Amniotic Membrane Dressing versus Nitrofurazone-Impregnated Dressing in the Treatment of Second-Degree Burn Wounds: A Randomized Clinical Trial

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ABSTRACT

Introduction. Both the amniotic membrane biologic dressing and nitrofurazone-impregnated dressing are treatment options for burn wounds. **Objective.** To compare the efficacy of these treatments in healing second-degree burns, a randomized clinical trial was conducted among patients with second-degree burns who had no comorbidities or history of addiction and were referred to a burn center in Urmia, Iran, between December 2017 and September 2019. **Materials and Methods.** Patients were randomly assigned to one of 2 study groups. Wounds were dressed in either amniotic membrane covered with moistened gauze/petrolatum or nitrofurazone-impregnated gauze. Comparative groups were matched according to percentage of burn (total body surface area). The dressing application occurred once daily in the nitrofurazone group and once weekly in the amniotic membrane group. The study was conducted until all wounds healed. The study outcomes included the infection rate of the wound, pain severity related to dressing changes, dressing change frequency, epithelialization rate, hospitalization length of stay, morphine use, and scarring. Data were collected in real time by the researcher via observation, interview, examination of the patient, and, eventually, completion of a checklist. Analyzed quantitative and qualitative variables were reported as mean ± standard deviation and percentage (frequency). **Results.** Each group included 35 participants (24 men, 11 women; age, 20.05 ± 3.60 years in the amniotic dressing group; and 20 men, 15 women; age, 21.60 ± 2.02 years in the nitrofurazone-impregnated gauze group). Assessment was performed on days 1, 7, 14, and 30 from the initial treatment and at discharge. No significant difference was noted in the rate of infection between the 2 groups. Epithelialization was complete (100%) by day 7 in the amniotic membrane group, versus 77% in the nitrofurazone group. Pain following dressing application, length of hospitalization, morphine use, and scarring at day 14 were significantly lower ($P < .05$) in the amniotic membrane group. **Conclusions.** This study indicated that the use of amniotic membrane dressing improved factors key to healing in second-degree burn wounds compared with nitrofurazone-impregnated dressing. Further research with a larger sample is warranted.

KEY WORDS

amniotic membrane dressing, nitrofurazone ointment, second-degree burn, burn wound repair, burns

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Burns are common causes of trauma in economically developing countries, accounting for substantial health care costs.[1] The mortality rates due to fire and burns have declined in the last few decades for several reasons, one of which is decreased wound infections because of improved wound dressings and antibiotic administration.[2,3] Globally, advanced burn treatment centers apply biological dressings at the beginning of burn management, which has decreased the mortality rate from 30% to 8%; however, this method is not frequently used in economically developing countries.[3]

Dressings

In general, a burn dressing should protect damaged epithelium, reduce bacterial and fungal colonization rates, and provide a layer of protection to reinforce the integrity of the dressing. In addition, a dressing should cover the wound to prevent heat from dissipating, reduce cold stress, and provide patient comfort.[4] When dressing burns, the degree of the burn needs to be considered. First-degree burn wounds have minimal tissue damage and should not require a dressing, and second-degree burns can be treated using dressings that incorporate local antibiotics, gauzes, and elastic bands, changed daily.[5,6] An ideal burn dressing should be tailored to the patient, including cost and comfort level; daily dressing

replacement contributes to the debridement of necrotic tissues and isolated scars in addition to cleaning the dressing.[7]

Topical treatment

Nitrofurazone. Several topical treatments are available for burn wounds. Nitrofurazone, previously approved by the FDA (now discontinued), as a water-soluble ointment for the treatment of burn wounds is used in various dressings; it inhibits the enzymes involved in carbohydrate metabolism and works as bactericidal agent, penetrating into burns eschars.[8] However, it is not without side effects, including hypersensitivity, itching, dermatitis, and delayed wound healing.[9]

Amniotic membrane. In patients with first-degree and second-degree burns, where a wide total body surface area (TBSA) is burned and therefore there is limited skin to graft from, the amniotic membrane may be an effective alternative wound covering. The rate of skin graft rejection has been shown to be much lower when using amniotic dressings compared with other materials, such as xenografts, homografts, and allografts.[10] Human amniotic membrane constitutes the innermost embryonic layer. It comprises epithelial cells, a basement membrane, and a vascular stromal matrix.[11] Human amniotic membrane was first used in skin grafts to cover wounds in 1910; in 1974, this method was used to treat third-degree burns with good results.[12,13] Since then, amniotic membrane has been commonly used to treat up to second-degree burn wounds.[14,15] Clinical trials have shown dressing a burn with amniotic membrane can alleviate pain and decrease bacterial infections.[16,17] Studies also have shown the use of amniotic membrane contributes to the prevention of severe fluid loss and electrolyte disorders, helping prepare the wound bed to accept skin grafts.[19]

A majority of studies have been concerned with burns of a higher degree (more severe), but few investigations have been performed on the role of amniotic membrane use in second-degree burns. Biological dressings may offer key therapeutic options. In a systematic review by Witt et al,[20] an amniotic membrane dressing used on acute and chronic burns was found to be effective due to the presence of antibacterial agents and human growth factors in the amniotic membrane. Thompson et al[18] showed amniotic membrane causes rapid epithelialization of the burn without any risk of metalloproteinase accumulation, improving the outcome and quality of life of patients with partial-thickness and full-thickness burns.

To enhance the research on biological dressing use in second-degree burns, the authors designed a randomized clinical trial (RCT) to compare an amniotic membrane dressing covered with a wet gauze dressing and petrolatum with a nitrofurazone-impregnated gauze dressing in the treatment of second-degree burns.

MATERIALS AND METHODS

Study design

This research was conducted as a single-center RCT at the Trauma and Burn Center of Imam Khomeini Hospital in Urmia, Iran. The study was conducted with the approval of the Institutional Review Board in accordance with the Declaration of Helsinki as well as the Ethics Committee of the university with ethics code IR UMSU.REC.139.245, which was registered according to the Registry of Clinical Trials in the Iranian Registry of Clinical Trials with the Registration number IRCT20181216041996N1.

Nitrofurazone 0.2% as a water-soluble ointment was selected as the comparator to amniotic membrane because it is the most commonly used product available in the authors' pharmaceutical market. An amniotic membrane (ITP Amniotic Membrane; Iranian Tissue Product Co.) in sterilized packaging was used to prevent transmission of infection.

Inclusion and exclusion criteria

Inclusion criteria stipulated study participants must have had a second-degree burn (TBSA < 10%) and could be of any age. Patients were eligible for inclusion if they were referred during hospitalization and did not require debridement in an operating room. Patients were excluded if they had any chronic conditions or comorbidities or if they had a history of smoking, drug, or psychotropic substance misuse or addiction. Burns on the face and/or genitalia and infected burns upon referral were excluded. Importantly, those with previous reaction and hypersensitivity to nitrofurazone ointment and/or to amniotic membrane dressings were not eligible for inclusion.

Randomization

For randomization, the sequences were assigned by an independent researcher using Random Allocation Software version 1.0 (Informer Technologies, Inc) in permuted blocks of 2 or 4. Of the patients meeting the accepted inclusion criteria, 2 patients declined to participate and 1 patient was discharged. The remaining patients hospitalized in the burn ward due to second-degree burns provided written consent and were enrolled. At the time of randomization, a nurse who was not involved in the study process or care of patients opened a numbered envelope containing patient allocation sheets and the patient was assigned to one of the 2 study groups.

Sample size

Calculation of the number of samples was based on a previous study[21] and the variable of epithelialization rate of second-degree burn.

Statistical parameters for calculation of sample size were $\alpha = 0.05$, $\beta = 0.2$, $Z_1 = 1.961150826$, $Z_2 = 0.841623031$, $\mu_1 = 14.2$, $\mu_2 = 13.3$, $SD_1 = 0.96$, $SD_2 = 0.95$, and $n = 18$.

The authors' calculations yielded an estimate of at least 18 subjects per group.

FORMULA

$$n = \frac{\left(z_1 - \frac{\alpha}{2} + z_1 - \beta\right)^2 (\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)^2}$$

In order to prevent attrition in the sample, at the beginning of the study a sample size of 35 subjects was selected as the total final sample size for each group.

Care protocol

The second-degree burns were dressed either using the amniotic membrane or nitrofurazone-impregnated gauze, which were matched based on TBSA and wound depth. In the first group, the amniotic membrane products, which were purchased by the authors' hospital, were applied and covered with 2 separate layers of gauze. The first layer was petroleum-impregnated gauze, and the second layer was wet gauze moistened by saline. Participants in the nitrofurazone-impregnated gauze group were provided 20 g of the ointment per TBSA under the gauze, which was covered by a layer of dry gauze. In the nitrofurazone group, dressing changes occurred once daily and in the amniotic membrane group dressing changes occurred once a week. For pain management, morphine sulfate was the only medication used in the study groups.

Data collection

Demographic (sex, age, clinical pain severity assessed using a visual analog scale [VAS], dressing change frequency, epithelialization rate, length of hospitalization, morphine intake, and scarring) information was assessed using the Vancouver Scar Scale [VSS] and were collected with a pen and paper checklist for all patients, where questions were range based. While in the hospital, assessment was performed on days 1, 7, 14, and 30 and continued after discharge from the hospital. Post-discharge, the variables were assessed during patient visits in the outpatient burn clinic on days 7, 14, and 30.

Study data were collected by the researcher via observation, interview, examination of the patient, and completion of the checklist and were documented into medical charts by the same researcher. Pain severity was documented on a numeric pain distress scale; individual charts on which the patients could mark their level of pain were used. The rate of wound healing (epithelialization) was evaluated by observation. Scarring was evaluated using the VSS; this tool comprises 4 subscales: pigmentation, 0–2; vascularity, 0–3; pliability, 0–5; and height, 0–3. Subscale scores then were summed for a total score of 0 to 13. Visual and direct examination also were employed. During dressing changes, data collection was done by the researcher based on observation and scales using the checklist.

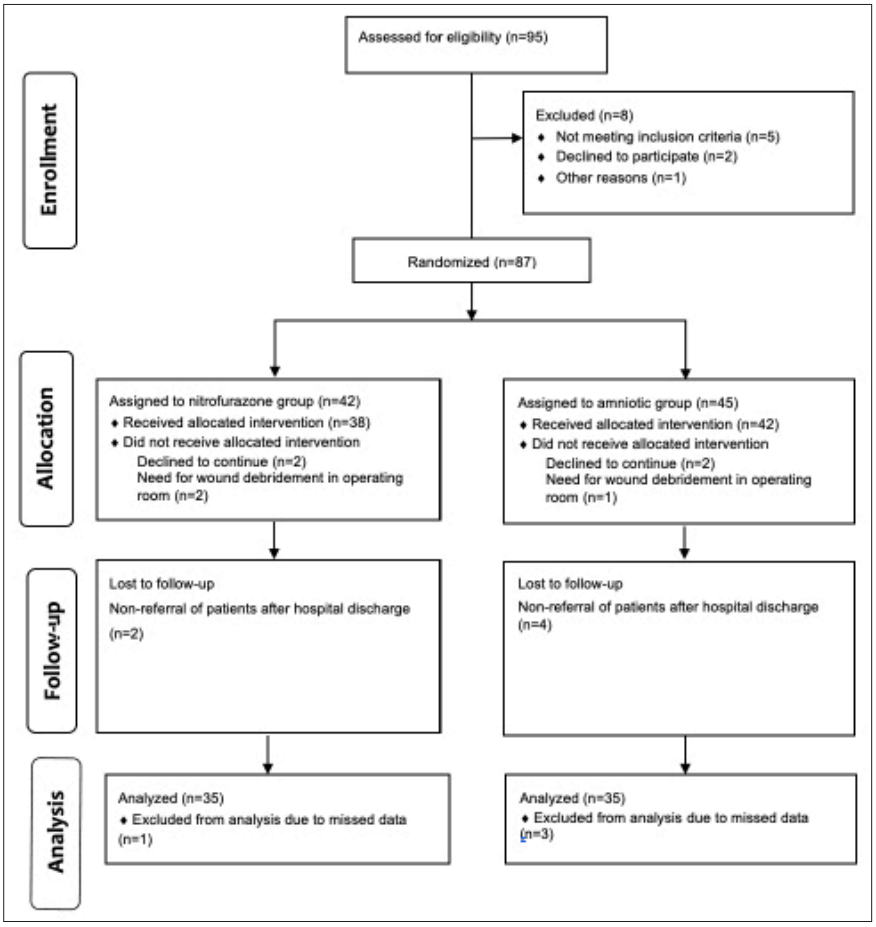

Figure. Consolidated standards of reporting trials flow diagram.

Statistical analysis

The collected data were analyzed by a statistics expert using SPSS software, version 17 (IBM Corporation). Quantitative and qualitative variables were reported as mean ± standard deviation and percentage (frequency) in the form of statistically standard tables, respectively. To analyze the quantitative variables between the 2 groups, an independent *t*-test (and if necessary, Mann-Whitney) was used; chi-squared tests were employed to compare the frequency. Wherever chi-square conditions were not met, the authors used its alternative, the Fisher exact test; $P < .05$ was considered significant.

RESULTS

Out of 95 patients assessed for eligibility, 8 were excluded (5 for not meeting inclusion criteria, 2 declined, 1 for other reasons); thus, 87 were randomized (45 in the amniotic membrane dressing group and 42 in the nitrofurazone ointment-impregnated gauze group). Of these, 2 in each group declined to continue. One patient in the amniotic membrane group and 2 in the nitrofurazone group needed surgical debridement and were excluded, 4 in the amniotic group and 2 in the nitrofurazone group were lost to follow-up, and 3 in the amniotic

Table 1. Demographic data of patients in the study groups

VARIABLE	AMNIOTIC MEMBRANE GROUP (n=35)	NITROFURAZONE GROUP (n=35)	*P* VALUE
Male	24 (68.6%)	20 (57.1%)	.32
Female	11 (31.4%)	15 (42.9%)	
Age (yrs)	20.05±3.60	21.60±2.02	.71
TBSA percentage of burn	12.72%±8.99%	12.61%±9.44%	.95

yrs: years; TBSA: total body surface area

Table 2. Clinical outcome measures[a]

VARIABLE		AMNIOTIC MEMBRANE GROUP (n=35)	NITROFURAZONE GROUP (n=35)	*P* VALUE
Pain severity with VAS criterion[b]	Day 1	3.02±0.70	3.28±0.12	.27
	Day 2	2.11±0.19	2.65±0.12	.02
Number of dressing changes		1	7	.001
Epithelialization[c]	Day 7	35 (100%)	27 (77.1%)	.002
Hospitalization days		2.94±1.18	4.14±2.04	.004
Morphine intake (mg)		3.75±1.54	4.81±0.60	.04
Scarring score with VSS criterion	Day 14	2.02±0.96	3.28±0.85	.001
	Day 30	0.73±0.82	0.88±0.67	.39

[a] The amniotic membrane group had 1 dressing change whereas the nitrofurazone group had 7 dressing changes; *P*=.001.

[b] The pain severity was only assessed on the first 2 days.

[c] Epithelialization was based on observation.

VAS: visual analog scale (range, 1–10); VSS: Vancouver Scar Scale (range, 0–13)

membrane group and 1 in the nitrofurazone group were missing data. Ultimately, data for 70 patients (35 in each group) were assessed for the study (**Figure**).

No significant difference was noted between groups regarding average burn TBSA involved (the TBSA of the amniotic membrane and nitrofurazone ointment groups were 12.72% ± 8.99% and 12.61% ± 9.44%, respectively; *P* = .95). Differences in demographic characteristics, including age (range, 15–50 years) and sex, were also not significant (**Table 1**).

Using VSS, the epithelialization rate of burn wounds on day 7 after beginning treatment was 100% and 77.1% in amniotic membrane and nitrofurazone groups, respectively, reflecting a statistically significant difference (*P* = .002). At day 14, the epithelialization rate was 100% in both groups.

No adverse events were noted. Wound cultures were taken based on clinician assessment. There was no clinical or laboratory evidence of infection in either of the 2 groups.

On day 1, pain severity reported using VAS was 3.02 ± 0.70 and 3.33 ± 1.29 in the amniotic membrane and nitrofurazone groups, respectively (*P* = .27). On day 2, pain severity was 2.11 ± 0.19 and 2.65 ± 1.2 in the amniotic membrane and nitrofurazone groups, respectively, indicating a significant difference between the 2 groups (*P* = .02). There were no reports of pain on assessment days 7, 14, and 30, and as such, no data were available for collection after day 7.

The dressing was changed once a week in the amniotic membrane group based on scientific literature. In the nitrofurazone group, it was changed 7 times daily, on average.

Mean length of hospitalization was 2.94 ± 1.18 days vs 4.14 ± 2.04 days in the amniotic membrane and nitrofurazone dressing groups, respectively (*P* = .004) (**Table 2**). Morphine administration level was 3.75 mg ± 1.45 mg and 4.81 mg ± 0.60 mg in the amniotic membrane and nitrofurazone groups, respectively (*P* = .04).

At day 7, epithelialization rates were significantly different between the amniotic and nitrofurazone groups (35 [100%] vs 27 [77.1%]; *P* = .002).

On day 14, the mean scarring score was significantly lower in the amniotic membrane group than in the nitrofurazone group (2.02 ± 0.96 vs 3.28 ± 0.85; *P* = .001) (**Table 2**). On day 30, the mean scarring score in the amniotic membrane group was lower than that of the nitrofurazone group (0.73 ± 0.82 vs 0.88 ± 0.67), but the difference not significant (*P* = .39).

DISCUSSION

The appropriate dressing should be selected based on its effect on healing, ease of application and removal, frequency of dressing changes, and patient comfort. According to various studies, including an RCT,[21-23] the use of biosynthetic dressing (ie, amniotic membrane) can accelerate healing and reduce pain during dressing changes. Tehrani et al[22] showed that an amniotic membrane dressing has antibacterial effects on mesenchymal and epithelial surfaces. A case study by Muhammadi et al[23] described a patient who received skin grafts to previously existing burns in both limbs. After grafting the skin, the authors covered one limb with amniotic membrane and used a conventional dressing (gauze moistened by saline) on the other. A significant difference was observed in skin graft take; the amniotic membrane was found to be

a more effective dressing for management of chronic burn injuries, owing to its antimicrobial effects.[23] These findings are consistent with the current results regarding the extent of wound healing (epithelialization) and the absence of infection at the site of wound.

Muhammadi et al[24] reported a median healing time of 6 days for limb repair managed using amniotic membrane among 50 patients. Pain severity was found to be significantly lower in the amniotic membrane group. In addition, amniotic membrane required only 1 dressing change; the amniotic membrane remained on the site of the second-degree burn wound in all cases to complete the wound healing process. These findings are consistent with the results of the current study in that pain intensity, frequency of dressing change, and VSS on day 14 was lower in patients with amniotic membrane dressing, the latter indicating wound healing over a shorter period.

Mostaque et al[21] compared silver sulfadiazine with amniotic membrane; the main difference was one amniotic membrane dressing was used vs repeated dressings and long-term washing of wounds in the silver sulfadiazine group. These findings are consistent with the results of the current study as it relates to the significant difference between the 2 groups in dressing change frequency ($P = .001$). The lower frequency of dressing changes and subsequently less manipulation of the healing wound reduces both the pain and dressing change-related anxiety of the patient, resulting in better patient tolerance and more adherence.[21]

In addition, results of the current study were similar to Mostaque et al[21] with regard to the duration of epithelialization, which was lower in patients treated with the amniotic membrane dressing. The difference in the epithelialization period can be a function of biological and pharmacological properties of the amniotic membrane, which reduces leakage from the wound site, helps decrease wound debris, and creates a barrier against microbe penetration. Also similar to Mostaque et al,[21] the number of days spent in hospital in the current study was less in the amniotic dressing group than in the control group.

Due to cultural beliefs that impede use of xenograft and allograft biologic dressings in Islamic countries, Adly et al[16] conducted a study that examined amniotic membrane dressings (N = 46); the amniotic membrane dressing was more effective and more acceptable than polyurethane membrane in terms of patient pain severity. Likewise, in the current study, pain intensity was reported to be significantly lower in the amniotic dressing group than in the nitrofurazone group ($P = .02$), accounting for the lower consumption of opioid and analgesic drugs in the amniotic group compared with the nitrofurazone group. These findings also were in agreement with results of a clinical trial conducted by Hosseini et al[25] that compared biological with conventional dressings. The lower severity of pain reported in the amniotic membrane dressing group could be attributed to the effect of different cytokines in the amniotic membrane (such as transforming growth factor-β) as well as decreased frequency of dressing changes, which would lessen pain and lead to higher satisfaction rates in patients using amniotic membrane dressings.[26]

Witt et al[20] found amniotic membrane dressing use resulted in rapid epithelialization of the burn without the risk of metalloprotein accumulation in both acute and chronic wounds. In their retrospective study (N=370), Ullah et al[27] found that amniotic membrane dressing use decreased the infection rate by suppressing bacteria, reduced plasma oozing from the wound, and created adhesion that developed a dry environment in the wound that lead to reduced infection rate and dressing change frequency as well as shorter duration of hospitalization. These results are consistent with the findings of the current study in terms of fewer hospital days and decreased scarring and pain in comparison with nitrofurazone.

LIMITATIONS

The main cause of sample dropouts was patients declining to continue the study. Based on previous studies, the sample size to achieve results was calculated to be 18; given the probability of dropout and to eliminate its impact on the results, the authors studied 35 patients in each group. Random error in the results can occur as a result of unwanted dropouts in a sample. Given that the authors only investigated second-degree burns, the present results can only be generalized to this specific population and cannot include other degrees of burns.

CONCLUSIONS

Results of an RCT comparing factors influencing the benefits of using amniotic membrane compared with nitrofurazone dressing in second-degree burn wounds indicated fewer dressing changes, fewer days in hospital, better epithelialization on day 7 of treatment, decreased morphine intake, and less pain severity in patients receiving amniotic membrane treatment. Improved healing and reduced pain suggest an amniotic membrane dressing is a viable choice for second-degree burn wound care. Future research in larger cohorts is warranted.

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