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Allogeneic vs. Autologous Skin Grafts in the Therapy of Patients with Burn Injuries: A Restrospective, Open-label Clinical Study with Pair Matching

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article

Abstract

Background. Early application of autologous skin may lead to the loss of split thickness skin graft due to unclarified wound bed. Allogeneic skin grafts are performed on patients with extensive burn injuries after escharotomy, tangential excisions and deep debridement for the purpose of stabilizing the general condition and reducing the scope of local complications.
Objectives. The aim of this paper is to determine how the use of allografts improves the conditions for the intake of autografts in burns treatment, and how it accelerates wound healing in comparison to the autografts-only option.
Material and Methods. In 2012–2013, allogeneic skin was grafted on 46 patients, and in 8 cases grafting was repeated several times. An autologous split-thickness skin graft was applied to 32 patients. The analysis included the relationship between the duration of hospitalization and the number of skin transplantations, the relationship between the time of admission to debridement of the necrotic tissues and the total duration of hospitalization. Statistical analysis encompassed also pain assessment.
Results. The results suggest that multiple applications of autografts not only do not lead to quicker recovery, but even lengthen the hospitalization time. The dependency is visible also in the patients who underwent the skin grafting procedure in allogeneic and autologous systems twice or more. There was a statistical significant difference between the duration of hospitalization in groups of patients who underwent STSG preceded by allogeneic skin graft transplantation when compared to the group of patients who underwent allogeneic skin application ($p < 0.05$) and the group of patients who were grafted with autologous skin ($p < 0.05$).
Conclusions. Allogeneic skin grafts are a perfect dressing when wound vascularization is insufficient to take free split-thickness skin graft. In patients with comparable burn surface areas, multiple applications of free autologous split-thickness skin grafts (STSG) extend the hospitalization time in comparison to application of allogeneic skin dressing as the first-line therapy (**Adv Clin Exp Med 2016, 25, 5, 923–929**).

Key words: pain, hospitalization, skin graft, burns.

The clinical standard in deep skin burn therapy has huge potential in the area of treatment of burn injuries and transforming them into a surgical injury, i.e. resection of necrosis and autologous split-thickness skin graft [1–2]. Autologous skin grafts were first described by Reverdin in

1871 [3–4]. The anastomoses of graft vessels with the vessels of the wound bed ensure the nutrition of the slice of autologous skin, and, therefore, its engraftment at the recipient site. If there are insufficient donor sites, it is possible to apply mesh skin grafting. Although this method enables us to cover a greater area and saves the healthy skin of the patient, the cosmetic and functional results of the treatment are worse in comparison to grafts of continuous skin flaps [5]. This advantage is caused by the presence of gaps in the grafting mesh, which leads to slower epithelialisation, greater graft contraction and the formation of scars and "crocodile skin". The lack or the limited number of donor sites results in the need for alternative mechanical barriers protecting the patient from the loss of fluids and bacterial contamination [6]. Temporal allogeneic skin dressing is used at the beginning of the therapy, when the condition of the wound raises doubts as to further tissue necrosis after the resection of the damaged skin [7]. The method enables the verification and, if needed, the radicalization of the skin resection; then the wound is closed with an autologous graft [2]. The application of allogeneic skin on the burn injury makes it possible to prepare skin graft components cultured *in vitro* in a way that is safe for the patient [8]. The culture of keratinocytes and fibroblasts lasts approximately 21 days and the patient with severe burns must endure this period in a good general and local condition [9]. Rejection of allogeneic skin takes place three to four weeks after the graft and in each subsequent application the reaction is quicker [10]. Immunosuppression cannot be given to heavily burnt patients at this stage of therapy [11]. The most frequent indication to use allogeneic skin grafts is to cover wounds after an escharotomy, tangential excisions or deep debridement in the case of heavy burns [1]. Allogeneic skin grafts play an important role in the healing of burn injuries, as biological dressing, protecting the wound bed against dehydration and infection, constitutes a mechanical barrier against the loss of heat, electrolytes and protein, and stimulates the healing processes [12]. Allogeneic skin grafts from living donors (family) are considered the best skin substitutes, if there is no sufficient autologous skin, but their limited availability significantly hinders their application [1, 3]. The application of allogeneic skin graft on a deep burn injury alleviates pain and serves as a temporal dressing during the first few weeks after the injury, when the immune response of the severely burned patient is limited [11]. The progressing vascularisation of the graft provokes the highly immunogenic epithelial cells to come into contact with the host cells, further stimulates an immune response and, as a result, induces graft rejection [12]. It must be remembered, though, that allogeneic skin grafts may undergo revascularization, similarly to autologous ones [3]. Furthermore, allogeneic skin grafts provide the wound bed with important growth factors and cytokines, promoting cell chemotaxis and proliferation. Increasing vascularisation of the wound bed stimulates angiogenesis and is conducive to wound bed preparation (WBP) for an autologous skin graft. Therefore, it is a procedure preparing the burn wound for final closure [12]. If the allograft is radiation sterilized, glycerolized or lyophilized, its cellular elements are destroyed, so the immune response of the recipient is reduced [13]. As a result, fragments of the graft dermis are partially incorporated into the wound and serve as a base for autologous skin [14, 15]. Allogeneic skin becomes adherent to the wound bed approximately 8.4 days before the rejection. Allogeneic skin adherence or vascularisation is a credible sign that the wound bed has sufficient blood supply to accept autografts. After the application of allogeneic skin on the wound bed, autograft acceptance-rate reaches as much 88.4% [3, 12].

The aim of this paper is to determine how the use of allografts improves the conditions for the intake of autografts in the treatment in burns, and how it accelerates wound healing in comparison to the autografts-only option. Another purpose of the study was to determine if multiple autologous spit thickness skin grafting is a more effective way of treatment and whether it shortens hospitalization time and reduces pain in comparison to only allogeneic skin treatment of medium depth burns and deep burns.

Material and Methods

All of the 46 subjects included in the study were patients hospitalized in the Centre for Burns Treatment between 2012 and 2013 due to severe thermal burns of on average 37% TBSA, who underwent 46 allogeneic skin grafts. Average hospitalization time was 48.2 days (Table 1). In total, 76464.5 cm^2 of allogeneic skin have been grafted in 46 patients. In 32 patients, the wounds were covered with free autologous STSG.

Due to clinical and procedural limitations, the group of patients who underwent both one allogeneic and one autologous transplantation was limited to 12 patients. The reason for that was that in the Centre for Burns Treatment, one STSG is always preceded by one allogeneic skin graft.

In 10 cases, the burns healed following the first application of STSGs. Patients aged between 18 and 85 years as well as those with wounds covering 5–70% of their total body area were included. Admission on the day of burn incidence was also

Table 1. General characteristics of patients who underwent allogeneic and autologous skin application

	Allogeneic skin application (n = 46)		Autologous skin application (n = 32)		p-value
	mean ± SD	min–max	mean ± SD	min–max	
Sex: female (%) male (%)	30 (n = 12) 70 (n = 34)	–	34 (n = 11) 66 (n = 21)	–	–
Age (years)	51 ± 28.5	26–83	43.3 ± 14.3	19–83	p ≥ 0.05
Total body surface area (TBSA) (%)	37 ± 17.9	8–70	35.64 ± 17.3	9–70	p ≥ 0.05
IIb/III° degree burn (%)	17.6 ± 12	0–48	16.9 ± 11.3	0–40	p ≥ 0.05
Hospitalization length (days)	48.2 ± 37.5	5–191	49 ± 32	5–149	p ≥ 0.05
Average surface area of allogeneic skin dressing per patient, cm^2	1371.69 ± 1009.01	15–5057	NN	NN	–

Mean ± SD – mean ± standard deviation; min–max – minimum–maximum; NN – not known; Mann-Whitney U test was used for continuous variables and χ^2 test for discrete variables. There were no statistically significant differences across two groups; statistical significance was set as p = 0.05.

one of criteria of inclusion. Intensive care unit patients were excluded. Study was unblinded due to procedure of gaining split thickness skin graft in one procedure with its application. Hospital treatment time has been chosen as the index of treatment efficiency and adequacy of chosen medical procedures. It is an imperfect index; other factors influencing the success of the therapy, understood as quick restoration of skin continuity and the patients' capability to leave the treatment center on their own, are described in the discussion.

Statistical hypothesis testing for two independent samples was determined by the Mann-Whitney U test. For comparing more than two groups of independent samples, The Kruskal-Wallis test was used. The significance level was set to 0.05 (5%). Correlation index was assessed by Spearman's rank correlation coefficient. For statistical analysis STATISTICA 10 was used.

The application of allogeneic skin graft was preceded by wound preparation in the form of wound debridement, necrosis demarcation – tangential excisions of the necrosis or deep resection of the necrotic tissues (Fig. 1). Resection procedures were performed in the classic manner, with the use of dermatomes and hydrocision procedures. Deep and tangential excisions constituted 63% of all procedures before the allograft application. Allogeneic and autologous skin was put on the freshly excised wound and covered by Jelonet (Smith & Nephew) and secured with bandages (1 layer was wet – soaked with neomycin or 3% boric acid and second was dry).

Allogeneic skin was grafted as the first-line treatment, after the resection of necrosis, or as a secondary therapy after the lysis of free autologous STSGs which were to be the final treatment method. The burn wounds were covered with continuous or mesh grafts (1 : 3). In 36 patients, the first dressing after the wound debridement was allogeneic skin, in 10 patients – free split-thickness skin graft (STSG, autogeneic system).

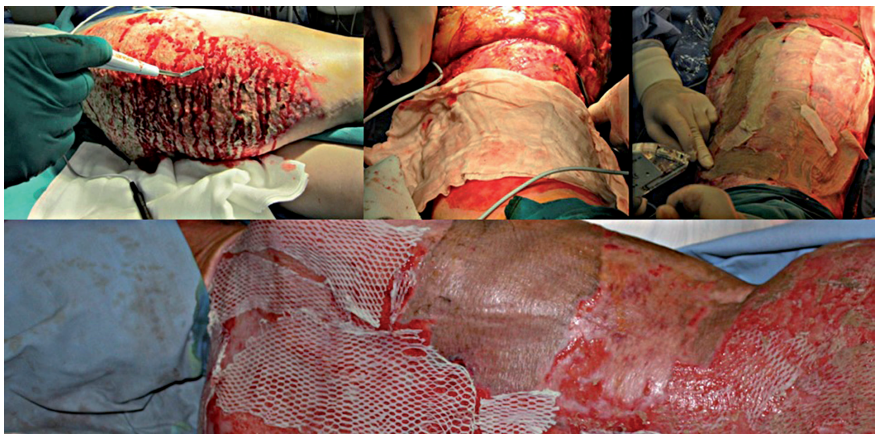

Fig. 1. On the upper left – tangential excision of necrotic tissue with VersaJet device. In the middle – deep necrosis resection, on the upper right – allogeneic skin dressing placed on the wound after the resection. On the lower left – multiple autologous application

Table 2. Description of study groups

Group no.	Group description
I	Patients whose wounds after the resection of necrosis were covered with allogeneic skin dressings (Fig. 1): in 33 patients, allogeneic skin was applied one time (average 35% TBSA, 18% III/IV), twice in 7 patients (average 27% TBSA, 15% III/IV; all males), three times in 1 patient (60% TBSA, 16% III/IV; male) and 4 times in 5 patients (average 35% TBSA, 5% III/IV; all males). Age did not vary more than 10 years between groups.
II	Patients whose wounds after the resection of necrosis were covered with free autologous split-thickness skin grafts (STSG): in 13 patients skin was applied one time (average 34% TBSA, 17% III/IV), twice in 6 patients (average 36% TBSA, 20.4% III/IV; 3 females), three times in 9 patients (average 44% TBSA, 21% III/IV; one female) and 4 times in 5 patients (average 30% TBSA, 10% III/IV; all males). Age did not vary more than 7 years between groups.
III	Patients whose wounds after the resection of necrosis were covered with allogeneic skin dressing, and in the next stage of treatment were finally closed with autologous split-thickness skin grafts (STSG): 12 patients (average 37% TBSA, 18% III/IV, 4 females).

In the paper, the therapy results for two groups of patients have been compared with a third group of patients who had both the autologous and allogeneic skin graft to emphasize the difference (Table 2).

Every day, the patients were examined by a doctor. The progress of healing and final healing of burns under the dressing were assessed. Photography documentation was taken during every visit, and in the case of signs of wound infection, microbiological diagnostic procedures were performed. Before and after the operations, all patients were treated with LMWH as prevention against thromboembolism, analgesics (NSAIDs, tramadol, opioids), as well as antibiotics, in accordance with the therapy standards of the Centre for Burns Treatment in Siemianowice Śląskie. Fluid resuscitation was also performed. The analysis included the number and cause of deaths during the hospitalization, total hospitalization time, number of allogeneic and autologous skin grafts in the patients in the study group and time from admission to surgical necrosis resection. The total hospitalization time was compared between the patients who were initially treated with allogeneic skin and the patients treated with autologous skin graft intended as the final wound closure. Pain was assessed by VAS scale. After the treatment, the patients with healed wounds were sent home or moved to a rehabilitation ward. The analysis included the relationship between the length of hospitalization and the number of allogeneic skin dressings, the relationship between the time from admission to debridement of the necrotic tissues and the total length of hospitalization. Statistical analysis encompassed also pain assessment and the comparison of the total hospitalization time in the groups of patients treated with allogeneic skin dressing initially after the debridement and free autologous split-thickness skin graft right after the debridement. Soft endpoints were used to help carry out the study.

Results

The analysis of the results showed a strong correlation (r = 0.76) between hospitalization time and number of free STSGs (Table 3). The correlation between the length of stay in the Centre for Burns Treatment and number of allogeneic skin grafts shows that there is no relationship between those quantities (r = 0.19).

Table 3. Analysis of dependencies between the chosen parameters

No.	Dependency	Spearman's rank order correlations	p-value
1	Hospitalisation time and the number of free split-thickness skin graft (STSG) procedures	r = 0.76	< 0.001
2	Hospitalisation time and the number of allogeneic skin grafts	r = 0.19	0.23
3	Time from admission of the burned patient to the application of allogeneic skin dressing and hospitalisation time	r = 0.06	0.007
4	Time from admission of the burned patient to the application of STSG and hospitalisation time	r = –0.069	0.74

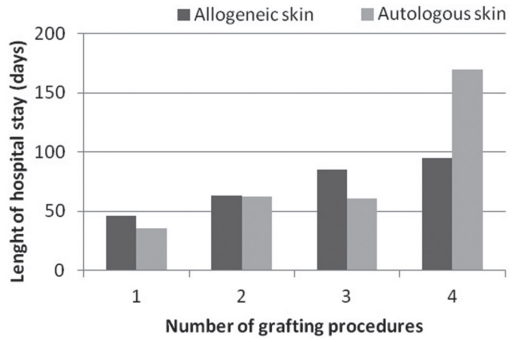

Fig. 2. Dependency between average hospitalization time and the number of allogeneic and autologous skin applications

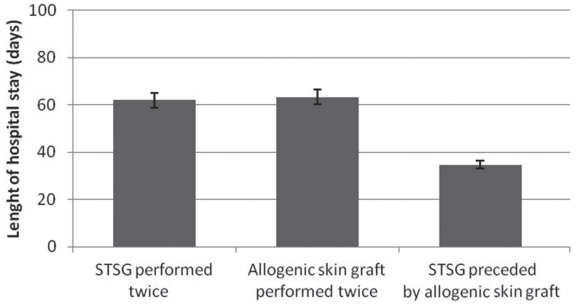

Fig. 3. Dependency between hospitalization length and the number and type of autologous and allogeneic grafts

Consequent application of another split-thickness skin graft results in hospitalization time increase of approximately 44% (Fig. 2).

The result suggests that multiple applications of autografts not only do not lead to quicker recovery, but even lengthen the hospitalization time. The patients' results were equal in the area of TBSA and varied in regards to treatment with allogeneic and autologous skin. The dependency is visible also in the patients who underwent the skin grafting procedure in allogeneic and autologous systems twice (Fig. 3). There was a statistically significant difference between the duration of hospitalization in the group of patients who underwent STSG preceded by allogeneic skin graft transplantation in comparison to the group of patient who had allogeneic skin application ($p < 0.05$) and the group of patients who were grafted with autologous skin ($p < 0.05$).

It has been proven that there is no correlation between hospitalisation time and the time that has passed from the admission of the patient to the resection of necrotic tissues and application of allogeneic skin ($r = 0.06$). There is no relationship with the time from admission to resection of necrotic tissue and application of free split-thickness skin graft ($r = -0.069$). There was a statistically significant difference between duration of hospitalization in the group of patients who underwent STSG

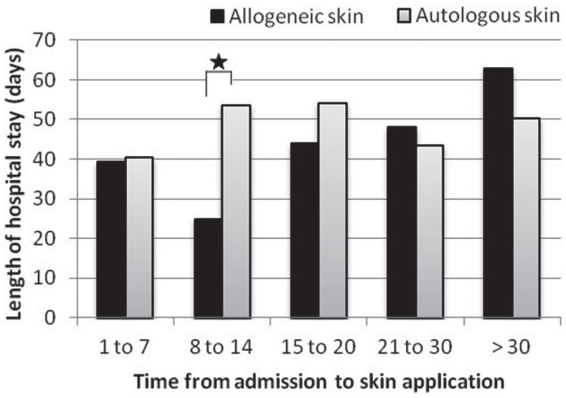

Fig. 4. Dependency between the hospitalization time and time between the admission to hospital and application of the allogeneic or autologous skin

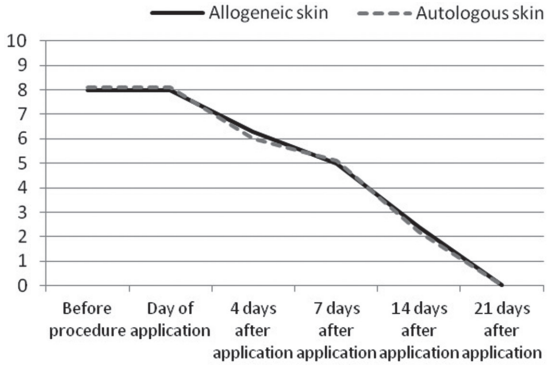

Fig. 5. Pain perception in group of patients who underwent allogeneic and autologous (STSG) skin application

graft transplantation in comparison to the group of patients who had allogeneic skin application only between 8 to 14 days from admission to the allografts' application procedure (Fig. 4). The length of the hospital stay was significantly longer in the group of patients who had STSG in comparison to the patients who had allogeneic skin grafts ($p < 0.05$).

Out of the patients initially treated with allogeneic grafts, there were 10 mortal cases, with the average burn surface area of 50.5%, including 25% of $3^{rd}/4^{th}$ degree. As far as the patients treated from the beginning with autologous skin are concerned, there were 4 mortal cases with the average burn surface area 40%, including 26% of $3^{rd}/4^{th}$ degree. All deaths took place as a result of a multiple organ dysfunction syndrome. There was no relationship ($p \geq 0.05$) between the application of free split-thickness skin graft (STSG) of allogeneic skin and the death of the patients.

There was no statistically significant difference between pain perception in the group of patients who underwent allogeneic skin application in comparison to that of the group of patients who were grafted with autologous skin (Fig. 5).

Discussion

The depth of burn injury is one of the factors determining both the mortality and the manner of treatment [16–18]. The procedure of early resection of necrotic tissue combined with autologous or allogeneic skin graft improved the survival outcomes of the patients [19, 20]. Early resections of necrosis in the burn wound are performed during the first few days after the injury and lead to better survival outcomes [5]. The mortality in the discussed group reached approximately 30%. All mortal cases had respiratory tract burns, which suggest a decisive influence of respiratory tract burns on the survival of the patient. Comorbidities have an impact on the hemodynamic stabilization of the patient, which is a prerequisite for full and split thickness excisions [21, 22]. In spite of the fact that the results suggest that early resection of the necrotic tissue and covering the wound with autologous skin grafts do not shorten the hospitalisation time, the procedure is deemed beneficial due to the removal of dead tissue which stimulates a systemic immune response, prevention of infection by means of temporal or permanent closure of the burn wound, and shortening of the inflammation period thanks to wound closure, which results in the reduction of hypertrophied scars [4, 23]. Surgical resection of the burn wound necrosis is usually performed to the fascia or as tangential excision. The degree of excision is limited by such factors as bleeding and hypothermia. Usually, not more than 20% of the burn area can be excised during one surgical procedure [1]. The open wound is covered by an autologous or allogeneic cryopreserved graft [5]. In adults with burns and no comorbidities, the process is repeated during several surgical procedures, until the whole wound has been debrided [6], which influences the length of hospitalization. The results obtained from the analysis of the study group data indicate a positive correlation between the hospitalisation time and the number of autologous STSG procedures. In the case of allogeneic skin dressings, this correlation is low. Furthermore, average hospitalisation time of the patients treated only with allogeneic skin dressings was 26.5 days, while in the case of the patients with more than 3 autologous STSGs it amounted to as many as 93 days. For patients with over 3 surgeries with STSGs, this dependency is not reflected in total burn surface areas (including $3^{rd}/4^{th}$ degree burns), which amount to 34.1% and 13.8% of $3^{rd}/4^{th}$ degree, respectively. The average surface area of the burn in the patients treated only with allogeneic dressing and not autologous free STSGs was 37.4% TBSA including 19.7% of $3^{rd}/4^{th}$ degree burns. The data shows that, in spite of comparable burn surface areas, multiple application of autologous STSGs leads to longer hospitalisation time in comparison to treatment with allogeneic skin dressings. It is probably caused by the fact that taking several STSGs from the patient generates new donor sites which are a possible infection route and further increase the surface of body without the skin which affects the general condition of patient, and thus also impacts his/her duration of hospitalization. Furthermore, the application of STSGs on an undefined burn injury causes repeated loss of the autologous graft. Cryopreserved skin grafts are a perfect dressing when the wound vascularisation is insufficient. Reepithelialisation of split-thickness skin wounds causes slow the separation of biostatic allogeneic graft without damage to newly formed layer of epithelium, which ensures protection against the microbial proliferation and loss of heat, reducing the hypermetabolic stress response and alleviating pain [24]. On the basis of the results, the author considers the usage of allogeneic dressings as appropriate even on old burns. The application of allogeneic dressing before autologous skin graft shortens the hospitalisation time by on average 27.5 days in relation to the hospitalisation time of patients who underwent autologous skin grafting twice. No differences between pain measured by VAS scale in group of patients who underwent allogeneic skin application in comparison to group of patients who were grafted with autologous skin was observed. However, allogeneic grafts have also some limitations, such as the availability of skin banks, rejection due to religious reasons and safety for the patient [10]. Strict screening tests for virus diseases and standard sterilisation techniques reduce the infection risk. Nevertheless, the risk of transfer of infectious agents still exists [3]. In this study, neither a microbiological analysis nor comorbidities were considered as confounding variables. Those two factors can influence the hospitalization length but they were considered to be a systematic bias. To sum up, the authors emphasize that allogeneic skin graft is definitely the best first-line therapy, as biosynthetic dressings continue to be problematic due to high costs [7] and lower functionality, compared to allogeneic skin. On the basis of the results, the authors think it appropriate to use allogeneic dressings in the case of wounds of uncertain depth or exhibiting signs of progression. It allows the medical practitioner to save the patient's skin and shorten their hospitalisation time, and consequently, reduce treatment-related costs. Autologous skin should not be applied between 8 to 14 days after injury, probably because of the high risk of wound progression, and allogeneic skin more reliable in securing burn wounds

without any risk of losing autologous skin. Since there is no difference in pain perception between autologous and allogeneic skin, authors suggest that best result is given by STSG preceded by allogeneic skin graft, because of the shortest hospitalization time. In the case of a multiple transplantation, a new procedure can be administered – first using the allogeneic skin (especially between first 2 week after injury). Furthermore, STSG will be considered at the second or third stage.

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