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Original Article

The effectiveness of skin allografts in survival rate of patients with major burns

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Abstract: Background: Burns are still one of the most prevalent injuries in the world. Allograft is in high demand as a biological dressing for any superficial open wounds, not just burn victims. Skin allograft is the gold standard for treating burns in people who do not have enough skin to cover all of the injured areas of their bodies. Studies have shown that skin allografts are superior to topical antimicrobial dressings in partial thickness burns and can reduce complications and length of hospital stay in burn patients. However, to the best of our knowledge very few studies have investigated these results in our country. The aim of the current study is to evaluate and report the outcomes of skin allograft on burn patient survival in Iran. Method: This prospective clinical trial study was performed on patients admitted to the burn center of Imam Khomeini Hospital in Tehran between July 15, 2017 and April 27, 2021. The control group consisted of patients admitted to the burn ward who were not undergoing skin allografts. This group was matched with the case group in terms of sex, age, and percentage of burns. We compared the outcome of the study was the duration of hospitalization, and status of patients at discharge. The study protocol was approved by Iranian Registry of Clinical Trials (IRCT) under the code of IRCT2016112431074N1 (https://fa.irct.ir/trial/24517). Result: Overall, 112 patients in the case group and 224 patients in the control group were studied. The length of hospital stay in the case group (41.13±11.7) was considerably longer than the control group (24.6±12.1) (P<0.001), but the mortality rate in the two groups was not statistically different (P=0.633). The average survival time of case group (53 days, 95% CI=45-56) was higher than the control group (49 days, 95% CI=39-58) (P=0.012). Number of allograft usage (OR=0.038, 95% CI=0.142-0.945) and also Age (OR=1.03, 95% CI=1.005-1.070) were predictors of death. Conclusion: Although the use of skin allografts in large burns (more than 50%) reduced mortality in burn patients, their use in burns less than 50% has not been effective in reducing patient mortality. Due to the limited access to this valuable product, its use in burns less than 50% should be done with caution and, due to the limited access to skin allografts in most burn centers in Iran, patients with extensive burns (more than 50%) should be used as a priority.

Keywords: Burn, allograft, survival

Introduction

Burns are still one of the most prevalent injuries in the world, with over one million patients treated each year in the United States alone [1]. The worldwide incidence of wildfires in 2004 was estimated at 1.1 per 100,000 population, with the highest rates in Southeast Asia and the lowest in the United States. The incidence of burns in low- and middle-income countries is 1.3 per 100,000 people, compared to 0.14 per 100,000 people in high-income countries [2]. A burn ensues when radiation, heat, chemicals, or electricity harm the skin. Severe complications from widespread or deep burns can occur, including sepsis owing to bacterial infection, hypovolemic shock, and scarring tissue contraction as a result of incorrect wound healing [3, 4]. Skin damage results in a massive loss of body fluids, causing the death of skin cells, followed by dehydration, electrolyte imbalance, and kidney and circulation disorders [5].

Advances in burn care have improved quality of life and decreased mortality rates. The mortality rate of burn injuries can be reduced by early debridement and skin grafting, although skin

autografting is difficult due to a lack of donor sites and the patient's inappropriate general condition for surgery. Allograft is in high demand as a biological dressing for any superficial open wounds, not just burn victims. Although the history of autograft skin grafting dates back to about 3000 BC in India, the widespread use of this method became common in the second half of the 19th century [6]. The history of using skin allograft is approximately equal to or slightly less than the skin autograft [7]. But until years later, skin allografts were used freshly, and since it was not possible to store skin allograft due to the difficulty of maintaining tissue viability, the rate of use of this method was directly dependent on the donor availability [8-10]. Skin allograft is the gold standard for treating burns in people who do not have enough skin to cover all of the injured areas of their bodies. However, severe burn patients do not have enough skin donor sites to resurface their burn wounds, necessitating the use of skin substitutes [11, 12]. Also, it is considered temporary covering, and several studies have shown that if allograft is not replaced by autograft, graft rejection would occur within two weeks. Partial-thickness burns have traditionally been treated with topical antimicrobial agents during twice daily dressing changes until the scar separated, which increases the risk of wound infection by leaving the wound open for long periods of time and exposes patients to the pain of dressing changes and daily cleaning [13-15]. In contrast, studies have shown that skin allografts are superior to topical antimicrobial dressings in partial thickness burns and can reduce complications and length of hospital stay in burn patients [13, 14, 16-18].

Epidemiologic data has indicated a vast range of success rates in different populations. So far, various studies have evaluated the impact of skin allograft on burn patient survival in different populations but to the best of our knowledge very few studies have investigated these results in our country. The aim of the current study is to evaluate and report the outcomes of skin allograft on burn patient survival in Iran.

Methods and material

Study design

This prospective clinical trial was performed on patients admitted to the burn center of Imam Khomeini Hospital in Tehran. Data on burn patients who underwent skin allografts was extracted from the hospital information system between July 15, 2017 and April 27, 2021. The study protocol was approved by Research committee of Tehran University of Medical Sciences and the Ethics committee has confirmed it (Ethics code: IR.TUMS.MEDICINE.REC.1392.207). Written informed consent was obtained from all patients to participate in the study.

Inclusion and exclusion criteria

The inclusion criteria were all patients admitted to the burn center of Imam Khomeini Hospital from July 2017 to April 2021, and signing the written informed consent to participate in this study. A known immunocompromised status, a poor prognosis, known sensitivity or allergy to any of the therapy substances, and known problems in wound healing were all exclusion criteria. Electrical burns, chemical lesions, frostbite, and/or ear burns were also excluded.

Study population

In total, in the mentioned time, allograft surgery was performed 219 times on 112 patients. The control group also consisted of patients admitted to the burn ward who were not undergoing skin allografts. This group was matched with the case group in terms of sex, age, and percentage of burns.

Measurements

The outcome of the study was the duration of hospitalization and the status of patients at discharge (alive, deceased). To increase the study power per case, two patients were selected as the control group. Except for the use of allografts, other therapeutic measures such as initial resuscitation, nutrition, wound care, and indications for the use of the burn intensive care unit were performed similarly in the two groups.

Statistical analysis

SPSS statistical software (version 25, IBM Corporation, Armonk, NY) was used to analyze the results. Log-rank and Kaplan-Meier tests were used to compare survival in the two groups and Cox regression to find death predictors. In all tests, values of $P<0.05$ were considered as a significant level.

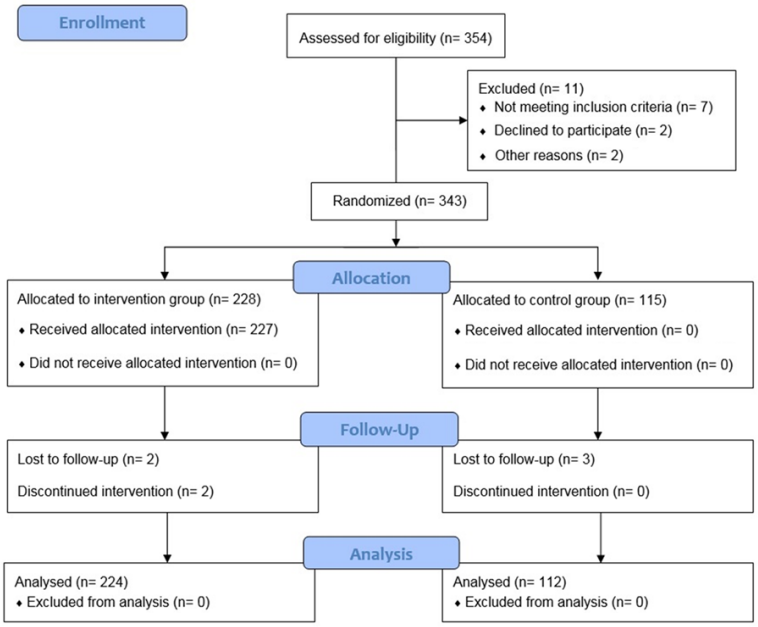

Figure 1. The CONSORT flow chart of the study.

Table 1. Comparison of demographic data among patients

Variable		Case (N=112)	Control (N=224)	*P*-value
Age (year) (mean ± SD)		25.31±14.77	26.18±13.91	0.72
Gender (n (%))	Male	63 (56.2%)	130 (58.1%)	0.61
	Female	49 (43.8%)	94 (41.9%)	
Burn percentage		51.29±15.11	52.74±13.29	0.42

Result

Study population

In the present study, we assessed 354 patients for eligibility. Eleven patients were excluded due to not meeting the inclusion criteria (N=7), not signing the written informed consent (N=2) and other reasons (N=2). Then 343 patients were randomized into intervention (N=228) and control (N=115) groups. Five cases were excluded during the study. Finally, data of 336 cases were analyzed. The CONSORT flow chart of the study is shown in **Figure 1**.

Population characteristics

One hundred and twelve patients in the case group and 224 patients in the control group were studied. Matching for sex, age (5-year interval), and burn percentage (10% interval) was performed correctly so that these variables were not significantly different between the two groups (**Table 1**).

Allograft outcomes

The Baux score is one of the predictors of mortality in burn patients, which is defined as the sum of the percent body burn and age in years, and was consistent in both groups and was 77 in the case group and 78 in the control group, respectively. The maximum number of allografts in the case group was five and the minimum was one. In 79% of cases (88 patients) fresh allografts and in other cases glycerol was used. Thirty-four percent (38 cases) of the case group and 37% (82 cases) of the control group had died before discharge.

Mortality of patients

Although the mortality rate was higher in the control group, this difference was not statistically significant (P=0.633). However, the number of hospitalization days in the case group (41.13±11.7) was significantly higher than the control group (24.6±12.1) (P<0.001). By excluding deceased patients from the analysis, the number of hospitalization days in the case group (43.3±11.5) was still significantly higher than the control group (22.4±11.2) (P<0.001). We divided patients into two groups of burns over 50% and burns below 50% based on the percentage of body surface burns (TBSA). Then it was found that the two groups were not significantly different in this regard (P=0.61). Overall, 39% of the case group (44 patients) and 39% of the control group (88 patients) had burns over 50% of total body surface area (TBSA). Also, while most of the patients who died in the control group (61%) had more than 50% burns, only 31% of the patients who died in the case group had more than 50% burns (P<0.001).

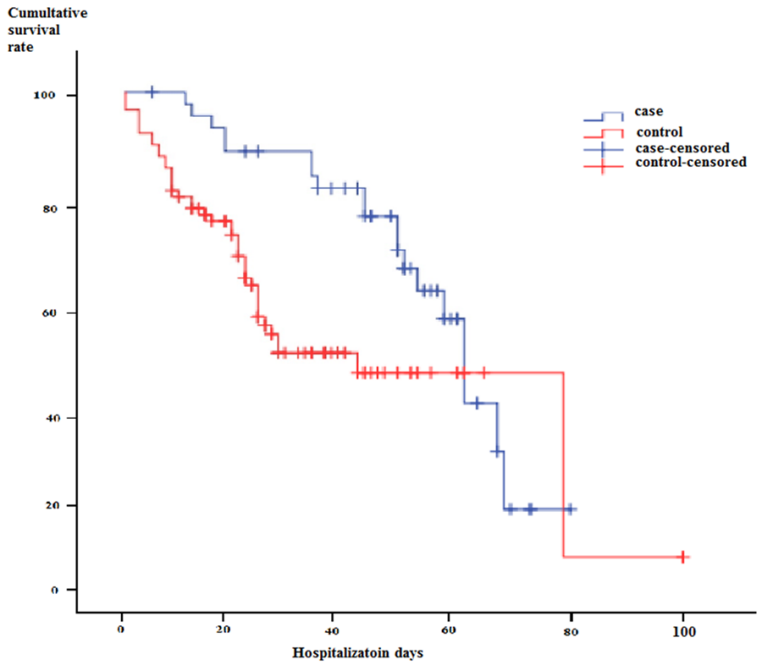

Figure 2. Comparison of survival rate in both groups.

Table 2. Evaluation of odds ratio for different factors

Variable	Odds ratio	CI 95%	*P*-value
Age	1.03	1-1.07	0.022
Gender	0.55	1.1-18.62	0.281
Burn percentage	1.02	0.1-98.05	0.232
Type of allograft	0.60	0.1-19.85	0.379
Time of allografts	0.36	0.0-14.94	0.038

Further assessments

Survival analysis showed that the average survival time in the case group (53 days, 95% CI=45-56) was higher than in the control group (49 days, 95% CI=39-58) (P=0.012). The results are shown in **Figure 2**.

However, because the left end of the survival curve is plotted against a small number of patients, the curve should be interpreted with caution. The results of Cox regression analysis using all the studied variables are shown in **Table 2**.

As has been shown, age (OR=1.03, 95% CI=1.005-1.070) leads to a slight increase in the chance of death, and conversely, the number of allograft usage (OR=0.038, 95% CI= 0.142-0.945) can be used as a good preventer of death.

Discussion

In the present study, we tried to evaluate and compared the outcomes of skin allograft on burn patient survival based on the length of hospital stay, mortality rate, number of allograft usage, age, and survival time. Although, the length of hospital stay in the case group was higher than the control group, the survival time of the case group was higher than the control group. Despite the limitations of our study, the use of skin allografts in large burns (more than 50%) reduced mortality in burn patients, their use in burns less than 50% has not been effective in reducing patient mortality.

Most studies on the use of allografts have shown the results of using skin allografts in the excision method and early grafting in burn wounds [19-21]. In these studies, the use of allografts with excision method and early grafts was associated with a reduction in mortality and length of hospital stay. However, in a retrospective study conducted by Chua et al. and used the allograft during 11 years in burn patients, the mortality rate was 2% and this figure was not statistically significant [22, 23].

In a study by Choi et al., they evaluated the mortality rate in patients with burns involving greater than 30% TBSA who had used cadaver skin allograft for treatment. In this study, 698 patients received cadaver skin allografts (cadaver group), while 584 received conventional treatment (non-cadaver group). They found that patients with major burns who underwent cadaver skin allograft had a lower mortality rate during 90-day hospital stays compared to those who received conventional treatment. In this study, they concluded that cadaver skin allograft may enhance the survival of patients with severe burns, particularly in the early stages of the injury [24, 25]. In another study that used cadaveric skin allografts to manage extensive burn wounds, they found that they reduced electrolytes, water, and protein loss, improved thermoregulation, and re-

duced pain and risk of wound infection. In addition, they improve the subsequent absorption of the autograft by stimulating epithelialization and preparing the wound bed. Furthermore, immediate excision of massive burns and temporary skin allograft covering reduce mortality and hospital stay length [26-28]. However, Sheckter et al. evaluated the effect of using allografts in patients with 20 to 50% total body surface burns. They found that allograft treatment increased inpatient mortality by an average of 2.8%. Secondary outcomes showed that allograft average treatment effects were significantly higher: the composite complication index increased by 0.13, total burn operations increased by 1.6, length of hospital stay increased by 8.4 days, and total charges increased by $139,476 [28, 29].

In another study on the use of glycerol-preserved skin allograft (GPA) in severe burns, the mortality rate was reported to be 40%, which is higher than the mortality rate in patients in the present study (34%) [30]. However, the percentage of burns in the patients of the study was 53% and in the present study was 50%. Also, the age of patients in the study was higher than in the present study and in general, the Baux index of the study was higher than the present study (105 versus 77). In our study, the mortality rate decreased by less than 3%, which is not statistically significant. However, in the study of patients according to the extent of burns, it is found that the mortality rate of patients with burns greater than 50% TBSA, in the case group is significantly lower than the control group (27.27 in the case group and 56.82 in control group). It seems that the control group is not uniform with respect to the severity, TBSA, and depth of the burn. That could be the reason for the observation of contradictory results in burns less than 50%. This finding is consistent with another study performed on patients with burns greater than or equal to 70% TBSA that showed a 24% reduction in mortality [31]. In fact, the indication for using allografts in patients with burns greater than 50% TBSA is different from that in patients with burns less than 50% TBSA in our center. While patients with burns greater than 50% TBSA are candidates for skin allografts due to limited donor sites, patients with burns less than 50% have either been candidates for emergency excision and use of allograft skin due to sepsis, or due to inhalation injury or pneumonia could not tolerate autograft and the wounds have been temporarily covered with allograft after excision. In this study, except for age and percentage of burns (Baux index), which were matched in two groups (77 in the case group and 78 in the control group), other burn prognosis indices were not evaluated, and it was not possible to compare the accompanying problems of patients who were candidates for allografts (such as sepsis, pneumonia, and respiratory injury) with the control group due to the retrospective study.

In this study, the length of hospital stay of patients in the group that received allografts was longer than the control group, while in most studies that use allografts in the excision and early graft method, the length of hospital stay was reduced [10, 20, 22]. One reason for this difference may be that we have severe allograft limitations and, except for the last 6 months of the study, the use of allografts has been limited to fresh skin allografts. For this reason, in fact, patients in need of allografts have remained on the waiting list to receive allografts, and their length of stay in the hospital has been increased. The need for a skin allograft at a burn center is estimated to be about one square centimeter per square centimeter of burn [32]. Given that approximately 700 new burn patients are admitted to this center each year, with an average of approximately 30% burns, and that each percentage of the adult body surface is equal to 170 square centimeters, we required more skin allografts during the study period than 20 million square centimeters. The total skin allograft at the disposal of this center as a leading center in providing skin allograft in Iran has been less than 200,000 square centimeters, which is less than 1% of their needs. On the other hand, while we use this product only in third- and even fourth-degree burns due to limited access to skin allografts, the depth of burns in our control group was not known, while the duration of hospitalization was affected by the depth of burns.

The present study shows that the more frequent use of allografts has increased the chance of patient survival. The maximum frequency of allograft use in patients in this study was five times and most patients in the case

group had only one chance to use allograft. However, in a similar study in which the average percentage of burn patients (53.8%) was close to the present study, the average use of allografts was 12.75 times per patient [33]. This finding once again demonstrates the importance of timely access to skin allografts in increasing patient survival. As mentioned, one of the limitations of the present study was the impossibility of matching patients in terms of burn depth (due to the lack of information). However, generally, only second- and third-degree burns require hospitalization in the burn ward. However, the use of 5-year data and accurate matching of the main confounding variables such as age, sex, and burn percentage are the most important strengths of this study. It should also be noted that our sample size was calculated by the sample size formula, and we are aware that this can be conflicting. However, we tried to select people from both the case and control groups in a way that was consistent in different ways. Whether it has no effect or has a negative effect can be due to the size of our sample, patient characteristics, underlying diseases, and different types of care. Therefore, we suspect that this part of our results is not very reliable, and therefore more studies are needed, especially for patients with burns of less than 50%. Therefore, we recommend that more studies be conducted on this method for patients with severe burns.

Conclusion

Although the use of skin allografts in large burns (more than 50%) reduced mortality in burn patients, their use in burns with less than 50% has not been effective in reducing patient mortality. Due to the limited access to this valuable product, its use in burns less than 50% should be done with caution and, due to the limited access to skin allografts in most burn centers in Iran, patients with extensive burns (more than 50%) should be used as a priority.

Disclosure of conflict of interest

None.

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