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# The impact of an open-label design on human amniotic membranes vs. silver sulfadiazine dressings for second-degree burns: a randomized controlled clinical trial

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## Abstract

**Background** Burn wounds require optimal medical management due to associated psycho-emotional and socioeconomic impacts and severe pain. The use of synthetic and biological dressings improves healing and reduces burn wound complications. The present study aimed to compare the outcomes of using human amniotic membrane (hAM) dressings and conventional silver sulfadiazine (SSDZ) ointment dressings in the management of second-degree burn wounds.

**Methods** Fifty patients who participated in this clinical trial were divided into two groups via simple randomization. All the enrolled patients, who had burnt in the last 24 h, had thermal damage mechanisms and were suffering from less than 20% second-degree heat-burn wounds on the skin surface. The target group ($n=25$) was treated with hAM, and the control group ($n=25$) was treated with SSDZ ointment. The researcher-designed checklist was used to determine the clinical performance in the follow-up assessments on days 7, 14, and 30.

**Results** No significant differences were detected in terms of sex, age, or percentage of burn wounds ($p>0.05$). Wound epithelialization at days 7, 14, and 30, scar formation, wound pigmentation, pain severity, analgesia requirements, and hospital stay length (on day 30) were significantly lower in the target group (treated with hAM) than in the control group (treated with SSDZ ointment) ($p<0.05$). However, treatment costs in the target group ($170) were significantly higher than those in the control group ($71) ($p<0.001$).

**Conclusion** Despite its higher cost, hAM, as a technology-based therapy dressing, demonstrates superiority over SSDZ ointment in terms of wound healing and pain management.

**Keywords** Burns, Amniotic membrane, Silver sulfadiazine, Clinical trial

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## Background

Burn wounds are currently a major concern for societies and healthcare systems [1]. Globally, burns rank as the fourth most common type of injury, following accidents, falls, and violence [2]. Historically, burn wounds have been associated with poor prognosis. Nearly half of burn patients are admitted to burn wards, and 200–300,000 people die from fire-related burns annually worldwide [3].

Burn wounds are classified as first-degree (epidermal injury), second-degree (dermal and epidermal injury), third-degree (damage to the entire skin layer), or fourth-degree (damage to the hypodermal layer) [4].

The most prevalent and painful burn wounds are second-degree burn wounds, accounting for more than 50% of all burn wounds [5]. Although second-degree burns are typically not life-threatening, their severe pain disrupts patients' social interactions and lifestyles [6]. Furthermore, the resulting scars significantly impact body image and mental health [7, 8]. Additionally, these wounds lead to physical disability, work absenteeism, and increased economic burdens on healthcare systems and society [9]. Annually, the UK and the US spend approximately 4.5–5.1 billion Euros and 7.9 billion dollars, respectively, on second-degree burn wounds [10, 11]. Additionally, they can lead to physical disabilities, work absences, and increased medical expenses [7, 8]. Despite their prevalence, effective treatment methods remain inadequately addressed in the literature, creating a knowledge gap. Moreover, concerns about dressing costs hinder their implementation in third-world countries, necessitating further exploration through health economics studies [12, 13].

Optimal treatment approaches can reduce clinical costs and physical impairments while enhancing wound healing [14]. For second-degree burn wounds, treatment options include daily dressing renewal using gauze, elastic wraps, systemic or topical antibiotics, excision and grafting, and biological dressings [15]. The treatment of heat-exposed burn injuries is complicated by inflammation, edema, bacterial infections, and prolonged healing [16]. Hence, choosing the best treatment plan remains challenging [17].

Among these, SSDZ dressing is the conventional and widely accepted method for managing second-degree burn wounds. Its antimicrobial properties make it effective in preventing microbial infections [18]. SSDZ offers advantages in terms of feasibility, cost-effectiveness, minimal systemic absorption and metabolic effects [19]. However, compared with biosynthetic dressings, SSDZ alone does not significantly improve healing outcomes [20].

Recent studies have proposed the use of biological dressings, such as the human amniotic membrane (hAM), to address second-degree burn wounds. hAM reduces pain, dressing renewal frequency, and fluid and electrolyte imbalances. Its transparency allows direct wound observation. Given the extended hospital stays for burn patients and associated complications (infections, permanent scars, severe pain, psychological distress, and economic burden), hAM represents an innovative treatment option that warrants further investigation [21]. The therapeutic properties of hAM involve various molecular pathways. These include the release of growth factors [21] and the presence of progenitor cells [22]. Additionally, numerous proteins and molecules contribute to its immunoregulatory, antimicrobial, and wound healing characteristics.

While treatments for third- and fourth-degree burn wounds have been extensively studied, research specifically focused on second-degree burn wounds remains scarce. Furthermore, the effectiveness of the hAM has not been clearly established in the current literature. Our study aimed to compare the therapeutic effects of hAM with SSDZ dressing in second-degree burn wounds at Ayatollah Mousavi Hospital, Zanjan, Iran, in 2018.

## Methods

### Study design

The present study was a randomized clinical trial conducted between March and October 2018 at the trauma and burn center of Ayatollah Mousavi Hospital in Zanjan, Iran, following CONSORT guidelines. The choice of silver sulfadiazine (SSDZ) as the comparator was based on its widespread use and established efficacy in treating second-degree burns, making it a relevant benchmark for evaluating the efficacy of new interventions such as human amniotic membrane (hAM). Compared to other ointments such as triple antibiotic etc. ointment, SSDZ remains the most commonly used treatment for second-degree burns [23, 24].

### Participants: inclusion and exclusion criteria

Drawing from the wound classification system proposed by Pabitha et al. (2021), we specifically focused on second-degree burns, and the depth of trauma was evaluated using clinical criteria based on this classification system. This choice was driven by the suitability of second-degree burns for investigating the study's target variables. According to this classification, second-degree burns manifest as partial thickness injuries affecting both the epidermis and a portion of the dermis (the middle layer of the skin). These burns typically present with redness, pain, swelling, and blistering, and they may heal within two to three weeks, albeit potentially leaving scars or pigment alterations [4].

We enrolled fifty burn injury patients who met the predefined inclusion criteria via a random number table.

The intervention group ($n$=25) received treatment with human amniotic membrane (hAM), whereas the control group ($n$=25) was treated with conventional silver sulfadiazine (SSDZ) dressings. The sample size, as per the methodology of Mostaque and colleagues, was calculated via the following formula: ($n$=20) [25]. To account for a potential 20% refusal rate, each group was ultimately composed of 25 patients.

$$n = \frac{\left(z_1 - \frac{\alpha}{2} + z_1 - \beta\right)^2 \left(\sigma_1^2 + \sigma_2^2\right)}{\left(\mu_1 - \mu_2\right)^2}$$
$$(\alpha = 0.05, \beta = 0.2, \mu_1 = 14.2, \mu_2 = 13.3, \sigma_1 = 0.96, \sigma_2 = 0.95, z_1 = 1.96)$$

According to a literature review [26–28], all the enrolled patients who had burnt in the last 24 h had thermal damage mechanisms, were aged above 18 years, and were suffering from less than 20% skin surface second-degree heat-burn wounds. The participants had no signs of burns on their head or neck; genital area; airway burn; previous burn; infectious wound site; necrotic tissue; or first-, third-, or fourth-degree burn wounds. The patients did not have any history of pregnancy; psychological disorders; substance abuse; smoking; cardiac, renal, or hepatic diseases; diabetes; malnutrition; corticosteroid therapy; or immunosuppressive treatment. Patients who presented signs of reaction and sensitivity to hAM were excluded (Fig. 1). Seventy patients with second-degree burns were selected for convenience sampling. Fifteen patients did not meet the inclusion criteria, and five patients refused to participate in the study. Fifty patients were divided into two groups, hAM ($n$=25) and SSDZ ($n$=25), via a table of random numbers by senior medical residents. We created a table with 50 rows (1–50) and two columns, with 25 rows in each column, one representing hMA and the other representing SSDZ. Each time a patient was admitted, we randomly selected a number and assigned it to either the hMA or SSDZ group, removing the corresponding row to ensure that it was not selected again. Fourteen days after the start of the study, two patients from the hAM dressing group ($n$=23) were excluded due to refusal to continue and early healing. Additionally, three patients from the SSDZ dressing group ($n$=22) were excluded due to refusal to continue ($n$=2) and early healing ($n$=1).

#### Procedures and intervention

Second-degree burn wounds in the target and control groups were treated with hAM and gauze soaked in SSDZ, respectively. hAM was supplied by the Iranian Tissue Product Company, Tehran, Iran, to treat the target group. A half centimeter greater than the wound length and width was covered by the membrane, which was retrieved from a sterilized human allograft amniotic membrane according to the American Association of Tissue Banks and the European Association of Tissue Banks standards [29, 30]. This product is used as a biological dressing for burns, trauma, and other complicated wounds of various sizes. It is processed as radiated, lyophilized and glycerolized [31]. The biological dressing was stored dry in a -40 °C freezer in the theatre room according to the manufacturer's instructions. The primary product was frozen and ready to use once it was placed in a sterile container filled with saline (NaCl 0.9%) for 20 min. Once the protective plastic layer is detached, the allograft is applied directly to the surgical wound, and the hAM is then stretched over the wound. The inner part of the hAM, which is slimy, was placed on the wound. Aseptically, sterile Vaseline gauze was placed on the membrane, followed by sterile saline-moisturized gauze (secondary dressing). Finally, it was wrapped in a crepe. At 36 h, the target group of patients was discharged from the hospital if they had no signs of infection (fever, pain, discharge, or odor) [32]. Four to five days after the first dressing, the patients were visited by a clinician in the outpatient ward, and the dressing was renewed. During the procedure, only the secondary dressing (moisturized gauze) was renewed, and the Vaseline gauze and the membrane remained untouched. The biological dressing is detached automatically once the wound is epithelialized.

In the control group, 20 g of SSDZ ointment per percentage of the wound was used to soak the gauze by tow expert nurse (MA and MT). The gauze was stretched over the wound daily while the dressing was renewed in the burn ward. The clinical effectiveness of the hAM and SSDZ dressings was assessed via the researcher-designated checklist on days 7, 14, and 30 after the first dressing.

#### Tools

To design the assessment tool, eight parameters were considered in a checklist according to the literature. These include wound epithelialization, scar tissue formation and pigmentation of the skin, pain severity, wound site infection, frequency of dressing renewal, hospital length of stay, painkiller consumption, and costs (Table 1) [18, 33].

The content and validity of this checklist were approved by seven academics of medical faculty and three other academics of the nursing faculty of Zanjan University of Medical Sciences, Iran. The eight parameters are as follows:

1. Wound epithelialization: Wound epithelialization was assessed by following patients and assessing the presence or lack of epithelialization and granulation

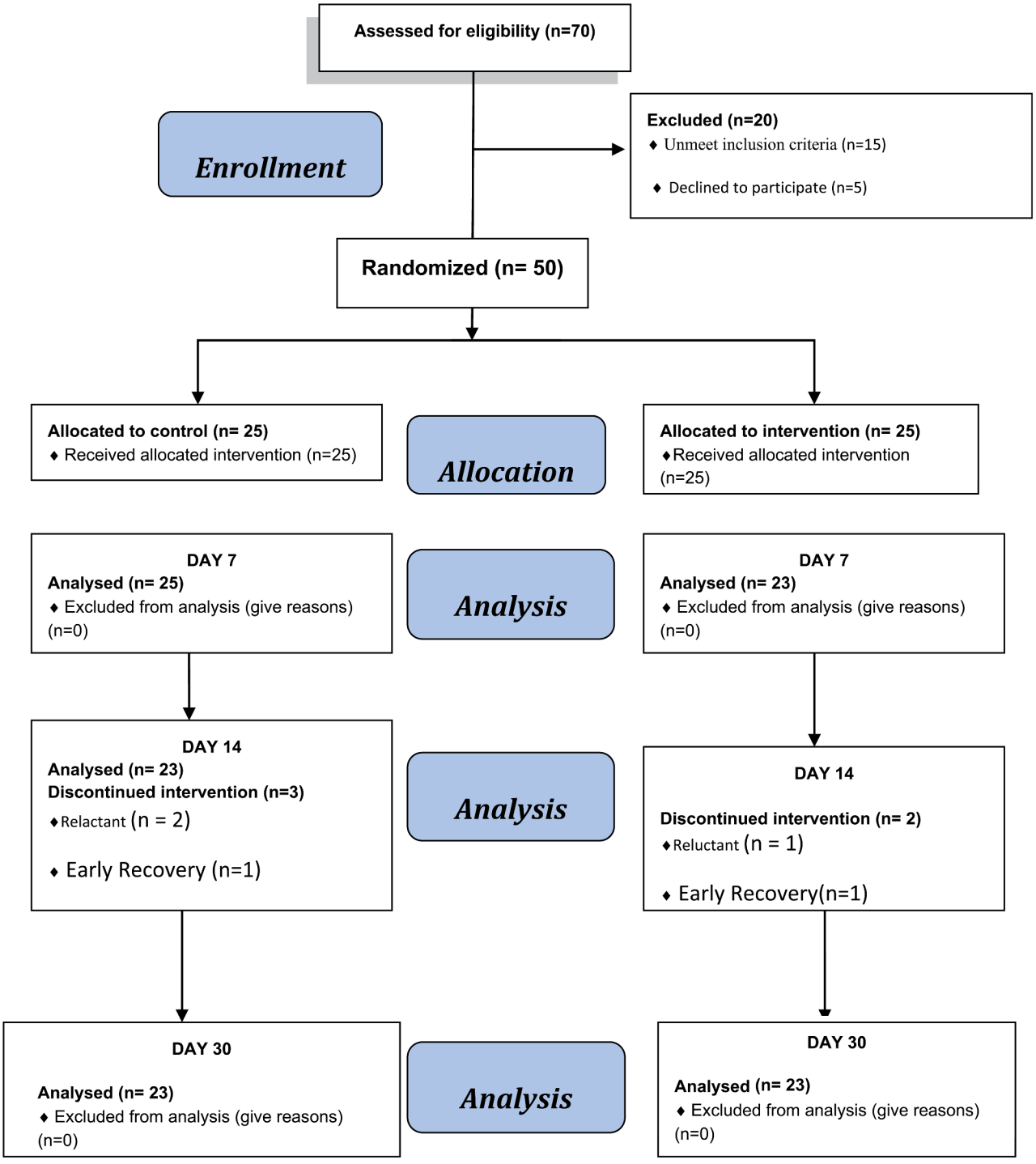


**Fig. 1** Inclusion and exclusion criteria. The diagram depicts the algorithm in which the participants were included and/or excluded from the study

of the burn wound on days 7, 14, and 30 after dressing [34].

2. Scar Tissue Assessment: On day 30, wounds in both study groups were evaluated via the numerical Vancouver scar scale. This scale considers four factors: pigmentation (scored 0–4), pliability (scored 0–5), vascularization (scored 0–4), and height (scored 0–4). The total scores range from 0 to 14, with interpretations as follows: 0–1 (no scar), 2–5 (mild scar), 6–10 (moderate scar), and 11–14 (severe scar) (Table 1) [35, 36]. Tehranian et al.'s (2016) psychological assessment tool was employed in this study [37]. Pain was assessed at each dressing change, with pain levels recorded fifteen minutes

**Table 1** The evaluation checklist of clinical effectiveness of the dressing

| | Item | Criterion |
|---|---|---|
| 1 | Wound epithelialization in days 7, 14, and 30 | Granulation exists on the wound? (Yes/No) |
| 2 | The amount of scar Vancouver Scar Scale (VSS) | VSS = 0–1 (No scar)<br>VSS = 2–5 (Mild scar)<br>VSS = 6–10 (Moderate scar)<br>VSS = 11–14 (Sever scar) |
| 3 | Pain severity Visual Analog Scale (VAS) | Quantitative (range between 0–10) |
| 4 | Wound site infection | Is fever (T > 38.2 °C), infectious discharge, redness, increase in WBC, CRP, and ESR present? (Yes/No) |
| 5 | Dressing renewal frequency | Recording the frequency |
| 6 | Painkiller consumption | Pethidine required in milligrams |
| 7 | Hospital stay length | Number of days |
| 8 | Cost | IRR and then converting to USD |

postapplication. Analgesics were administered on the basis of the assessment results, and the means and standard deviations of the data were compared.

3. Pain severity in patients was assessed via the visual analog scale (VAS). A self-reported tool, a 10-centimeter ruler, was used. On the one end, there is zero, and on the other end, there is ten. A score of zero indicates "no pain", a score of 1 to 3 indicates mild pain, a score of 4 to 6 equals moderate pain, and a score of 7 to 10 is interpreted as severe pain [38, 39]. Ismail and colleagues' (2015) psychology assessment tool is approved in Iran [40].
4. Wound site infection: After daily visits, a swab was taken from the wound if clinical signs of infection, including fever (T > 38.2 °C), infectious discharge, redness, or cellulitis, were present. Additionally, laboratory findings such as an increase in white blood cell count (WBC), C-reactive protein, and erythrocyte sedimentation rate (ESR) are considered indicators of infection [41].
5. The dressing renewal frequency was also considered in each group.
6. Hospital stay length: the number of days patients stayed in the hospital was counted.
7. Painkiller consumption: The number of milligrams of pethidine required during the hospital stay and during the dressing procedure was considered [42].
8. Costs: The expenses were in IRR currency; however, for better understanding, they were converted to USD (conversion rate on the basis of the 2018 ratio). The costs in this study were related to hospital admission costs that were taken from the discharge ward, and other costs were not calculated.

### Blindness

Pictures taken from wounds in both the cohort and control groups were sent anonymously to an analyst. The analyst assessed the epithelialization stage and improvement without knowledge of group assignments. Additionally, the laboratory analyst who tested the blood samples for inflammatory markers received the samples anonymously.

### Data and statistical analysis

The data were processed via SPSS software (version 24; IBM, Armonk, NY). To define the participants on the basis of the categorized and demographic parameters, descriptive statistics were used. The descriptive results are studied in terms of variance, mean value, and abundance percentage. In addition, various tests, including chi-square tests, *t* tests, ANOVA, Kolmogorov–Smirnov tests, and Fisher's exact tests, were used to analyze the data. The significance threshold was considered to be a value of less than 0.05.

## Results

The present study investigated one group treated with hAM ($n=25$) and the other treated with SSDZ ($n=25$). The mean age value and its variance were 26.72 and 7.49 in the hAM group, respectively. In the SSDZ group, the mean and variance were 27.16 and 8.13, respectively. The mean and variance percentages of skin burn injuries in the hAM group were 13.64 and 2.60, respectively. In the SSDZ dressing group, these values were 14.72 and 2.50, respectively. Before intervention, both groups were analyzed according to sex, age, and percentage of skin burn damage. There was no significant difference between the two groups ($p>0.05$) (Table 2).

Two participants (from the target group), one due to early healing owing to the small size of the wound and the other due to being reluctant to be involved in the study, were excluded on the 7th day of the study. Additionally, three patients were excluded from the control group on day 7; two of them were reluctant to be involved in the

**Table 2** The demographic details of the participants in each group

| Demographic details | | hAM group | SSDZ group | Test used | *P* value |
|---|---|---|---|---|---|
| Gender | Male N (%) | 14 (56%) | 14 (56%) | Chi square | 1 |
| | Female N(%) | 11 (44%) | 11(44%) | | |
| Age | MD (SD) | 26.72 (7.49) | 27.16 (8.13) | Kolmogorov–Smirnov | 0.178 |
| Percentage of skin surface burn | MD(SD) | 13.64(2.60) | 14.72 (2.50) | ANOVA | 0.142 |

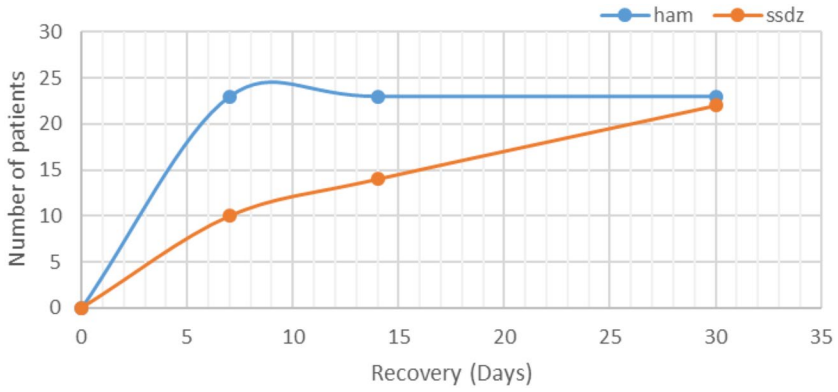


**Fig. 2** Epithelialization presence in hAM and SSDZ groups. Wound healing was significantly quicker in hAM group compared to SSDZ counterparts ($p < 0.001$)

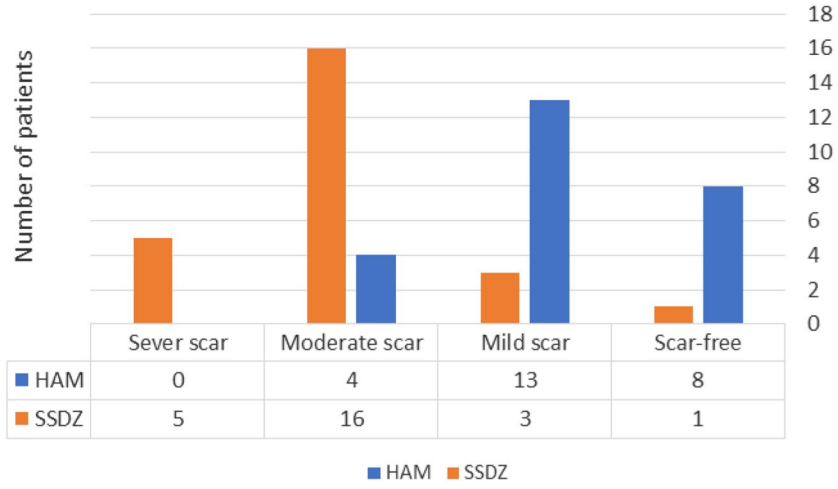


**Fig. 3** Scar of wound in hAM and SSDZ groups. Patients who had hAM dressing reported did not have severe scar of wound as opposed to SSDZ cohorts ($p < 0.001$)

study, and the other was excluded because of the low percentage of skin surface burns and early healing.

Wound healing (i.e., Epithelialization) in the target (hAM) and control (SSDZ) groups was assessed on days 7, 14, and 30, and the results were [23 (96%) vs. 10 (40%)], [23 (100%) vs. 14 (63%), and 23 (100%) vs. 22 (100%)], respectively (Fig. 2).

The findings revealed a significant difference between the two groups on the seventh and fourteenth days ($P<0.001$). However, there was no significant difference on day 30 ($P=1.00$). Additionally, the remaining scar tissue was assessed on day 30. In the hAM group, the percentage of scar tissue was as follows: 32% for patients without any scar tissue, 52% for patients with mild scarring, 16% for patients with moderate scarring, and 0% for patients with severe scarring. In contrast, the SSDZ group had the following percentages: 4% scar-free, 12% mild scar, 64% moderate scar, and 20% severe scar tissue (Fig. 3). These differences were statistically significant ($P<0.001$). Pain severity, measured via the visual analog scale (VAS), averaged 5.4 out of 10 (moderate level) in the control group throughout the 30 days. In the hAM dressing group, the average pain severity was 3.56 out of 10 (mild level) (Fig. 4). Notably, significantly fewer complaints related to pain were reported in the hAM group ($P<0.001$).

Neither of the groups reported signs of wound infection, including redness, an increased number of white blood cells, ESR, or CRP. The dressing renewal frequency differed significantly between the two groups ($p<0.001$). Additionally, patients treated with hAM had significantly shorter hospital stays than those treated with SSDZ did ($p<0.001$) (Fig. 5).

Patients treated with hAM had a significantly shorter hospital stay than did those in the SSDZ cohort ($p<0.001$). Specifically, patients were discharged within 36 h after hAM dressing. The average and standard deviation refer to the total length of hospital stay, which sometimes includes waiting time for hAM transplant. In

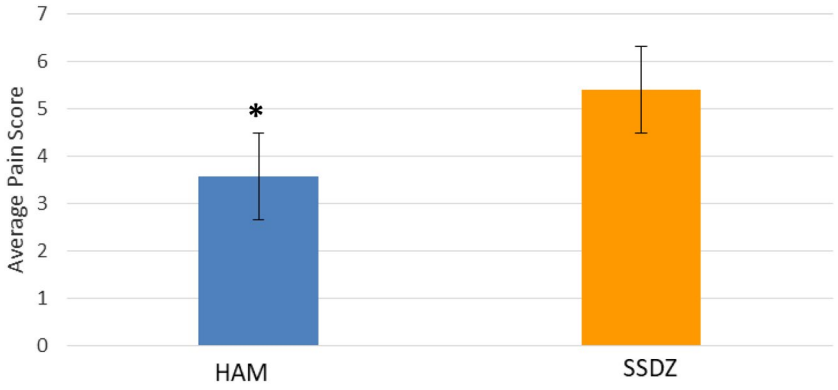


**Fig. 4** Average pain score in the hAM and SSDZ groups. Patients who had hAM dressings reported significantly lower pain scores than SSDZ patients did ($p < 0.001$)

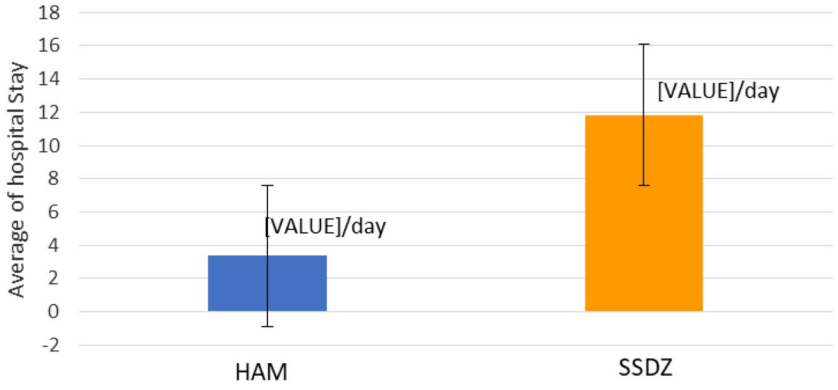


**Fig. 5** Average hospital stays for hAM and SSDZ groups

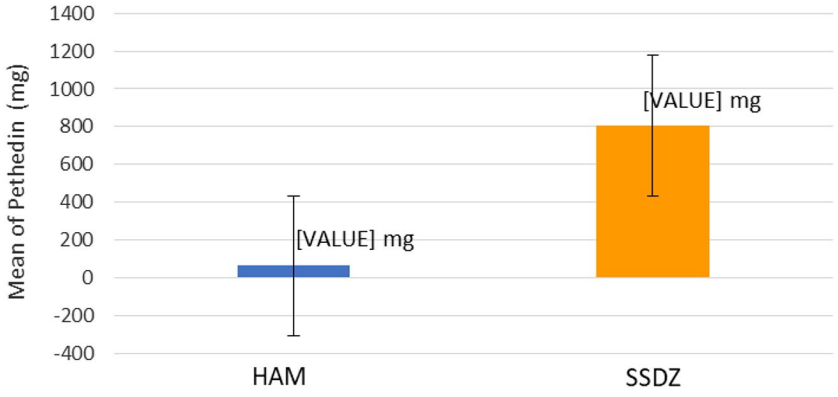


**Fig. 6** Mean of pethidine consumption in hAM and SSDZ groups. Administration of pethidine in hAM dressing group was significantly lower than SSDZ cohorts ($p < 0.001$)

contrast, for the control group, the entire hospital length of stay was considered.

To relieve the pain in the SSDZ group, 806 mg of pethidine per person was administered (on average). However, this effect was significantly lower in the hAM group (72 mg) ($P < 0.001$) (Fig. 6).

The total treatment and hospital stay costs for each patient in the hAM group were 170 USD, whereas they were 71 USD per person in the SSDZ dressing group (Fig. 7). The SSDZ dressing was significantly less expensive than the biological dressing was ($P < 0.001$) (Table 3) (Fig. 8).

## Discussion

The results of the present study indicate that the hAM dressing is superior to the SSDZ dressing for second-degree burn wounds. Specifically, hAM outperforms SSDZ in terms of wound epithelialization, scar formation,

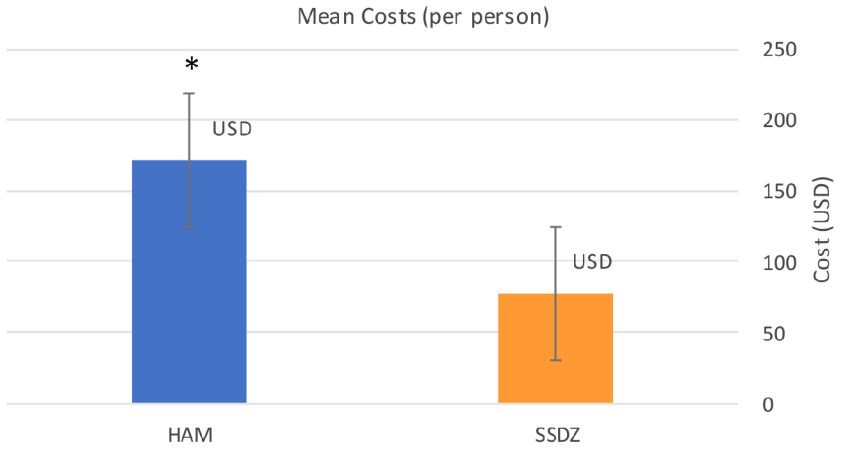


**Fig. 7** Average treatment expenditure for HAM vs. SSDZ. Treatment utilizing HAM dressing was significantly more expensive than SSDZ ($p < 0.001$)

**Table 3** The comparison between the clinical effectiveness of the hAM group and the SSDZ group

| Items assessed | Day | hAM group | | | SSDZ group | | | *P*-VALUE |
|---|---|---|---|---|---|---|---|---|
| | | *N*(%)_ | Presented | Not presented | *N*(%) | Presented | Not presented | |
| Wound epithelialization and granulation | 7 | 25(100%) | 23(96%) | 2(4%) | 25(100%) | 10(40%) | 15(60%) | < 0.001 Chi square |
| | 14 | 23(100%) | 23(100%) | 0(0%) | 22(100%) | 14(60%) | 8(40%) | = 0.001 Fisher exact test |
| | 30 | 23(100%) | 23(100%) | 0(0%) | 22(100%) | 22(100%) | 0(0%) | = 0.1 Fisher exact test |
| Scar on day 30 | Scar-free | 8(32%) | - | - | 1(4%) | - | - | < 0.001 Fisher exact test |
| | Mild scar | 13(52%) | - | - | 3(12%) | - | - | |
| | Moderate scar | 4(16%) | - | - | 16(64%) | - | - | |
| | Sever scar | 0(0%) | - | - | 5(20%) | - | - | |
| Pain severity | The entire period | Median | M | SD | Median | M | SD | < 0.001 |
| | | 4 | 3.56 | 1.15 | 5 | 5.4 | 1.44 | t test |
| Dressing renewal frequency | The entire period | 1 | 1 | 0.001 | 12 | 3.44 | 5.67 | < 0.001 *t* test |
| Painkiller consumption | The entire period per person | Median | M | SD | Median | M | SD | < 0.001 |
| | | 50 | 72 mg | 29.15 | 700 mg | 806 mg | 49.3 | |
| Number of hospital stay | The entire period | 3 | 3.36 | 0.952 | 10 | 11.84 | 5.13 | < 0.001 *t* test |
| Costs per person | The entire period | 7,100,000(IRR*) 170$ | 7,214,000* 172$ | 2078988.13* 49$ | 2,970,000* 71$ | 3,216,800* 77$ | 1408506.60* 36$ | < 0.001 *t* test |

* IRR: Iranian Rial, $:U.S. dollar

skin pigmentation, pain severity, dressing renewal frequency, hospital stay length, and painkiller administration. However, it is important to note that biological dressing is more expensive than SSDZ treatment. Owing to its similarity to natural human tissue, hAM is a superior alternative to conventional chemical agents (such as SSDZ) for treating burn wounds. The thin, transparent hAM layer has low immunogenicity, minimizing graft rejection reactions. Proinflammatory cytokine release in the wound bed decreases in the presence of hAM, particularly interleukin-1 alpha (IL1-α) and interleukin-2-beta (IL2-β) [43, 44]. Additionally, human leukocyte antigen-G (HLA-G), which is released by mesenchymal stem cells in hAM, helps mitigate the immune response [45]. Notably, hAM stem cells express minimal major histocompatibility complex-2 (MHC2) and major histocompatibility complex-1 (MHC1) receptors, contributing to low immunogenicity [46–48]. Amniotic membrane dressings also protect burn wounds against microbial pathogens and reduce the microorganism load [49, 50]. It contains antimicrobial and anti-inflammatory agents, including β-defensin, cystatin C, and lactoferrin [51, 52]. hAM is also involved in adaptive immunity because it possesses the PRAC protein; moreover, the therapeutic proteins of hAM are present in the fluid extracted from the placenta after processing [51].

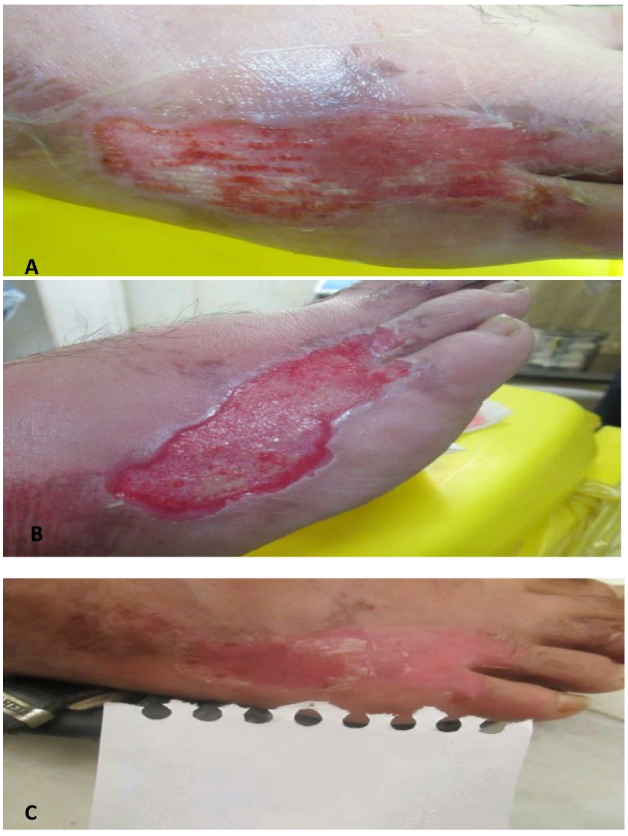


**Fig. 8** The patients' wound who have been treated with human amniotic membrane and silver sulfadiazine. (**A**) Second-degree burn wound on the edge of the right foot on the first day have been treated with human amniotic membrane. (**B**) Second-degree burn wound on the edge of the right foot on day 7 have been treated with human amniotic membrane. The amniotic membrane gradually peels off the skin as the wound heals, leaving a smooth and scarless surface. (**C**) Second-degree burn wound on the edge of the right foot on day 30 have been treated with human amniotic membrane

Although studies confirm its feasibility in burn wounds [26], no signs of infection were observed in either studied group during this trial. The participants had second-degree heat-burn wounds with less than 20% skin damage, and high-risk areas (such as the head, neck, genital areas, and airways) were excluded. Epithelialization is a crucial stage in wound healing [53, 54], and hAM promotes this process through various growth factors (EGF, HGF, KGF, TGF-α, TGF-β1, TGF-β2, TGF-β3, and bFGF) and their receptors [55–57]. Mesenchymal cells in hAM activate the PI3K/AKT and GSK3β/β-catenin pathways, preventing cell apoptosis and enhancing wound healing [48].

Navas et al. (2018) reported that mesenchymal stem cells in hAM reduce inflammation not only in heat-induced burn wounds but also in other types of burn wounds, including chemical burns [58]. These cells promote wound healing through immunoregulatory and antifibrotic paracrine effects [58–60]. Similarly, Salehi and colleagues (2015) reported a significantly shorter wound healing duration in the hAM group (17.61±2.56 days) than in the control group (21.16±3.45 days) [61].

A meta-analysis by Yang and colleagues (2020) examined the efficacy of amniotic membrane for burn patients. It revealed that amniotic membrane, when compared to dressings containing silver sulfadiazine, polyurethane membrane, and honey, shortened healing time and hospital stay in six studies [26]. Mostaque et al. (2011) also reported faster wound healing in the hAM group (10.69±3.87 days) than in the control group (13.43±5.13 days) ($P$=0.003) [23]. Notably, differences in study methods, such as the lyophilization method we used (freezing hAM at -80 °C and removing water by sublimation), can impact viability and factor levels [25]. Extensive second-degree burn wounds result in various scars, affecting patients' psychological well-being, body image, and functionality. The use of biological dressings, especially human amniotic membranes, is crucial for scar reduction [62].

Studies consistently report that scar reduction with hAM dressing leads to improved self-esteem, confidence, and sociability [57, 63].

Pain management is crucial for burn patients, especially considering the discomfort caused by wound healing processes, wound debridement, physiotherapy, and dressing changes [64]. The use of hAM dressings can significantly impact patient comfort during therapeutic interventions. Numerous studies have reported that amniotic membrane dressings reduce pain severity in burn patients, leading to a decrease in analgesic administration [65–68]. Insausti et al. reported that hAM does not induce tumorigenic effects or cell contact growth inhibition [69]. To address this knowledge gap, our present study includes a control group. In our study, intravenous analgesic administration was significantly lower in the amniotic membrane group than in the control group. Specifically, to manage pain in the SSDZ group, an average of 806 mg of pethidine per person was used. The average length of hospital stay (11.4 days) was approximately 68.07 mg of pethidine per person per day in the control group. In contrast, the hAM group had a shorter average hospital stay (3.36 days), with a total of 72 mg of pethidine per person and approximately 21.42 mg per person per day administered. This difference may be attributed to the shorter hospital stay and less frequent dressing changes in the amniotic membrane group, which not only contributes to cost-effectiveness but also enhances patient satisfaction [70].

As mentioned above, frequent dressing renewal leads to increased pain severity and bleeding. Consequently, owing to changes in the healing environment, such as humidity and heat, as a result of frequent dressings, the healing process is prolonged, increasing the urge for

analgesia. By utilizing the hAM, the healing process is observable. In addition, since the dressing is applied once every 3–4 days, less analgesia is needed. However, the entire SSDZ dressing should be renewed daily [71]. In the present study, the redressing procedure was significantly less common than it was in the SSDZ group. Mostaque and colleagues (2011) reported the same results [25]. Less frequent redressing lessened pain and psychological suffering and promoted patients' compliance with the treatment in the hAM group.

Another aspect of the study focused on the comparison between the amniotic membrane group and the SSDZ group in terms of cost-effectiveness. In the present study, the cost of treatment with the amniotic membrane was significantly greater than that of SSDZ treatment, which contradicts Hossain and colleagues (2020) and Silverstein and colleagues [72, 73]. The difference could be related to not taking into account the loss of income as the result of the burn wound, the psychological disorders caused by the scar and the length of sick leave. In fact, this is one of the limitations of the present study, and only treatment and hospital stay costs were taken into account. Future studies should be carried out to clarify and compare the actual costs. Despite higher treatment costs, the hAM is accepted by clinicians and patients because of shorter hospital stays, less frequent redressing and, eventually, less severe pain, a lower infection rate, and better patient quality of life [74]. However, in Iran's healthcare sector, as insurance companies compensate for the majority of amniotic membrane dressing costs, the costs for patients and the healthcare sector are acceptably reduced to 10%. Burn wounds are prevalent in developing countries and require considerable funds and facilities. Hence, accelerating the healing process and rapid recovery are important issues in healthcare management. Correspondingly, finding and selecting the optimum methods and materials to address this problem has always been highly important [13, 75].

Considering the effects of hAM in the treatment of second-degree burn wounds, establishing skin and biological dressing banks worldwide seems to be a priority. By expanding such centers, the availability of products is improved for clinicians, and delivery costs are decreased. Additionally, taking the invisible costs into account by healthcare economy experts in a larger sample size with a longer follow-up period is recommended. Future studies are needed to probe the effectiveness of the hAM dressing in other burn wound degrees and different age groups to provide better insight into the optimal guidelines for various burn wounds. Studies have shown that hAM is a novel yet not fully understood product for healthcare professionals [63, 76].

### Strength

The study evaluates multiple important outcomes, including wound epithelialization, scar formation, skin pigmentation, pain severity, analgesia requirements, and hospital stay length. This comprehensive approach provides a holistic view of the treatment effects. The study addresses a clinically relevant issue, as burn wounds are common and require effective management. The findings have practical implications for improving patient care and outcomes.

### Limitation

This study has several limitations that should be acknowledged. Firstly, it did not account for hidden costs such as income loss resulting from burn wounds, psychosocial expenses, and other unforeseen outlays. Consequently, drawing a conclusive comparison between the costs of the two studied groups remains impossible. Future investigations are necessary to illuminate the actual treatment costs comprehensively.

Additionally, no infection incidents were reported in either the cohort or the control group. This limitation restricts our exploration of the antimicrobial properties of the human amniotic membrane (hAM) and precludes a direct comparison. The absence of infections could be attributed to stringent exclusion criteria, such as excluding patients with high-risk infections (e.g., genital burn wounds) or the specific wound size included in the study. Further research should explore the anti-inflammatory and antimicrobial effects of hAM.

Another limitation was the short observation period of 30 days, which is insufficient to assess the long-term outcomes of scar formation. Scar maturation can take 1–2 years, and our 30-day assessment period may not capture these long-term outcomes. The use of the Vancouver Scar Scale (VSS) as a physician-led scar rating tool may also introduce some risk of bias. Future studies should incorporate longer follow-up periods, such as the 6-month scar stabilization period, and utilize standardized, objective tools for scar assessment to minimize bias and provide more accurate ratings.

## Conclusion

The availability and feasibility of hAM dressings make them suitable for treating superficial partial-thickness burn wounds. Compared with SSDZ, hAM reduces pain, enhances patient mobility, and shortens hospital stays. In summary, hAM is recommended for treating partial-thickness burn wounds. To ensure its effective use, incorporating relevant training hours into medical education and continuous professional development is advisable.

#### Abbreviations

hAM human amniotic membrane
SSDZ conventional silver sulfadiazine

| | |
|---|---|
| HTLV | Human T-lymphotropic virus |
| CMV | Cytomegalovirus |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |

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**Author contributions**
M.S. and M.HM. designed the study. M.A. and M.T. collected data. K.K. analyzed data. M.A. and A.S. wrote the manuscript. All authors revise the manuscript. All authors read and approved the final version of the manuscript.

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**Data availability**
All data are available in the article.

## Declarations

**Ethical approval and consent to participate**
The current trial was conducted in accordance with the Declaration of Helsinki, was approved by the ethical approval committee of Zanjan University of Medical Sciences, Zanjan, Iran, and is registered with the code IR.ZUMS.REC.1395.226. It has also been registered on the clinical trial website www.irct.ir with the registration number IRCT2015110824947N1 on 6/02/2017. Patients were informed about the advantages and disadvantages of the study before signing the confidential written consent letter to enroll in the study. Written informed consent was obtained from all participants to participate in the study. The participants took part in the study voluntarily. The participants experienced no financial burden, as they had full insurance coverage. The participants were assured that all tissue-transmissible diseases, such as viral infections (including HTLV, CMV, HBV, HCV, and HIV), bacterial and fungal infections, and allergic reactions, were screened by the manufacturer of the hAM. The researchers were guaranteed the ability to support and treat participants free of charge if any potential side effects caused by SSDZ or hAM occurred. The involved hospital and ward were informed of the results of the study. The data used in this study were anonymized before use.

**Consent for publication**
Not applicable.

**Conflicts of interest**
The authors declare no conflicts of interest.

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## Publisher's note