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# The effect of hyperbaric oxygen therapy on burn wounds covered with skin allografts

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SUMMARY

**Introduction.** Human cadaveric cutaneous allografts are used in burns surgery usually as a temporary dressing preparing wound bed for further surgical procedures. In many cases concurrent application of mentioned grafts and hyperbaric oxygen therapy results in definitive burn wound closure and eliminates the necessity of autologous skin transplantations.
**Aim.** The aim of this study was to investigate the effect of allogeneic skin dressing on the burn wounds healing rate and wound bed preparation to the subsequent surgical procedures.
**Materials and Methods.** The study was conducted in two groups consisted of twenty patients each. Patients were treated in Burn Treatment Center in Siemianowice Slaskie due to thermal or electrical burns. On the 3rd day of hospitalization, after wound debridement, in both control and experimental group allogeneic skin transplantation in the operating room was performed. Patients from the experimental group also underwent hyperbaric oxygen therapy. Autologous skin graft was carried out on the 14th day on average among patients in whom epithelialization under allogeneic skin dressing did not succeed.
**Results.** In control group the total epithelialization an complete wound closure under allogeneic skin occurred in 7 patients, while in the remaining 13 patients autologous skin transplantation in operating room was performed due to burn wound deepening. Hospitalization time of each patient was equal to an average of 30.4 day. Among the 14 patients from experimental group complete wound healing under allogeneic graft succeeded and they did not need further surgery, but among the remaining 6 patients split-thickness skin graft was performed in order to definitive closure of the wound. The average hospital stay was 22.5 day.
**Conclusions.** The results of this study confirm that simultaneous application of allogeneic skin dressing and hyperbaric oxygen reduces the length of hospitalization and number of subsequent surgical procedures and frequently results in complete burn wound closure.
**Keywords**: burn wound, allogeneic skin graft, hyperbaric oxygen therapy

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## INTRODUCTION

Burn is a damage of skin integrity and depending on depth also of subcutaneous tissues or organs due to high temperature, electricity, chemicals or radiation [1]. The classifications of burns are distinguished based on depth expressed in degrees and their corresponding symptoms:

- First degree – includes only the epidermis, erythema occurs, it comes to transitional stasis of blood in the papillary region of the skin and swelling of the dermis.
- Second degree 'A' - includes the epidermis and the superficial layer of dermis, erythema and blisters occur, an increase of endothelial permeability take place.
- Second degree 'B' – includes the epidermis and most dermis, destruction of papillary region microcirculation, dermis inflammatory infiltration
- Third degree – full-thickness burn - includes epidermis and all dermis, lack of blisters, complete destruction of skin vascular system
- Fourth degree – necrosis of skin, subcutaneous tissue, muscles, tendons and bones, charring occurs [2].

Regardless of burn cause skin barrier, serves as protection from external environment factors, is interrupted which results in homeostasis and physiological functions disruption. In superficial burns (first and second 'A' degree) damage of epidermis' protective layer leads to swelling and blisters. Treatment for injuries of this type most often requires the use of sterile dressings and ointments. In the case of deep dermal and full-thickness burns, lack of skin barrier results in loss of water by evaporation from the wound, loss of thermoregulatory function and drop in the number of electrolytes and proteins [3, 4]. Progressive dehydration causes

cell damage, disruption of repair processes and inhibition of the regenerative changes in the wound environment. At the same time, cell membrane damage and increased vascular permeability results in body fluids leakage into the intercellular spaces followed by onset of swelling, as water leaks through the burn wound to the environment [5, 6]. Swelling affects development of hypoxia in burn wound adjacent tissues and causes accumulation of harmful cellular metabolites. Inflammation and necrotic tissues are formed, which significantly delays the process of healing. Necrosectomy should be performed in 5-7 days after the injury at the latest. It significantly reduces the likelihood of the transfer of microorganisms to tissue and eliminates the absorption of toxins released by the necrotic scab system and pathogens. In the fifth day after the injury, microorganisms begin to colonize necrotic tissue, which serves as a good medium [7]. In order to normalize the patient physiological condition, and thus restore homeostasis, after surgical debridement of burn wound, its protecting through the application of autologous skin graft or skin substitutes should be the priority [8].

Despite the rapid development of tissue engineering and the emergence of increasingly sophisticated skin substitutes and dressings, skin grafting of the patient's own skin, made after prior resection of necrotic tissue, is still the best way to close the burn wound [9]. Unfortunately, patients with extensive burns have a limited number of donor sites. Moreover, each harvest of the skin leads to another wound which in turn may cause further complications, pain and subsequent scarring. At the time, a good solution is application of allogeneic skin graft [10, 11]. The first use of allogeneic skin graft was reported in 1881 [12]. Currently, allograft skin has many applications in burns treatment, because:

- serves as temporary burn wound coverage when patient's own skin is not possible to obtain,
- accelerates a partial-thickness burn wound healing,
- serves as a dressing for wounds previously covered with mesh autograft, helping to reduce metabolic stress and wound infection,
- allows skin bed preparation before autografting,
- serves as a scaffold for keratinocytes cultured *in vitro*,
- provide a dressing (for example in Stevens-Johnson syndrome and Toxic epidermal necrolysis) [13, 14].

Allogeneic skin is mostly obtained from dead donors, less often from living donors (donor family). After harvesting, skin is usually preserved in a twofold manner: in a freezer at -80°C or in 85% glycerol at +4°C, lyophilization is rarely used technique of preservation. The main difference dependent on the method of allogeneic skin storage is the level of viability of the cells in the skin. It was observed that glycerol-preserved allograft cells retain their morphology but stop to function while cryopreserved allograft cells stored at -80°C are viable to a certain extent after thawing and can secrete cytokines and growth factors which accelerate epithelialization. Skin harvested from donors is always examined microbiologically and virologically. 85% glycerol possesses antibacterial and antiviral properties which depend on incubation time. Allografts preserved at -80°C are sterilized radiative in order to obtain the highest level of graft purity [15, 16].

Cadaveric skin allograft possesses several key characteristics of an ideal wound dressing, including protection, promotion of healing and pain relieving. Moreover, its advantage is ease of obtainment, the possibility of achieving a large graft area, low toxicity and antigenicity, simple storage and comparatively easy application [17].

Temporary dressings made of allogeneic skin are very promising in full-thickness burn treatment. Applied on the wound after surgical debridement prevents rapid water, electrolytes and proteins loss, thereby reducing the possibility of dehydratation of other tissues. Moreover, allogeneic skin serves as a barrier protecting internal environment against external factors and contributes to reduction of microorganisms proliferation. The pain that accompanies patient after thermal injury decrease, he better tolerates hospitalization and is able to work with the therapeutic team. Due to reduced heat loss through the wound, hypermetabolic response to burn injury decreases. Full-thickness burns have no regeneration potential, in this case allogeneic graft stimulates granulation process and wound epithelialization, preparing wound bed for further surgical procedures [18, 19]. Allogeneic skin is also a good biological dressing that works in the treatment of superficial dermal partial thickness burns including epidermis and dermis part. Allograft initiates the blood vessels growth in the wound bed and stimulates revascularization. Strictly adhering to the wound it reduces the sensation of pain and number of dressing changes; skin

formation within the wound progresses, meanwhile allograft gradually separates from her, without damage to the newly formed epidermis. Allografts secure wounds after necrotic tissues removal until 3 weeks, the longest documented period of maintaining such a graft was 67 days. Second degree burns covered with skin from deceased donors do not usually require the use of subsequent surgical procedures, which may contribute to the reduction of pain, scars and costs, and shorten hospitalization period. Further, such allografts are cheaper than synthetic dressings that must be changed more frequently [20].

In clinical practice, as a result of fluid loss, significant swelling, infection and hypoxia, it is often observed that burn wound becomes deeper due to formation of secondary necrosis. If the wound was already covered with autologous skin graft and comes to its loss, it is necessary to harvest another autograft, which can lead to the deterioration of the patient's health. In this case utilization of allogeneic skin dressing is a good solution and can contributes to the optimization of wound bed. The graft can be also applied in cases where it is impossible to accurately determine the depth of the burn wound (chemical and electrical burns), and there is a risk that wound will get deeper which leads to graft loss [21, 22].

One of the basic conditions that must occur in the wound environment in order to initialize allogenic skin graft epitialisation and vessel growth, is well blood supplied wound and hence good oxygenation [23]. Various types of burn injuries result in circulatory disorders, blood clot formation or interruption of the capillaries, which significantly impair the microcirculation. Although hypoxia initiates angiogenesis via vascular endothelial growth factor (VEGF) stimulation, chronic hypoxia significantly interfere with wound healing. Hypoxia inhibits fibroblast proliferation, slows down cell metabolism, stops the synthesis of collagen and reduces the formation of granulation tissue. It may also cause low efficacy of antibiotics as it reduces the availability of antimicrobials administered to burn wound, which is the source of systemic infection [24]. In order to improve the healing process of wounds covered with allogeneic skin graft the hyperbaric oxygen therapy, which dates back to the seventeenth century, is often used. Hyperbaric treatment consists of pressurized 100% oxygen supply increasing oxygen in the plasma, therefore, the oxygen level in hypoxia is greater than under physiological conditions [25]. Effects of hyperbaric oxygen include improved vascular permeability, creation of reactive oxygen species (ROS), which significantly affect inflammation elimination by microorganisms destruction and neutrophils activation. ROS stimulate proliferation and migration of keratinocytes and affect the fibroblasts, endothelial cells and myofibroblasts differentiation [26, 27].

Treatment of burns is an interdisciplinary problem. Pharmacotherapy and surgical treatment of patients with burns often brings better results in conjunction with hyperbaric oxygen therapy. It is likely that treatment of patients with burns using skin allograft together with hyperbaric oxygen therapy may improve epitelialisation and eliminate the bacteria colonizing the wound. It may also reduce the number of successive split-thickness skin grafts.

The aim of this study was to investigate the effect of the allogeneic skin dressing on burn wounds healing rate and wound bed preparation to the subsequent surgical procedures.

**Tab. 1.** Profile of burn patients treated with allogeneic skin graft and hyperbaric oxygen therapy

| | Control group: patients treated with allograft | Experimental group: patients treated with allograft and HBOT |
|---|---|---|
| **Number of patients in the group** | 20 | 20 |
| **Sex** | | |
| Females (N) | 6 | 1 |
| Males (N) | 14 | 19 |
| **Average age (in years)** | 50,40 | 48,15 |
| Standard deviation | 15,09 | 14,80 |
| **TBSA (%)** | 13,60 | 15,90 |
| Standard deviation | 7,75 | 15,09 |
| **Depth/burn degree (%N)** | II/III (100%) | II/III (100%) |

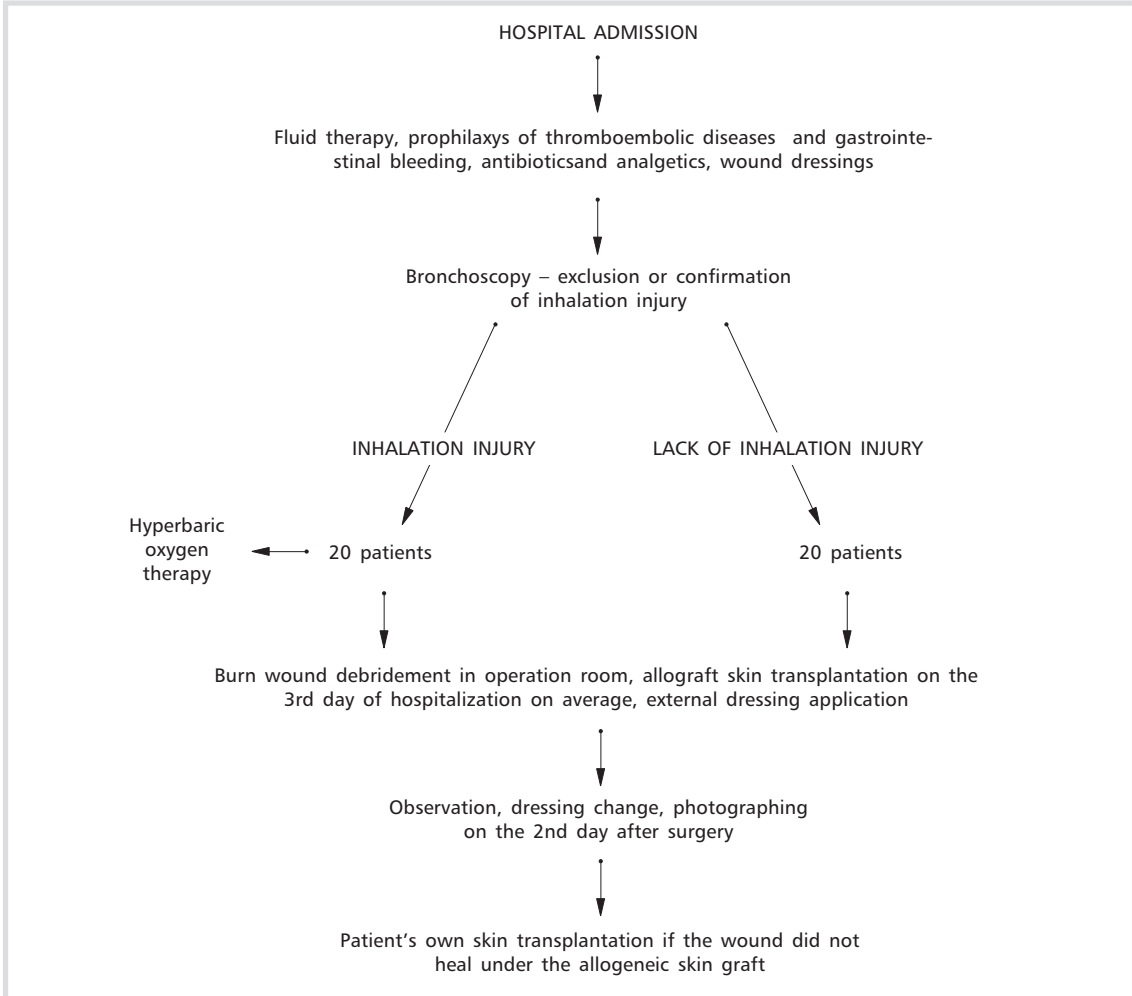
**N** – number of patients
**TBSA** – total body surface area
**HBOT** – hyperbaric oxygen therapy

## MATERIALS AND METHODS

### Patients population

The study was conducted in a population of 40 patients treated at the Burn Treatment Center (CLO) in Siemianowice Slaskie due to thermal and electric burns in the years 2013-2015. The patients were divided into two groups of 20 people: in both groups allogeneic skin graft was performed, furthermore patients from second group underwent therapy in a hyperbaric chamber. Table 1 shows the basic data includes age, sex, area and burn of patients treated at the Burn Treatment Center.

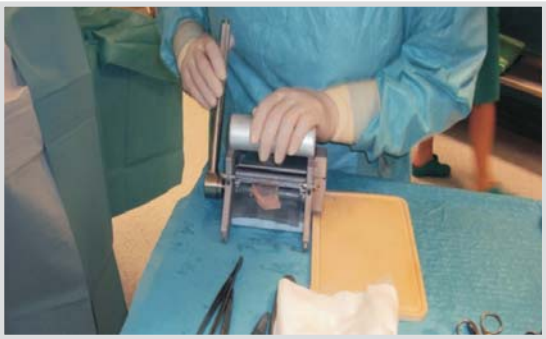
After admission to CLO's burn department all patients underwent fluid therapy, prophylaxis of thromboembolic diseases and gastrointestinal bleeding, received antibiotic and analgetic. Bronchofiberoscopy were performed to confirm or exclude inhalation injury. Inhalation injury was confirmed in 20 patients who had subsequently been treated with hyperbaric oxygen. Burn wound necrosis was resected in operating room conditions three days after admission on average, and then allogeneic skin graft was performed, on which external dressing consisting of gauze soaked in paraffin (jelonet) and neomycin compress in both groups (experimental and control) was applied. The first external dressing changing and first photographing have taken place two days after surgery. Photos of wounds as well as a new external dressing consisted of gauze soaked in paraffin (jelonet) and octenisept compress were performed every day. Autologous skin graft was carried out on the 14th day on average among patients in whom epithelialization under allogeneic skin dressing did not succeed. Scheme 1 shows subsequent stages of patients treatment.



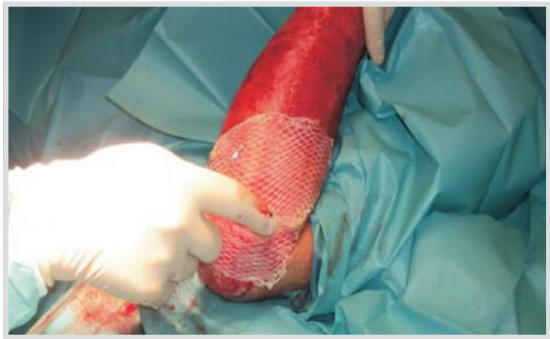

**Scheme 1.** Subsequent stages of patients treatment

**Phot. 1.** Burn wound IIB after necrotic tissue removal

**Phot. 2.** Allogeneic skin, sterile instruments



**Phot. 3.** The process of allograft meshing



**Phot. 4.** Allogeneic skin graft application

**Phot. 5.** Allogeneic skin graft application

**Phot. 6.** External dressing application

**Tab. 2.** The comparison of treatment results among two research groups

| | Patients treated with skin allograft | Patients treated with skin allograft and HBOT | P value |
|---|---|---|---|
| **Number of patients** | 20 | 20 | — |
| Percentage of TBSA (mean) | 13,6 | 15,9 | — |
| Number of patients with complete wound closure under allogeneic skin graft | 7 (35%) | 14 (70%) | — |
| Mean number of body regions covered with allogeneic skin graft | 2,05 | 1,75 | — |
| Mean duration of graft adherence to wound bed (days) | 12,4 | 16 | p<0,05 |
| The number of autologous skin grafts in the group (%) | 13 (65%) | 6 (30%) | p<0,05 |
| Mean length of hospital stay (days) | 30,4 | 22,5 | p<0,05 |

## Allogeneic skin

Allogeneic skin grafts harvested from human cadaver in accordance with 'The Cell, Tissue and Organ Recovery, Storage and Transplantation Act of July 1st, 2005'were prepared in Tissue and Cell Bank of Burn Treatment Center. Next, they were subjected to sterilization and examined microbiologically and virologically to control the sterilization process. If the test results were negative skin substitutes were stored at -80°C until application. In a next step after surgical wound purification from necrotic tissue, allogeneic skin was meshed and applied to the wound. Photos 1-6 show the successive stages of the burn wounds treatment supplied with allogeneic skin graft obtained from deceased donors.

## Hyperbaric oxygen therapy

Patients with inhalation injury confirmed by bronchofiberscopy were compressed in hyperbaric chamber in Burn Treatment Center in Siemianowice Slaskie. Each of the 20 patients underwent 10 procedures in multiplace hyperbaric chamber at 100% oxygen at a pressure of 2.5 atmospheres absolute. Sessions lasted 80 minutes each.

## Statistical analysis

Statistical analysis was performed to show whether there is any statistical difference between groups in the average values of the examined characteristics:

1. the adhesion time of the graft to the wound (in days),
2. hospitalization time (in days),
3. number of autologous skin regrafting.

Statistical significance was set at p-value of 0.05. Normality of distributions was verified using Kolmogorov-Smirnov test and on the basis of received results appropriate tests were performed: Student's t - test for first characteristic of

**Phot. 7-8.** Admission day to burn center (Patient, 40 years old)

**Phot. 9-10.** The second day after allogeneic skin grafting (Patient, 40 years old)

**Phot. 11-12.** The fifth day after allogeneic skin grafting (Patient, 40 years old)

**Phot. 13-14.** The eighth day of hospitalization – discharge from the burn center (Patient, 40 years old)

the normal distribution and Mann–Whitney *U* test for second and third characteristics of non-normal distributions. Data were analyzed using the STATISTICA software version 12.

## RESULTS

### Patients treated with allograft without HBOT. Control group 1

The group of patients treated with an allogeneic skin grafts consisted of 20 people (6 women and 14 men), the mean age of the patients in this group was 50.4 years. 19 patients suffered from thermal burns grade II/III, 1 patient was hospitalized due to electrical burn grade II/III. The average area of burns in all 20 patients was 13.6%.

Allogeneic skin graft in described group was perfomed in the following parts of the body: back, shoulders, arms, forearms, hands, chest, abdomen, buttocks, thighs, crura, foots. The average number of body's areas covered with allograft skin per 1 patient was 2.05, and the average time of its adherence to the wound was 12.4 day. The total epithelialization an complete wound closure under allogeneic skin occurred in 7 patients, while in the remaining 13 patients autologous skin transplantation in operating room was performed due to burn wound deepening. Hospitalization time of each patient was equal to an average of 30.4 day, all patients were discharged from hospital in good condition.

### Patients treated with allograft and HBOT. Research group 2

The group of patients treated with an allogeneic skin and hyperbaric oxygen consisted of 20 persons (1 woman and 19 men), mean age was 48.15 years.18 patients were hospitalized because of thermal burns grade II/III, and the remaining two due to the electrical burns grade II/III. The average area of burns in the group was 15.9%. All patients underwent therapy in hyperbaric chamber.

Allogeneic skin graft in described group was performed in the following parts of the body: back, neck, chest, shoulders, forearms, wrists, hands, abdomen, thighs, crura, foots. The average number of body's areas covered with al-

**Phot. 15.** Admission day to burn center (Patient, 50 years old)

**Phot. 16.** The second day after allogeneic skin grafting (Patient, 50 years old)

**Phot. 17.** The fifth day after allogeneic skin grafting (Patient, 50 years old)

**Phot. 18.** The eleventh day of hospitalization – day of patient's discharge from the burn center (Patient, 50 years old)

lograft skin per 1 patient was 1.75, and the average time of its adherence to the wound was 16 days. Among the 14 patients complete wound healing under allogeneic graft succeeded and they did not need further surgery, but among the remaining 6 patients split-thickness skin graft was performed in order to definitive closure of the wound. The average hospital stay was 22.5 day, patients were discharged home in good condition. Table 2 shows a comparison of treatment results in two groups.

The following photos show burn wound healing process under allogeneic skin graft among selected patients from the day of admission until hospital discharge.

**Phot. 19.** Admission day to burn center (Patient, 63 years old)

**Phot. 20.** The second day after allogeneic skin grafting (Patient, 63 years old)

**Phot. 21.** The fifth day after allogeneic skin grafting (Patient, 63 years old)

**Phot. 22.** The sixteenth day of hospitalization – day of patient's discharge from the burn center (Patient, 63 years old)

## DISCUSSION

This paper presents a comparison of treatment results between two group of patients. In the first group patients underwent the allogeneic skin grafting and in the second group patients were treated with the allogeneic skin graft and hyperbaric oxygen therapy. The results indicate that in 70% of patients (14 people) from group treated with hyperbaric oxygen complete closure of the burn wound under skin allograft performed, in group of patients who were not treated with hyperbaric oxygen this result was 35% (7 persons). The number of autologous skin transplantations in HBOT group was lower compared to the group without HBO, 6 and 13 transplantations respectively.

In both groups allogeneic skin dressing served as a barrier against microorganisms and physiological fluids loss and it significantly contributed to the production of granulation tissue and definitive closure of the wound through the initiation of epithelialization process. Similar results were presented in studies performed by Oliver et al., their results indicate that allografts may modulate the proliferation and differentiation of regenerating granulation tissue and epithelium [28]. Double number of patients with completely healed burn wounds under skin allograft and also treated in hyperbaric chamber can be caused by beneficial effects of one hundred percent oxygen administered under increased atmospheric pressure. Larger amount of oxygen in the blood plasma, and therefore better tissue oxygenation in an environment where because of burn injury critical stenosis of blood vessels occured, activates the process of granulation tissue formation under allogeneic skin and stimulates the synthesis of angiogenesis by activation of vascular endothelial growth factor [29]. VEGF is involved in the stimulation of vascular endothelial cells division and in regulation of inflammation process. Baynosa et al. indicated that longer time of allogeneic skin adherence among patients who underwent hyperbaric treatment can also be caused by greater concentration of oxygen in the wound bed which also prevents postreperfusion syndrome [30]. According to Thom et al. higher oxygen concentration reduces swelling

**Phot. 23.** Admission day to burn (Patient, 25 years old)

**Phot. 24.** The second day after allogeneic skin grafting (Patient, 25 years old)

**Phot. 25.** The fifth day after allogeneic skin grafting (Patient, 25 years old)

**Phot. 26.** The tenth day of hospitalization – day of patient's discharge from the burn center (Patient, 25 years old)

in wound environment which may prolong allogeneic skin graft rejection time and accelerate processes such as collagen synthesis, regeneration of the basement membrane, fibroblasts and keratinocytes proliferation, epithelialization and in thus definitive healing of the wound under allogeneic skin graft [31]. Besides effective wound protection against microbial colonization by allogeneic skin graft, hyperbaric oxygen also contributes to bacterial growth inhibition and bacterial endotoxins release suppression thus promoting faster wound healing [32, 33].

The positive effect of hyperbaric oxygen on the process of wound healing is also confirmed by the differences in hospitalization time. Hospital stay was on average 7.9 day shorter in cases of patients undergoing hyperbaric treatment compared to patients from control group. Cianci et al. also demonstrated a positive impact of hyperbaric therapy on hospitalization time reduction among burn patients [34].

## CONCLUSIONS

1. Hyperbaric oxygen affects the faster healing of burn wounds covered with skin allogeneic grafts (p=0,0025).
2. Length of hospital stay of patients who underwent hyperbaric therapy and allogeneic skin graft is shorter than the duration of hospitalization of patients who were not treated with hyperbaric oxygen (p=0,0091).
3. Among patients treated with 100% oxygen under increased atmospheric pressure and the allogeneic skin graft the autologous skin transplantations were performed less often (p=0,0016).

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