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The effect of propranolol on post-accident stress and clinical outcomes of burn patients: a clinical trial

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Abstract: **Objective:** The hypermetabolic response has undoubtedly evolved to help survive burns, but this physiological response has inconsistent consequences and increases the clinical consequences, such as increased heart work and ultimately its decline, decreased immune system function, risk of sepsis, increased long-term hospitalization, which increases the mortality of patients. This study aims to examine the effect of propranolol on post-traumatic stress disorder and clinical outcomes in burn patients.
Methods: This was an open-labeled randomized clinical trial in a single center with two parallel groups without placebo control. Propranolol was given 48 hours after starting of resuscitation.
Results: In this study, the burn wound of the patients who used propranolol healed faster. In addition, the administration of propranolol reduced the size of the burning surface, the size of the tissue required skin graft, the rejection rate of skin grafts, and also the length of stay in the hospital.
Conclusion: Using propranolol in treating burns can play an influential role in the recovery of burn patients, and reduce the post-traumatic stress disorder.

Keywords: Burn; Post Traumatic Stress Disorder; Propranolol; Skin Graft

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1. Introduction

Burn is one of the significant causes of injury worldwide (1). Burn injuries are caused by the use of heat, chemicals, electric current, or radiation on the external or internal surface of the body, which causes tissue destruction (2). Nearly 300 million patients suffer from burns worldwide every year (3). Burn is the sixth cause of death in Iran (4). Every year, 40,000 people are hospitalized due to severe burn injuries (5). Severe burn injuries affect almost all body organs and lead to significant morbidity and mortality (6).

Severe burns cause an inflammatory reaction followed by a hypermetabolic response that begins immediately after the burn and can persist for years (7). Hyper metabolic reactions have evolved to help survive burns (8), but this physiological response has maladaptive consequences (9).

Acute care for severe burns has five stages. Phase I is the initial assessment and triage, in which the injurious cause is removed and the primary and secondary surveys are conducted. Phase II is focused on fluid resuscitation to address hypovolemia. In phase III, the wound is covered to promote healing and reduce infection risk. Phase IV focuses on supportive or critical care. If the patient survives, phase V of care focuses on rehabilitation, which includes physical and mental health support to enable the patient in returning to regular life (10).

One of medications that may use in these patients are anti-catabolic drugs is adrenergic antagonist (11). One of the β-adrenergic antagonists is propranolol, which inhibits sympathetic stimulation and catecholamine secretion (12). More than 90% of oral propranolol undergoes extensive hepatic metabolism (13). For various reasons, propranolol has been suggested as the most effective anti-catabolic treatment in burn patients (9,11). Findings have shown that the administration of propranolol by inhibiting the increase of catecholamine and, as a result improving the effects of hypermetabolic response leads to improvement of heart and immune system function, reduction risk of sepsis, and hospitalization time (14). By decreasing heart rate and blood pressure, propranolol reduces myocardial oxygen consumption (MVO2) and stress on heart muscles in burn patients. (15). Based on depth, burn wounds are classified as superficial (first degree), partial thickness (second degree), or total thickness (third degree) (16). The degree of burn is determined by the extent of

damage to the skin. In this way, first-degree burns are the most minor, and third-degree burns are the most severe.

One of the most common treatments for deep burns is skin grafting (17). Skin grafting is the transfer of skin tissue from a healthy part of the body to another part with damaged skin. After skin graft surgery, there may be infection, bleeding, nerve damage, loss of sensation, and graft rejection. So, care after surgery plays a significant role in the success of skin grafting (18).

Graft rejection usually occurs within the first few days. The reason for that could be the loss of graft contact with the wound bed due to hematoma, infection, or mechanical damage (19). Skin grafts are suitable for covering the wound because it is an effective method that reduces surgical bleeding and infection, prevent deformation, and accelerate wound healing (20). Propranolol increases the effectiveness of amino acids in wound catabolism (11) and increases the activation of keratinocytes and cell proliferation (12).

Propranolol helps to heal the wound by reducing stress, which has negative physiological effects (increasing the production of vasopressin and glucocorticoids, reducing the inflammatory immune response and cell proliferation) in the wound healing process (21).

Burn injuries can lead to psychological complications (2). Because burn injuries are associated with terrible events that are very stressful and affect the person's ability to deal with them, which causes most burn patients to have post-traumatic stress disorder (PTSD).

Standards and strategy for burn care (2001) recommends that all burn patients be tested for PTSD within the first four days of admission to the burn unit due to psychological distress. To diagnose delayed PTSD cases, a reassessment should occur within four weeks after the burn (22). PTSD usually continues 3 to 6 months after the burn or even years later (23). These statistics indicate the need for PTSD screening, prevention, and treatment policies, specifically for burn patients (22). Propranolol is very effective in reducing post-accident stress as one of burn patients' most common psychological problems (24,25). By reducing attention to negative emotional distress, propranolol moderates stress and emotional arousal and significantly improves cognitive function (24).

According to the limitations of the studies conducted in the field of investigating the effect of propranolol on the clinical outcomes of burn patients, more studies are needed. In this regard, the impact of propranolol on post-accident stress and clinical outcomes in burn patients has been discussed in this research.

2. Methods

2.1. Study design

The present study was a parallel clinical trial with a control group within 48 hours after being admitted to the hospital and after stabilizing the hemodynamic status and fluid therapy. This was an open-labeled randomized clinical trial and the patients randomly assigned into two intervention and control groups. In the intervention group, propranolol treatment was started for patients along with standard burn care treatment. In the control group, patients were treated with standard burn care. The prescription of propranolol by a burn specialist doctor and after consultation with cardiologist advice was set orally with the same dosage of 10 milligrams (mg) twice a day at 6 am and 6 pm which corresponds to the control of vital signs. Daily monitoring of hemodynamic status (heart rate and blood pressure of the left hand using non-invasive cuff measurement) was performed before drug administration in the intervention group and after drug administration in both groups in the wards (14). Therapy with propranolol was continued to discharge time which was about 5 days. The defined clinical criteria of low blood pressure and bradycardia required immediate evaluation and reporting to the physician, in case of systolic blood pressure below 70 mmHg or bradycardia as heart rate HR<60, the administration of propranolol was stopped. Patients used propranolol during hospitalization and it was discontinued after discharge (26). Also, this study is registered with IRCT code: 20190919044819N2 in the Clinical Trial Registration Center of Iran and has the code of ethics: IR.QUMS.REC.1399.195.

2.1.1. Inclusion criteria

Age between 18 and 65 years (13), able to speak (27), having wounds that cover 20% to 50% of the total body surface and second and third-degree burns (28), requiring treatment with at least one transplant operation skin (26), 48 hours after hospitalization in the intervention group, receive propranolol for at least four continuous days (13), satisfaction with participating in data collection (26).

2.1.2. Exclusion criteria

Not having medical conditions that prohibit the use of propranolol (beta-blocker contraindications), pregnancy, bipolar disorder, head injury (24), not suffering from cardiopulmonary diseases, asthma, and inhalation injuries (28), not having a history of malignancy, history of diabetes mellitus (29). Systolic blood pressure less than 90 mmHg, heart rate less than 60 beats/min (28).

2.2. Data collection

Data collection was done by demographic checklist, clinical background information, and post-traumatic stress questionnaire in patients. In this way, on the first day, all questionnaires and demographic checklists were completed by the patients in the presence of the researcher. During the hospitalization period, the researcher collected the clinical background information through clinical examination and using the data from the patient's file. Clinical background information included burn characteristics, laboratory conditions, clinical outcomes, drug side effects, and control of hemodynamic status during propranolol administration. Also, the wound was evaluated in terms of how many days after hospitalization the doctor underwent skin graft surgery, the number of debridement surgeries before skin grafting,

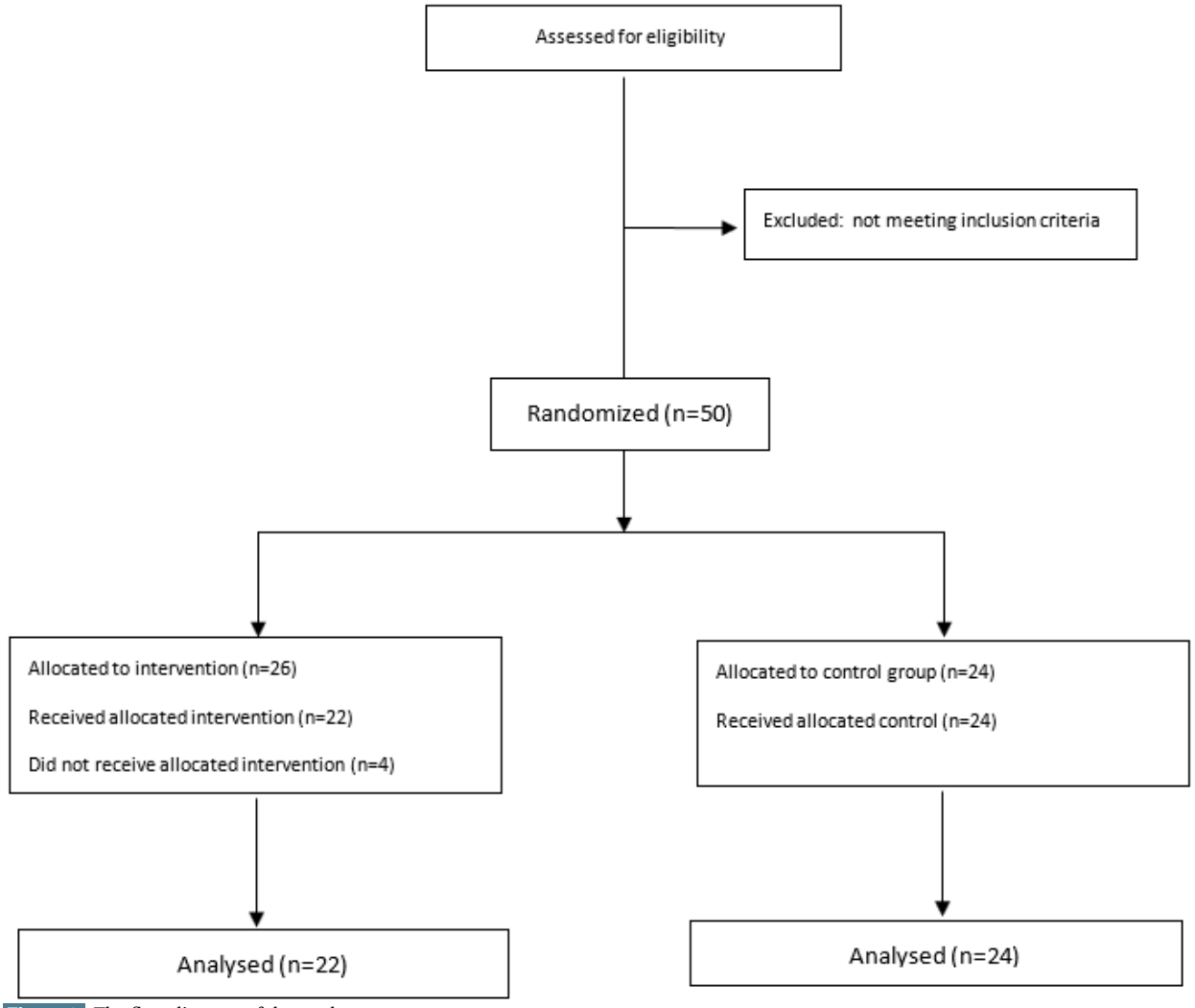

Figure 1 The flow diagram of the study

Table 1 Examining the homogeneity in terms of demographic variables

Group	Variable	Frequency (percentage)		Chi-squared result
		Intervention group (22)	Control group (24)	
Marital status	Single	3 (13.6)	5 (20.8)	P=0.702
	Married	18 (81.8)	18 (75)	Fishers' exact=2.30
	Widow, widower	0 (0)	1 (4.2)	
	Divorced	1 (4.6)	0 (0)	
Smoking	Yes	10 (54.4)	12 (50)	P=0.758
	No	12 (54.6)	12 (50)	X^2=0.095
Drugs	Yes	5 (22.7)	6 (25)	P=0.857
	No	17 (77.3)	18 (75)	X^2=0.033
Quantitative variable		Mean±standard deviation		Independent t -test
Age		10.85± 90.36	84.12 ± 36.95	P=0.098, t=0.014
Duration of smoking (year)		12.73 ± 13.5	10.18 ± 13	P=0.92, t= -0.01
Duration of drug use (year)		3.36±6.40	9.45±10.66	P=0.36, t=0.952

and the area of the graft during the hospitalization period examined (28). Wallace's table was also used to determine the percentage of burns and skin graft area.

2.2.1. Demographic checklist

Demographic checklist and background information including age, height, weight, gender, marital status, place of residence, education, economic status, employment status, suffering from other diseases, history of mental and nervous problems, history of smoking and addiction.

2.2.2. Impact of event scale- revised

Table 2 Examining the homogeneity in terms of burn characteristics

Group	Variable	Frequency (percentage)		Chi-squared result
		Intervention group (22)	Control group (24)	
Burn agent	Hot water	2 (9)	4 (16.6)	P=0.139
	Acid burns	0 (0)	1 (4.2)	Fisher's exact=6.18
	Burn with fire	16 (72.7)	13 (54.2)	
	Electricity	4 (18.3)	2 (8.3)	
	Other	0 (0)	4 (16.6)	
Upper limbs burns	Yes	21 (95.4)	20 (83.3)	P=0.187
	No	1 (4.6)	4 (16.7)	X^2=1.74
Lower limbs burns	Yes	10 (45.4)	13 (54.1)	P=0.55
	No	12 (54.6)	11 (45.9)	X^2=0.348
Chest burns	Yes	2 (9)	2 (8)	P=0.927
	No	20 (91)	22 (92)	X^2=0.008
Head burn	Yes	5 (22.7)	7 (30)	P=0.619
	No	17 (77.3)	17 (70)	X^2=0.247
Degree of burn	I	5 (22.7)	2 (8.3)	P=0.175
	III	17 (77.3)	22 (91.7)	X^2=1.84
Quantitative variable		**Mean±standard deviation**		Independent t -test
Total body surface area (TBSA)		16.40±10.43	14.20±7.80	P=0.42, t= -0.81

Table 3 Average post-traumatic stress scores and related areas before and after the intervention

Group	Variable	Mean ± standard deviation		Paired t-test
		Pre intervention	Post intervention	
Intervention group	Avoid	11.17±8.02	8.58±7.44	P=0.019, t=2.62
	Unwanted thoughts	10.42±7.94	8.70±6.18	P=0.001, t=4.23
	Overstimulation	9.66±6.91	7.61±5.95	P=0.103, t=1.72
	Total stress	27.80±23.30	22.73±18.48	P=0.004, t=3.28
Control group	Avoid	13.69±23.30	14.13±5.66	P=0.512, t= -0.66
	Unwanted thoughts	12.78±5.93	13.30±5.37	P=0.180, t= -1.38
	Overstimulation	13.00±6.04	13.30±5.37	P=0.633, t=0.485
	Total stress	38.91±19.30	39.65±16.08	P=0.607, t= -0.522

Table 4 Average length of hospitalization after the intervention

Group	Variable	Mean±standard deviation		Independent t-test
		Intervention group	Control group	
Length of hospitalization (days)		7±2.52	7.13±2.52	P=0.873, t=0.161

Table 5 Frequency of graft success

Group	Variable	Frequency (percentage)		Fisher's-exact result
		Intervention group (22)	Control group (24)	
Graft success	Yes	21 (95.4)	17 (70.8)	P=0.893
	No	1 (4.6)	7 (29.2)	Fisher's-exact=1.38

PTSD symptoms before the start of the intervention during the initial 48 hours and four weeks after hospitalization were assessed by the impact of event scale-revised (IES-R) (23,30). The revised impact of event scale is a 22-item self-report questionnaire that measures the frequency of posttraumatic symptoms, avoidance, hyperarousal, and distressing symptoms (in separate subscales) during the last week. The internal reliability of this test is high, and Cronbach's alpha is 0.79-0.92. This test has high validity for measuring helplessness after an accident (27). Respondents complete the frequency of experiencing each symptom during the past week from 0 (never) to 4 (very much). Several types of research have been done on the tool's characteristics (validity and reliability). The total score of 22 items includes the total score of the test. In addition, each subscale is graded according to the full scores of its constituent objects. The total score of IES-R is the total of 3 clinical subscales, between 0-88.

2.2.3. Burn characteristics

The characteristics of burns include the date of hospitalization in the ward, the duration of hospitalization in the ward, the cause of the burn, the burn sites on the body, the degree of burn, the area of the affected area, the number of days of

admission for skin graft surgery, the total number of debridement surgeries, the date of the first debridement, the number of surgeries and the result was a transplant.

2.2.4. Hemodynamic conditions of patients

The researcher examined the vital signs and the oxygen demand of the heart's myocardium, which was also calculated with the rate pressure product (RPP) index as the product of heart rate (beats per minute) and systolic blood pressure (mmHg).

2.2.5. The consequences of burns

The outcomes for the patients are the success of the transplant and the duration of the post-accident stress hospitalization. The method of diagnosing the consequences of burns was that the consequences and complications of burns were obtained through follow-up by the researcher, the doctor's diagnosis, and using the history of patients in the burn department. Examination and follow-up were planned for all patients from admission to discharge. Evaluation of graft success means a graft with a pink color and firmly fixed to the base of the graft area, performed by the attending physician (31). Studies have shown that most burn wounds heal within 2 to 4 weeks after initial wound debridement and skin grafting. The time required for the patient to successfully transplant and release from the dressing and complete healing of the wound in both groups was evaluated within two weeks and four weeks after discharge (32).

2.2.6. Side effects

Adverse effects of propranolol include bradycardia (<60 beats per minute), bradypnea (<12 breaths per minute), low blood pressure (systolic<90 mmHg, diastolic<60 mmHg), and ischemia (mean arterial pressure<60 mm Hg) (13). If the above conditions were observed in the intervention groups, the data were recorded in the data collection sheets and reported to the doctor.

2.3. Study population and sampling method

This study was conducted as a randomized clinical trial on 52 burn patients hospitalized in the Burn Department of Shahid Rajaei Hospital, Qazvin. By considering the mean and standard deviation of similar articles (33) and by considering the confidence coefficient of 95% (β=0.2) and the intervention power of 80% (α=0.05), and the minimum error of 2.1, the sample size estimate for each group had 25 people and considering 10% dropout, the final sample was estimated to be 52 people, which was considered 26 people for each group. In the intervention group, 4 patients because of changes in vital signs were excluded from the study. Sampling to reach the expected number was continued. Two groups were assessed in the primary outcome which was the successful graft and also in the secondary consequence which was the length of hospitalization (Figure 1).

2.4. Statistical analysis

Version 24 of SPSS software was used to analyze the data. examine the frequency distribution (percentage) and mean

$$n=\frac{(z_{1-\alpha/2}+z_{1-\beta})^2(\sigma^2_1+\sigma^2_2)}{(d)_2}=\frac{(1.96+0.84)^2(2.56^2+3.45^2)}{2.1^2}=25$$

(standard deviation) of the demographic variables of the studied patients in the two experimental and control groups using chi-squared (Fisher) and independent t-tests. the average scores of post-traumatic stresses and its related areas before and after the intervention have been examined using the paired t-test in each group separately. To be sure of the data normality we used the Kolmogorov-Smirnov test.

Table 1 is presented to check the homogeneity of the demographic variables of the study in the two experimental and control groups. The table shows intervention and control groups were homogeneous (P-value>0.05).

According to table 2, there is not a significant difference in the burn agents, the locations of burns on the body, and the degree of burn between the intervention and control groups. The two groups were homogeneous (P-value>0.05).

Tables 3 to 5 are presented to examine the results of the study in two groups after the intervention.

Table 3 illustrates the significant difference in the intervention group before and after intervention (P-value<0.05) except in the overstimulation factor (P-value>0.05). The patients who were in the control group did not have a significant difference (P-value>0.05). According to the results, despite the average length of hospitalization after the intervention being shorter than in the control group, there was no statistically significant difference (P-value >0.05).

According to the results, the number of patients who had successful grafts in the intervention group was more than in the control group, but there is no significant difference between them (P-value >0.05).

3. Discussion

In this study, propranolol was effective for the patients' burn wounds. Studies have been conducted on the effect of propranolol on wound healing. Mohammadi et al. (2009) conducted a clinical trial study in adult burn patients with and without propranolol treatment, and the patients in the propranolol treatment group had faster recovery and a shorter time for wound preparation for transplantation. In addition, in the end, the administration of propranolol reduced the burning surface size, the tissue required for transplantation, decreased the rejection rate of the skin graft, and the length of stay in the hospital (28). Stormer et al. (2019) also showed that antihypertensive drugs improve wound healing to some extent (34), which was in line with the results of this study. The administration of propranolol improves wound contraction and causes proper repair of some superficial parts at the border of the deep burn area, thus improving the healing process and reducing graft preparation time (35,36). Avoiding wound infection, reducing catabolism, and maintaining pro-

tein stores as potential benefits of propranolol may be other reasons for reducing the time to be ready for transplantation. Grafting as soon as possible can help minimize scar formation on the wound surface (37).

Also, the results of this study showed that PTSD, which usually occurs after exposure to a life-threatening event and is characterized by disturbing memories, was reduced after taking propranolol. It is the most common drug which has been investigated for the treatment of memory consolidation in clinical trials (38). On the other hand, the shorter the wound healing time, the less chance of wound infection and the patient experiences less stress (33). A study by Fallah et al. (2019) showed that faster wound healing reduces the anxiety and pain of burn patients (20).

A study by MA J et al. showed that the use of beta antagonists in burn patients reduces the length of stay in the hospital in adults, shortens the preparation time for transplantation and reduces the burden on the heart, without increasing mortality, and reduces sepsis and PTSD compared to people who received usual care. Therefore, beta antagonist can be considered as a suitable treatment strategy in burn patients (35). It should be noted that the amount of reducing the harmful effects of burn injury depends on the dose of propranolol and the duration of use. Therefore, it is safe to treat burn patients with propranolol at doses that reduce the heart rate by 20% of its value at admission and with constant monitoring for side effects (35). Therefore, administering propranolol to patients with severe burns may become a standard of care in the not-too-distant future. However, few side effects have been associated with propranolol, and despite the beneficial effects, propranolol can be safely prescribed in burn patients. Burn care providers should also be aware of the possible hemodynamic effects of propranolol. For example, the use of propranolol in severely burned patients can improve cardiac physiology, but repeated doses may be associated with hypotension and bradycardia (10).

In this study, no statistically significant difference was observed between the length of hospitalization of the control and intervention groups. The cause of this issue can be the routine of the Burn Department of Shahid Rajaei Hospital. In this center, all patients are discharged one day after skin grafting and continue their treatment as an outpatient in the surgical clinic. Therefore, using propranolol can speed up wound healing, but it does not affect the length of hospitalization of patients.

4. Limitations

Because of the type of study, we needed deep collaboration between the research team and the doctors. In some situations, we faced challenges in conducting our study. On the other hand, some factors affected the result, such as deciding on discharge time.

5. Conclusion

Using propranolol in treating burns can play an influential role in the recovery of burn patients and reduces the PTSD. Since it is essential to identify the most effective interventions to reduce the burden of burns, and given the potentially significant benefits of using propranolol for adult patients with severe burns, further studies on the effects and dosage of propranolol protocols in this specific population group are needed.

6. Declarations

6.1. Acknowledgement

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6.2. Authors' contribution

Conceptualization, methodology, and data collection: SM, NH; Writing – review & editing and resources: LY, AA; Data analysis and writing – original draft: LY, AT, AA; Approval of final manuscript: SM.

6.3. Conflict of interest

The authors declare no conflict of interest.

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