact burn, 3 vs. 4	Acute (<72 h)	<20% (11.90 ± 3.80% vs. 12.30 ± 4.14%)	2nd and 3rd degree	AM vs. silver sulfadiazine ointment	104 vs. 107	Every 3–4 d vs. every day	9.5 ± 2.13 vs. 14.3 ± 2.6	NR
Mohammadi et al. (2009b)[16]	Randomized, controlled trial	Iran	Inpatient	<60 (mean, 24.29)	44	Most was flame followed by flash	Acute	20–50% (31.25 ± 8.32% vs. 32.37 ± 8.96%)	2nd and 3rd degree	AM vs. silver sulfadiazine and gauze	63 vs. 61	Every 3–4 d vs. twice daily	20.7 ± 5 vs. 30.47 ± 8.59 (hospital stay)	NR
Adly et al. (2010)[6]	Randomized, controlled trial	Egypt	Inpatient	Mean, 18.04	54	Scald, 12 vs. 11; flame, 9 vs. 12; chemical, 2 vs. 0	Acute	1–22% (8.7826 ± 6.42 vs. 7.7826 ± 4.90)	2nd or 3rd degree	AM vs. polyurethane membrane	23 vs. 23	Every 3 d in both groups	11.909 ± 6.086 vs. 14.117 ± 6.688	NR
Mostaque et al. (2011)[4]	Randomized, controlled trial	Bangladesh	Inpatient	1 d to 12 y (mean, 3.82)	52	Scald, 42 vs. 25; flame, 9 vs. 26	Acute (<72 h)	Superficial second degree, 7.39% vs. 9.39%; deep second degree, 5.22% vs. 5.20%	2nd degree	AM vs. topical silver sulfadiazine	51 vs. 51	1.33 ± 0.55 vs. 65.53 ± 18.23	10.69 ± 3.87 vs. 13.43 ± 5.13 (hospital stay)	NR
Mohammadi et al. (2013a)[18]	Randomized, controlled trial	Iran	Inpatient	<60 (mean, 23.54)	50	Scald, 20; flash, 20; flame, 68	Acute	4–15% (9.03 ± 2.69%)	2nd and 3rd degree	Skin graft was covered with AM vs. skin graft was fixed with skin staples	54 vs. 54	Every 2 d in both groups	6.98 ± 1.35 vs. 13.9 ± 1.66 (mean duration of graft take)	NR

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Mohammadi et al. (2013b)[3]	Randomized, controlled trial	Iran	Inpatient	16–60 (mean, 27.18)	NR	NR	Chronic (median time, 53 d)	29.18 ± 7.23%	Chronic burn wounds (with more than 2 wk after granulation tissue formation)	Skin graft was covered with AM vs. skin graft was covered with Vaseline gauzes and then dry gauzes	38 vs. 38	Every 2 days in both groups	NR	No adverse events
Mohammadi et al. (2017)[5]	Randomized, single-blind, controlled trial	Iran	Inpatient	<60 (mean, 23.54)	50	Scald, 20; flash, 20; flame: 68	Acute	4–15% (9.03 ± 2.69%)	2nd and 3rd degree	Skin graft was covered with AM vs. skin graft was fixed with skin staples	54 vs. 54	NR	NR	NR

NR, not reported.

Pain

Both continuous and dichotomous outcomes for analgesic efficacy were assessed. According to the continuous outcome from the two studies,[12,16] AM is significantly better than silver sulfadiazine for pain relief in burns, both before (MD, −2.35; 95% CI, −2.72 to −1.98; $p < 0.00001$) and after (MD, −3.75; 95% CI, −4.03 to −3.11; $p < 0.00001$) dressing changes (Fig. 3*A*). Effective rates defined as painless during dressing change were available in three studies.[4,6,17] Patients receiving AM treatment were more likely to feel no pain during dressing changes than those treated with silver sulfadiazine (RR, 3.91; 95% CI, 2.29–6.69; $p < 0.00001$) or polyurethane membrane (RR, 1.58; 95% CI, 1.03–2.44; $p = 0.04$). When compared with honey, however, the analgesic effect of AM was not superior to honey for burn wounds (RR, 0.67; 95% CI, 0.35–1.27; $p = 0.22$) (Fig. 3*B*).

Scarring

The formation of a hypertrophic scar after burn injury was reported in two studies.[9,17] From the combined analysis, AM has no advantage over the control with respect to scar formation (MD, 0.21; 95% CI, −0.41–0.83; $p = 0.50$) (Fig. 4*A*) or honey treatment (RR, 0.9; 95% CI, 0.74–1.1; $p = 0.31$) (Fig. 4*B*) in inhibiting postburn scarring.

Number of Dressing Changes

Most of the articles mentioned the frequency of dressing changes throughout the hospitalization; however, only two articles provided data suitable for extraction.[4,9] According to the combined analysis, the number of dressing changes in the AM group was significantly lower than that in the control group and the silver sulfadiazine group (SMD, −3.53; 95% CI, −6.26 to −0.80; $p = 0.01$; heterogeneity, $I^2 = 97\%$, $p < 0.00001$) (Fig. 4*C*).

Healing Time

Six studies reported the difference in healing time or length of hospital stay for the treatment and control groups.[4,6,9,12,16,17] In general, according to the analysis, AM could shorten the healing time of burn wounds or the patient's hospital stay (SMD, −0.76; 95% CI, −1.52 to 0.01; $p = 0.05$). Subgroup analysis showed that AM had a statistically significant advantage in reducing burn wound healing time or length of stay compared with placebo (SMD, −0.99; 95% CI, −1.40 to −0.58; $p < 0.00001$) and silver sulfadiazine (SMD, −1.34; 95% CI, −2.15 to −0.52; $p = 0.001$) and is equivalent to polyurethane membrane (SMD, −0.34; 95% CI, −0.92 to 0.24; $p = 0.25$) but less effective than honey (SMD, 0.88; 95% CI, 0.35–1.41; $p = 0.001$) (Fig. 5*A*).

Average Expenses

Mohammadi et al.[16] reported that the average expenses in the amnion group were significantly less than those in the silver sulfadiazine group (MD, −841.47; 95% CI, −905.91 to −777.03; $p < 0.00001$) (Fig. 5*B*). Although there was only one study[16] on the average hospitalization cost, based on the reported wound healing time and number of dressing changes in reports, we can infer that AM treatment for burn wounds can significantly reduce the treatment cost.

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TABLE 2. Characteristics of AM Used in the Included Trials

Study	Amnion Source	Amnion Type	Amnion Preparation	Amnion Storage	Disease Tests	Amnion Fixation
Sharma et al. (1985)[15]	Human AM	Fresh	Separated, cleansed at room temperature for 1 h before application. (Using sterile technique, the membrane is separated from the placenta and rinsed three times in sterile physiological saline solution. The membrane is agitated thoroughly during rinsing, and occasionally, a gauze is used to remove the clots between rinses. Next, the membrane is rinsed once in modified Dakin's solution followed by three more rinses with saline[19]).	Stored at room temperature	No dressings were applied except in case of circumferential burns.	No dressings were applied except in case of circumferential burns.
Subrahmanyam (1994)[17]	Human AM, obtained in a fresh condition after cesarean delivery or normal delivery	Fresh	The AM, after separation from the chorion and placenta, was washed with normal saline.	NR	NR	NR
Andonovska et al. (2008)[8]	NR	Preserved	The placenta is first rinsed of blood with physiological solvate. Then, the amnion membrane is separated from the rest of the chorion and is rinsed again.	Preserved in 76% alcohol in a sterile glass vessels. For the first 24 h, it is kept at room temperature and then at +4°C. Before use, the vessel with the AM is placed in room temperature for 10 min and is then rinsed with sterile physiological solvate.	NR	NR

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Branski et al. (2008)[9]	Human AM, from placenta during caesarean sections	Preserved	In accordance with internal tissue bank guidelines and the guidelines of the American Association of Tissue Banks, placentas were washed with Ringer's solution; chorion and amnion were separated. The tissue was then transferred to a sterile container in the delivery room and immediately transported at 4°C to the processing site, where it was processed within 12 h of arrival. Amniotic membrane was rinsed and soaked in saline and Dakin's solution (0.25% sodium hypochlorite solution). It was then stored in RPMI 1640 with antibiotics (amphotericin B, 50 mg/L; vancomycin, 50 mg/L; ciprofloxacin, 50 mg/L; and trimethoprim, 50 mg/L) at 4°C for a minimum of 3 d and up to 7 d. After 1 h, a sample of the storage medium was aliquoted for microbiological testing. The epithelial surface of the AM was removed by treatment with 0.25% trypsin–EDTA diluted 1:4 with phosphate buffer solution. The AM was placed on a rotator and agitated for 24 h at room temperature. After draining off excess trypsin, the AM was placed in Triton X-100 detergent diluted 1:100 with phosphate buffer solution and placed on a rotator for 24 h at room temperature. Finally, the AM was rinsed with phosphate buffer solution.	Preserved in 12.5% glycerol for 20 min, cut into 250 cm 2 pieces, folded in fine mesh gauze, and sealed in sterile plastic pouches. The plastic pouches were placed into foil pouches, frozen in a control rate freezer, and stored at −80°C (tissue bank).	The presumptive female donors were tested for hepatitis B and C, rapid plasma reagin for syphilis screening, and HIV 1 and 2. The testing was done at the time of delivery and 60 to 90 d after delivery.	NR

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TABLE 2. *(Continued)*

Study	Amnion Source	Amnion Type	Amnion Preparation	Amnion Storage	Disease Tests	Amnion Fixation
Mohammadi et al. (2009a)[12]	Human AM, from placenta during elective caesarean sections	Preserved	The AM was delicately separated from chorion and placenta and washed thoroughly with normal saline until a whitish, smooth transparent layer remained.	Put in a sterile pot containing normal saline and 80 mg gentamicin and stored in refrigerator at 4°C for more than 1 wk.	A blood sample was drawn from umbilical cord and checked for VDRL, HIV, and HCV and HBS antigen.	covered with Vaseline gauze and dry gauze dressing
Mohammadi et al. (2009b)[16]	Human AM, from placentas achieved from elective caesarean sections	Preserved	The AM was delicately separated from chorion and placenta and washed thoroughly with normal saline until a whitish, smooth transparent layer remained.	Put in a sterile pot containing normal saline and 80 mg of gentamicin and stored in refrigerator at 4°C for more than 1 wk.	A blood sample was drawn from umbilical cord and checked for VDRL, HIV, HCV, and HBS.	A layer of Vaseline gauze was applied, and dressing with gauze and band was done
Adly et al. (2010)[6]	Human AM	Lyophilized AM (Biomembrane): a product of matrix health care company	Freeze dried to only 5% water content and then γ radiated at 25 kGy.	NR	NR	Covered by paraffin tulle and dressing and fixed by compression bandage
Mostaque et al. (2011)[4]	Human AM	Vacuum-packed, radiation-sterilized membranes (supplied from Tissue Banking and Biomaterial Research Unit of Bangladesh Atomic Energy Commission)	After collection of the placenta, the membrane was separated, cleaned, and tagged on a sterile gauge (secondary dressing). The membrane was then irradiated with Co-60 γ radiation (2.5 mrad) and then oven dried in a controlled temperature oven at 40 ± 1°C for 14 to 16 h.	NR	Serological tests for HIV, hepatitis B and C, and syphilis	Covered by gauze
Mohammadi et al. (2013a)[18]	Human AM, from placentas retrieved from the elective cesarean deliveries	Preserved	The amnion is separated from the chorion and placenta and washed thoroughly with normal saline until a whitish, smooth, transparent layer remains.	Stored in normal saline–gentamicin solution at 4°C (tissue bank)	HIV, HBS, HCV, and VDRL tests for both mother and umbilical cord	Covered by dressing
Mohammadi et al. (2013b)[3]	Human AM, obtained from placenta during elective cesarean deliveries	Preserved	Washing with normal saline	Placed in a pot containing normal saline and 80 mg/L of gentamicin, and stored in refrigerator at 4°C (tissue bank)	HIV, HCV, and HBS tests for mother.	Was covered with Vaseline gauzes and then dry gauzes as a dressing
Mohammadi et al. (2017)[5]	Human AM, from placentas retrieved from the elective cesarean deliveries	Preserved	The amnion is carefully separated from the chorion and placenta and washed thoroughly with normal saline until a whitish, smooth, transparent layer remains	Stored in normal saline–gentamicin solution at 4°C (tissue bank)	HIV, HBS, HCV, and VDRL tests for both mother and umbilical cord	Covered with dressing

EDTA, ethylene diamine tetraacetic acid; HBS, hepatitis B surface; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NR, not reported; VDRL, venereal disease research laboratory.

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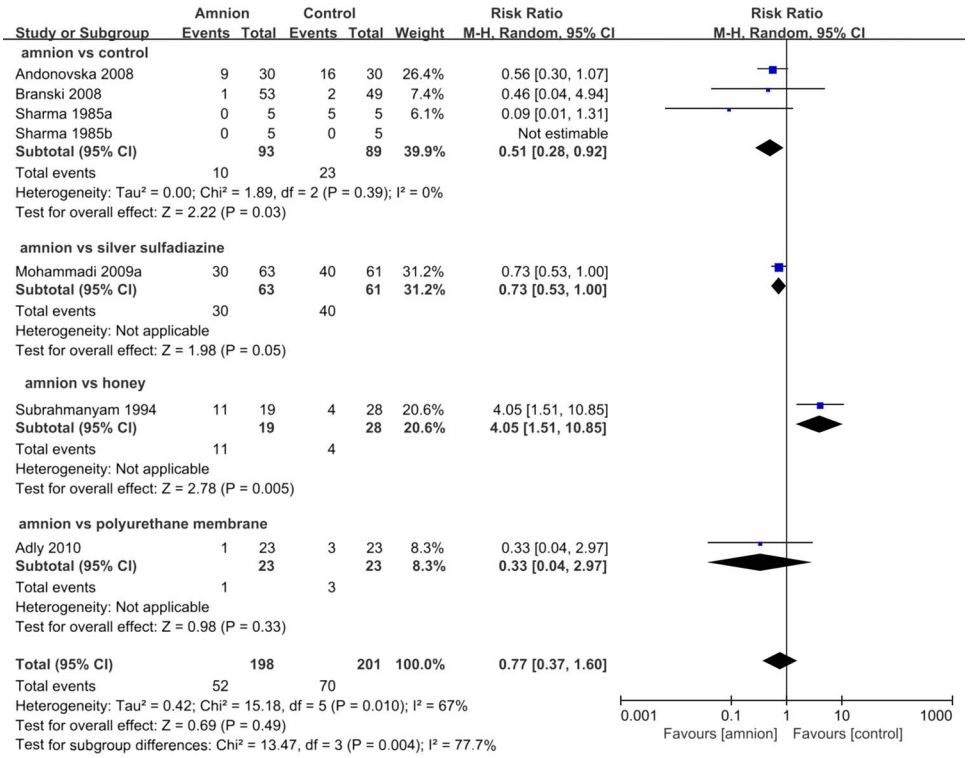

Figure 2. Effect of AM in the treatment of burn wound infection.

Skin-Grafted Burn Wounds

Itching

Itching is a common and unpleasant sensation in burn patients. From the included controlled trials, one trial discussed the role of AM in itching experienced by burn patients.[5] The results showed that AM, as an adjunct to a split-thickness skin graft, could significantly relieve the itching sensation in burn patients (MD, −0.72; 95% CI, −0.96 to −0.48; $p < 0.00001$) (Fig. 6*A*). Similarly, the amnion group was also superior to the control group in the effective rates defined as the absence of itching (RR, 1.96; 95% CI, 1.43–2.68; $p < 0.0001$) (Fig. 6*B*). However, more well-designed prospective studies are needed to confirm this result.

Scarring

Burn scar hypertrophy is a common and distressing condition that causes physical and psychological trauma to patients and, thus, reduces their quality of life. The formation of a hypertrophic scar has been reported in only one article.[5] In the analysis of continuity, AM-covered skin grafts seemed to be better than those with skin staples in preventing scar formation (MD, −0.72; 95% CI, −0.94 to −0.50; $p < 0.00001$) (Fig. 6*C*); the same held for the analysis of dichotomy (RR, 13; 95% CI, 0.75–225.2; $p = 0.08$) (Fig. 6*D*).

Duration of Graft Take

One of the three studies reported on the duration of graft take between the AM and control groups,[18] and the result was encouraging. The mean duration of graft take was 6.98 days in the amnion group and 13.9 days in the control group, with a statistically significant difference (MD, −6.92; 95% CI, −7.49 to −6.35; $p < 0.00001$) (Fig. 6*E*).

Quality Assessment

Supplemental Digital Content (Supplemental Figure, http://links.lww.com/TA/B863) shows the quality of the included studies according to the Cochrane risk of bias method. The overall quality of studies was rated as moderate to high. The majority of these studies were at unclear risk with respect to the methods of randomization and allocation concealment. In addition, because of the recognizability of amniotic dressings, it is difficult to blind the participants, so most were not double-blind studies.

DISCUSSION

This meta-analysis provided an overview of the efficacy and acceptability of AM in the treatment of burn wounds. We identified 11 trials comparing AM with conventional methods and other treatments, involving 816 patients with burns. Because acute burns can result in wound infection, severe pain, and high cost, the effects of AM on burn-related infection and pain, healing time, and expense were discussed.

Among the outcomes that could be quantitatively analyzed, AM was found to be significantly more effective than conventional methods in reducing bacterial invasion, decreasing the number of dressing changes, relieving itching, and shortening the healing time of burn wounds. Amniotic membrane dressings were more effective than silver sulfadiazine in reducing bacterial invasion, pain, dressing changes, treatment cost, wound healing time, and duration of hospitalization. Patients treated with AM seemed more likely to experience painless and shorter

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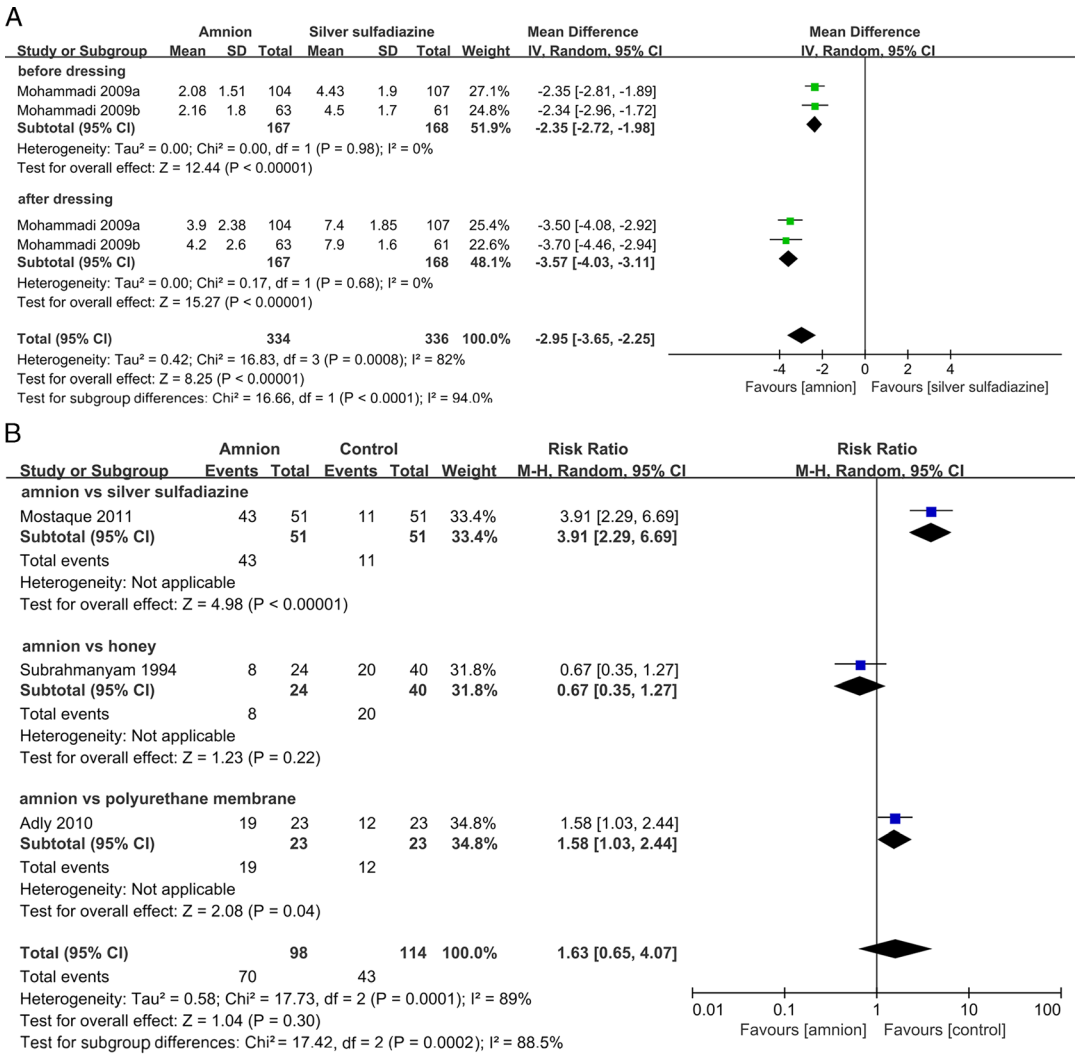

Figure 3. (*A*), Effect of AM in the treatment of burn wound related pain. (*B*), Treatment response rate of AM in burn wound related pain.

healing time than those treated with polyurethane membrane, but the treatments were equally effective in reducing bacterial invasion. However, AM was less effective than honey in reducing bacterial invasion, pain, scarring, and healing time. For skin-grafted burn wounds, AM-covered skin grafts significantly relieved the itching sensation, prevented scar formation, and shortened the mean duration of graft take. In addition, there were no reports of AM-related disease transmission or rejection in the included articles.

In general, the AM products in most of the articles were self-prepared and self-stored human AM. The most commonly used method of AM storage was to place it in a sterile pot containing normal saline and 80 mg/L of gentamicin and store it in a refrigerator at 4°C, which is a relatively easy procedure. Because of the light, thin, elastic, adhesive, and easily moldable characteristics of AM, the membrane adheres to itself when smoothly placed on the wound. In the majority of cases, petrolatum gauze and/or dry gauze dressings have been used to secure the amnion to the wound. Regular testing (at 1- to 7-day intervals) of the wound and dressing are then done to determine whether to replace the dressing. Therefore, in clinical practice, AM could be stored in an operating room, outpatient room, or inpatient ward. The application of AM is also simple, and monitoring the dressing is convenient for medical staff. The main concern with AM is the potential for disease (such as human immunodeficiency virus, hepatitis C virus, or hepatitis B virus) transmission and unpleasant smell, but these issues can be prevented by screening for viral markers and changing the dressing.[3,5] However, in the literature review, there were no reports of AM causing disease transmission or odor complaints.

The majority of included studies were conducted in low- or middle-income countries. These countries are where the burden of burn morbidity and mortality is largely concentrated and where, as outlined by the World Health Organization, more than 95% of the 300,000 fire-related deaths occur annually.[1] In developing countries, economic considerations are important. Compared with other biological dressings, AM is relatively cost-effective in preparation, storage, and application.[10] Furthermore, AM use reduces the number of dressing changes needed, the length of hospital stay, and the infection rate. Furthermore,

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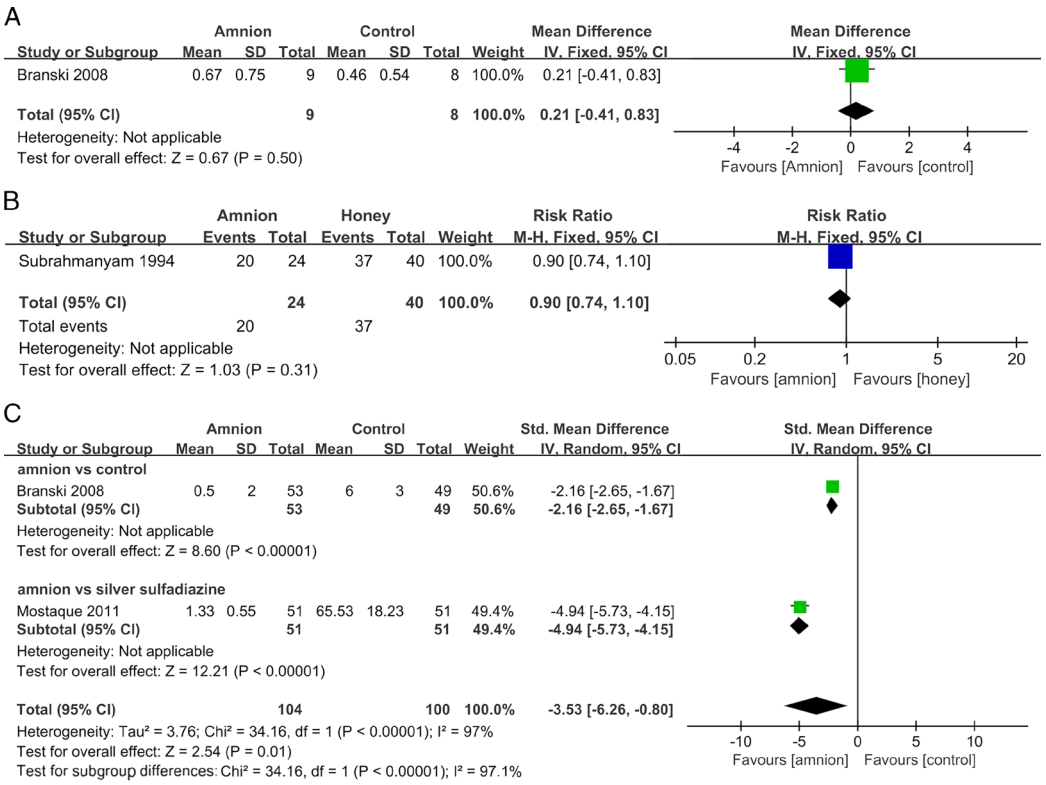

Figure 4. (*A*), Effect of AM in the treatment of burn associated scar. (*B*), Treatment response rate of AM in burn associated scar. (*C*), Comparison of No. dressing changes between AM group and control group.

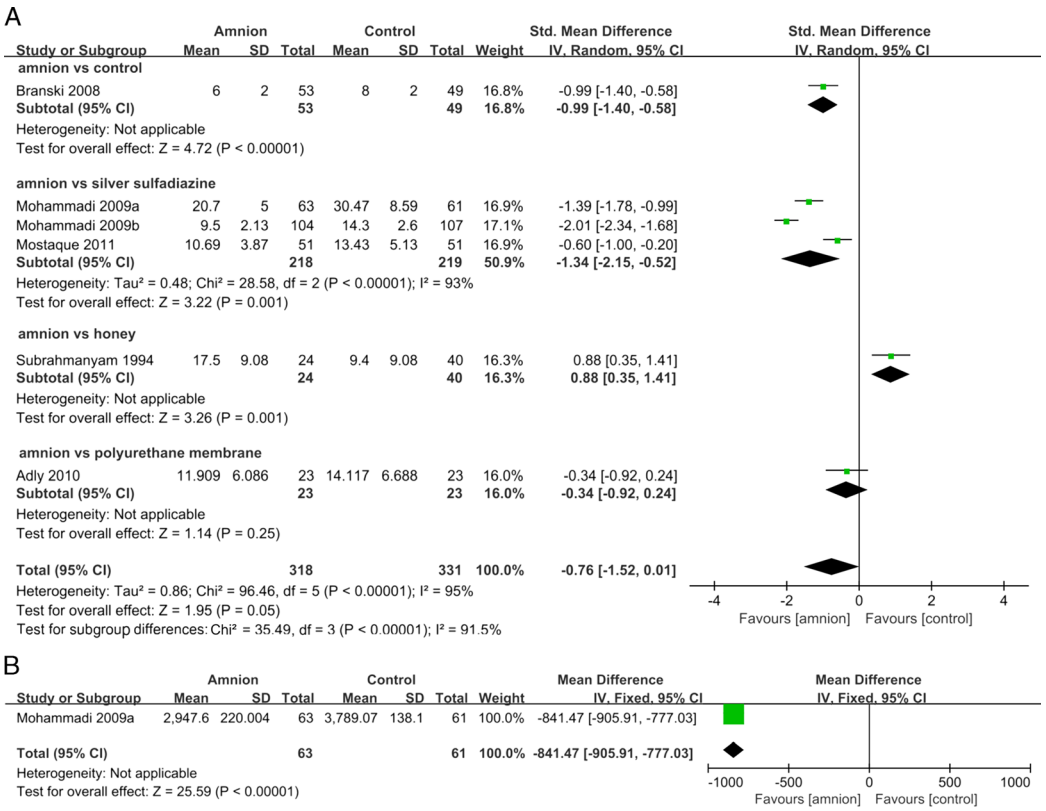

Figure 5. (*A*), Comparison of healing time between AM group and control group. (*B*), Comparison of average expenses between AM group and control group.

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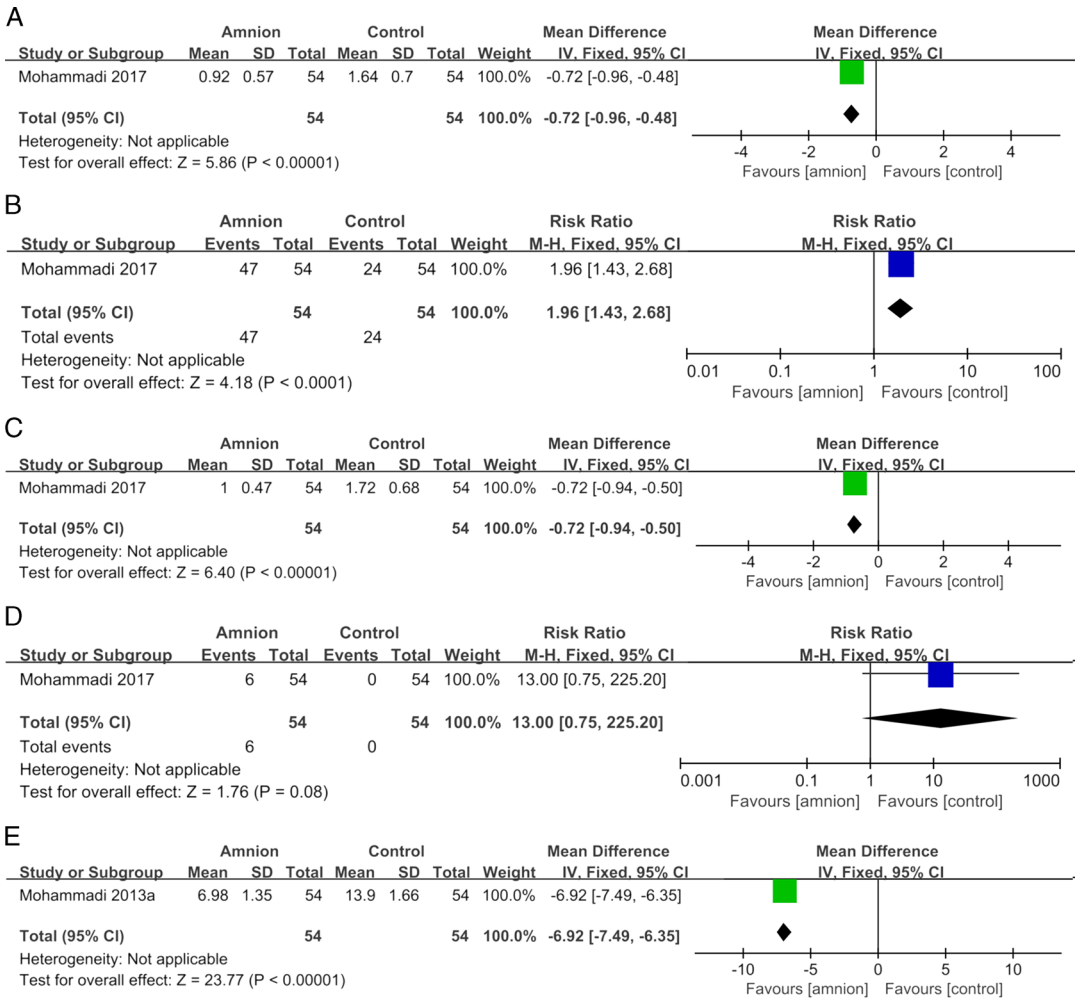

Figure 6. Skin grafted burn wounds. (*A*), Effect of AM in the treatment of itching. (*B*), Treatment response rate of AM in itching. (*C*), Effect of AM in the treatment of scar. (*D*), Treatment response rate of AM in scar. (*E*), Comparison of mean duration of graft take between AM group and control group.

the economic benefits become more prominent, which also increases patient and guardian compliance.

A strength of our meta-analysis is that we performed substantially extensive searches. To reduce the potential bias, two reviewers independently performed searches, scanned through the search output, extracted data, and evaluated the quality of each trial. In addition, we included analysis of data on wound infection, pain, itching, scarring, and healing time, all of which are clinically relevant parameters that are important for clinicians in making appropriate treatment choices.

Several limitations should be addressed, however. First, because of the heterogeneity of the trials and limited data reporting, data analysis for each parameter was restricted, which may have limited our ability to reveal the potential therapeutic effect of AM on burns. An important concern for doctors is the timing of the use of AM on a burn wound. In the included reports, the time between wound occurrence and AM use was not consistent, and it was not described in most of the trials. Therefore, we have no idea about the relationship between the initial time of use of AM on burn wounds and its therapeutic effect. This is a question that future research should address. Second, almost all of the RCTs included in this review were conducted years ago, and thus, the comparison groups did not always receive standard "modern burn care," which leads to a very high risk of bias toward AM as an intervention. In addition, silver sulfadiazine is a suboptimal treatment strategy for burn wounds and is rarely used in second-degree/partial thickness burns today. Perhaps more trials comparing AM with modern burn care or other novel biological dressings are needed to guide clinical treatment. Third, most of the included trials did not provide details on randomization and allocation concealment. Because of the recognizable characteristics of AM dressings, most of the trials were not double blinded, potentially leading to a high risk of bias.

In conclusion, our investigation revealed the beneficial roles of AM in the treatment of burn wounds. Given the limitations of currently available clinical studies and the promising positive impacts of AM on burn wounds, further robust RCTs are needed to strengthen our conclusions.

AUTHORSHIP

C.Y. and H.Y. initiated the study concept. C.Y. and A.b.X. developed the search strategy. C.Y., A.b.X., X.c.H., and X.l.T. performed the literature

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search, screened the literature, and appraised the selected publications. C.Y., X.b.D., and H.Y. performed the data analysis. C.Y., X.c.H., X.l.T., and Y.L. interpreted the results of the systematic review. C.Y. drafted the article, and H.Y., A.b.X., and C.Y. read and revised the final version of the article.

DISCLOSURE

The authors declare no conflicts of interest.

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