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Burns and donor site treatment using allogeneic type I collagen

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Abstract

Introduction. *The search for methods to reduce the time of treatment of burns and wounds of the donor sites currently remains relevant.*

Aim. *Objective of this retrospective study was to evaluate the effectiveness of local treatment of II–IIIA degree burns and donor site wounds with dressings based on allogeneic type I collagen.*

Material and methods*. The study included 434 patients hospitalized in 2018−2021. Collagen dressings were used in 280 patients (234 with II–IIIA degree burns and 46 with donor site wounds); 154 patients of the comparison group received traditional treatment in accordance with the standards of care for burns. Patients did not differ statistically significantly in age and the area of burns (general, superficial, deep). Lyophilized, sterile dressings based on type I collagen (RC No. FSR 2009/06370 December 8, 2014) were manufactured in accordance with TU No. 9393-002-01967081-2008 by the Department for Tissue*

Preservation and Graft Manufacturing of our Institute. We compared the timing of wound epithelialization when using collagen dressings versus the conventional treatment, and the pain intensity in the donor sites as assessed by the visual analogue scale (VAS) for pain.

Results. *The terms of complete epithelialization of II-IIIA degree burn wounds made 10 (7;12) days when collagen-based dressings were used, and 18 (14;20) days without collagen, the difference being statistically significant ($p<0.001$). Epithelialization of the donor site wounds took 9 (8;10) days with using collagen dressings, and 11 (10;12) days with conventional treatment ($p<0.001$). The VAS-assessed pain intensity in the donor site wounds after collagen application was statistically significantly lower on days 1, 4, and 7 than in patients on conventional treatment ($p<0.001$, $p<0.001$, $p=0.003$, respectively).*

Conclusion. *The use of dressings based on type I allogeneic collagen for the treatment of superficial burns and the donor sites reduces the time of re-epithelialization, decreases the pain intensity in the donor site wounds, which proves the greater efficacy of this treatment method.*

Keywords: burns, donor site, collagen, collagen dressing, re-epithelialization

Conflict of interests Authors declare no conflict of interest

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LQ; UQ, quartiles

Me, median

PDGF-BB, Platelet Growth Factor

VAS, Visual Analogue Scale

Introduction

The issues of improving the treatment of both superficial and deep burns remain relevant [1, 2].

With a large area of superficial burns, as well as in elderly patients, self-epithelialization of wounds can be delayed and culminate in the formation of hypertrophic scars. E.A. Deitch et al. showed that in epithelialization within 3 weeks, the scars are formed on the area up to 30% of healed superficial burns. If re-epithelialization lasts for more than 3 weeks, scars form on 80% of the area of the healed skin defect [3].

Currently, a three-degree classification of the burn depth is used, according to ICD-10. First-degree burns represent superficial damage to the epidermis. Second-degree burns include damage to the epidermis up to the basal layer and part of the papillary dermis. The third-degree burns include total damage to the skin and deeper structures. Previously, in the Russian Federation, a four-degree classification was used, in which burns currently classified as the II degree ones were divided into two classes: II degree burns with the damage to the epidermis to the basal layer, and IIIA degree burns with the damage to the epidermis and part of the papillary dermis [4].

Mean healing time is up to 10-12 days for II degree burns, up to 21-28 days for IIIA degree burns [4]. Integration of II degree and IIIA degree burns in one class (the II degree burns) in the ICD-10 classification led to a formal increase in the timing of epithelialization of these burns up to 3-4 weeks. In this study, we considered it most appropriate to apply a four-degree classification of skin burns.

The principal method of local treatment of deep burns is autodermoplasty (i.e. autografting); while the resulting wounds of the donor site are equivalent to IIIA degree burns, according to the four-degree classification, and require treatment. Their re-epithelialization

after taking skin flaps can last for 3 weeks [5, 6]. Traditional methods of treating the donor site wounds are painful, and the prolonged re-epithelialization, as in the case of superficial burns, is in some cases complicated by the development of hypertrophic scars [5, 7, 8].

The search for local treatment methods that reduce the time of re-epithelialization of both burns, and donor sites continues. One such method is the use of lyophilized, human type I collagen. We have previously shown that the use of platelet-derived growth factor (PDGF-BB) enriched type I collagen dressings accelerated the epithelialization of grade IIIA burns [9]. Blood serum of donors with the phenotype AB(IV), Rh-Kell- was used as a source of PDGF-BB, which the dressings were impregnated with before they were applied to the wound. Given the difficulties with the use of native (only after the approval of the Ethics committee) and recombinant (high cost) PDGF-BB, we conducted a study on the use of type I collagen dressings without adding stimulating factors for the treatment of burns and donor sites.

The aim of the study was to evaluate the efficacy of local treatment of II-IIIA degree burns and donor site wounds using allogeneic type I collagen-based dressings.

Material and methods

The retrospective study included 434 patients treated at our Burn Center in the period between 2018 and 2021. Collagen dressings were used in 280 patients: for the treatment of II–IIIA degree burns in 234, for the treatment of donor sites in 46 cases.

The comparison group for patients with burn wounds consisted of 102 patients with similar burns who were treated with atraumatic mesh dressings (conventional treatment). The comparison group for patients

with donor site wounds consisted of 52 patients in whom dry sterile gauze wipes were used (traditional treatment).

The donor sites were the anterolateral surfaces of (one or two) thighs. Of 46 patients, collagen and gauze dressings were applied simultaneously: on one thigh in 5 patients, on both thighs in 4 patients.

The patients (Tables 1 and 2) were comparable in age and the area of burns (general, superficial, deep).

Table 1. Comparative characteristics of patients with burns depending on the method of local wound treatment

Patients with superficial burns	Wound treatment method		p
	using collagen Me (LQ;UQ)	without collagen Me (LQ;UQ)	
Number of patients, n	234	102	—
Age, years	39 (27;58)	47 (31;57)	0.293
Total burn area, %	21.5 (11;31)	30 (8;35)	0.702
Superficial burns, %	20 (8;30)	24 (7;31.5)	0.381
Deep burns, %	3 (2;7)	3 (1.5;10)	0.486

Notes: Me is the median; LQ, UQ stand for quartiles

Table 2. Comparative characteristics of patients with donor site wounds depending on the method of local wound treatment

Patients with donor site wounds	Wound treatment method		p
	using collagen Me (LQ;UQ)	without collagen Me (LQ;UQ)	
Number of patients, n	46	52	—
Age, years	54 (43;68)	46 (39;61)	0.339
Total burn area, %	35 (10;40)	25 (8;35)	0.445
Superficial burns, %	8 (5;25)	13 (2;20)	1.000
Deep burns, %	12 (3;30)	11 (5;15)	0.589

Lyophilized, sterile type I collagen-based dressings (RU No. FSR 2009/06370 dated December 8, 2014) were manufactured in accordance with TU No. 9393-002-01967081-2008 by the Department for Tissue Preservation and Graft Manufacturing of N.V. Sklifosovsky Research

Institute for Emergency Medicine. The tendons and fascia of the lower limb of cadaveric tissue donors were the initial material for obtaining allogeneic type I collagen. Collagen was isolated by acid extraction method. The final concentration of collagen in the solution was 0.7–0.8%. The collagen solution in the amount of 10–12 ml was added on a carboxyl-coated film (substrate) into plastic Petri dishes 12x12 cm and carefully distributed by shaking over the entire surface of the film, after which it was lyophilized in an Ultra-35 lyophilic chamber. The size of the finished collagen dressing was 10x10 cm; the thickness was 100 μm (Fig. 1). Ready-made dressings were sealed in plastic bags and sterilized by radiation treatment at 25 kGy. A bacteriological study of control samples of the dressing after sterilization was performed to control the biological safety.

Fig. 1. View of collagen dressing

In the first two days after burn injury, collagen-based dressings were applied on the IIIA degree burn wounds that were covered then with a mesh atraumatic dressing from above. Subsequent change of dressings were performed every 3–4 days with atraumatic mesh dressings and antiseptic agents until the wounds completely healed. In conventional treatment, the atraumatic mesh dressings with antiseptic agents were

applied to burn wounds at the first dressing, which were changed every 3-4 days until the wounds completely healed.

Collagen-based dressings were applied on the donor site wounds after taking the split autodermal graft; they were covered from above with a dry sterile gauze dressing. In conventional treatment, dry sterile gauze pads were applied on the donor site wounds. The wound dressings were fixed with a sterile gauze bandage in all patients. The first dressing change for the wounds on which collagen dressings were applied, was performed on the 4th–5th day. In conventional treatment, the gauze dressing was not removed from the wounds of the donor site until they were completely epithelialized.

The treatment efficacy was assessed considering the timing of wound re-epithelialization with the use of collagen dressings compared to the conventional treatment. Re-epithelialization was considered complete when the entire surface of the wound was covered with epithelium, and the wound dressing peeled off on its own. In addition, in patients with donor site wounds, the pain intensity was assessed daily for 7 days using a Visual Analogue Scale (VAS).

Statistical analysis was carried out using the Statistica 13.3 software. Descriptive statistics are presented in median (Me) and quartile (LQ;UQ) format. Comparison of continuous data of two independent groups was performed using the Mann–Whitney U-test. The value of $p<0.05$ was taken as the statistical significance level.

Results

Treatment of wounds in patients with superficial burns

After opening the blisters filled with transparent liquid or jelly-like wound discharge and removing the desquamated epidermis, a II-IIIA

degree burn wound (Fig. 2A) represented by a shiny bright pink surface with areas of ischemia was covered with collagen dressings (Fig. 2B).

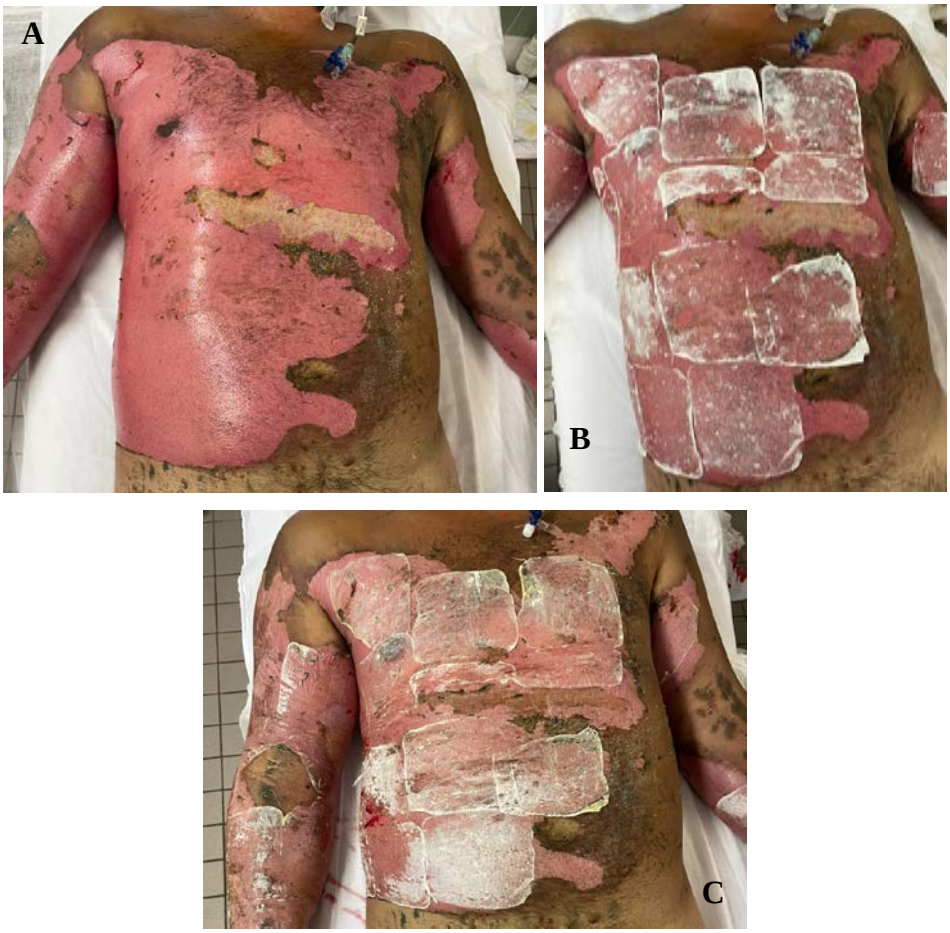

Fig. 2. View of II-IIIA degree burn wounds before (A), immediately after (B), and 3 days after (C) the application of collagen dressings

On the 3rd-4th day, the secondary dressings in the area of the II degree wounds, which were treated with collagen, were dry. The wounds were almost completely covered with a thin newly formed epithelium, and therefore they had a pink matte surface (Fig. 2C, 3A). Secondary dressings in the area of IIIA degree wounds were moderately wet with serous discharge; the surface of the wounds was shiny, pink in color with multiple islands of epithelialization (Fig. 3B).

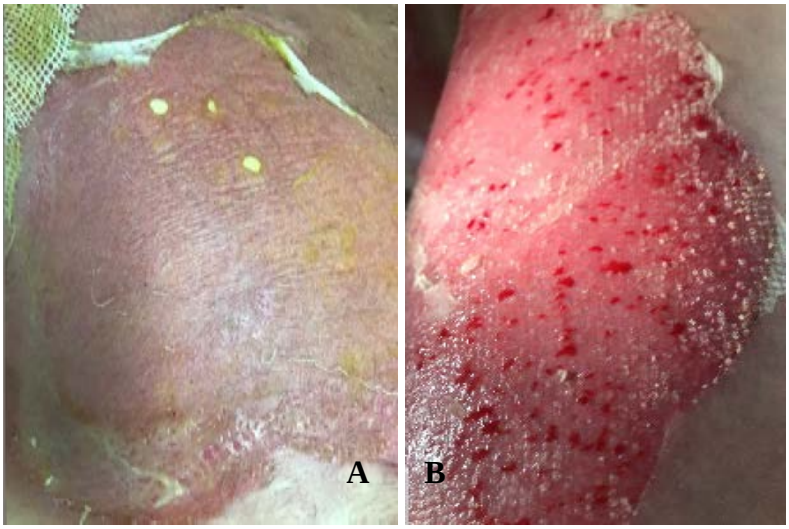

Fig. 3. View of II-IIIA degree burn wounds on the 3rd day after the application of the collagen dressing: A, II degree burn; B, IIIA degree burn

At the same stage, the secondary dressings over the II degree wounds in patients who received a conventional treatment were abundantly wet with serous wound discharge, the surface of the wounds was shiny, pink, devoid of epidermis (Fig. 4A). Secondary dressings over IIIA degree wound were also abundantly wet with serous discharge; the surface of the wounds was shiny, bright pink in color with areas of persistent ischemia (Fig. 4B).

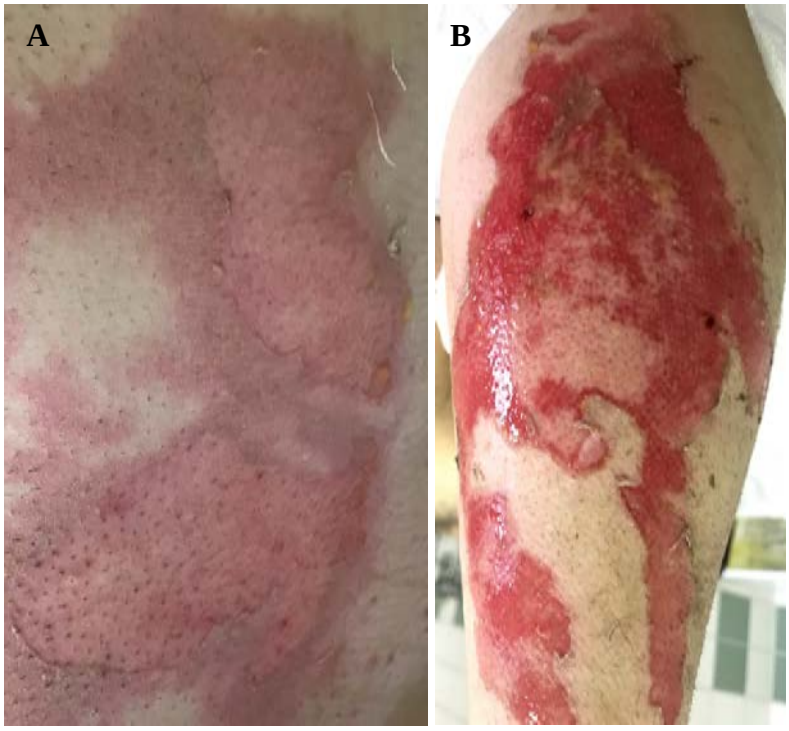

Fig. 4. View of II-IIIA degree burn wounds on the 3rd day with conventional treatment: A, II degree burn; B, IIIA degree burn

In the cases of applying the collagen dressings, the wounds re-epithelialized on days 7–12 in all patients (Fig. 5).

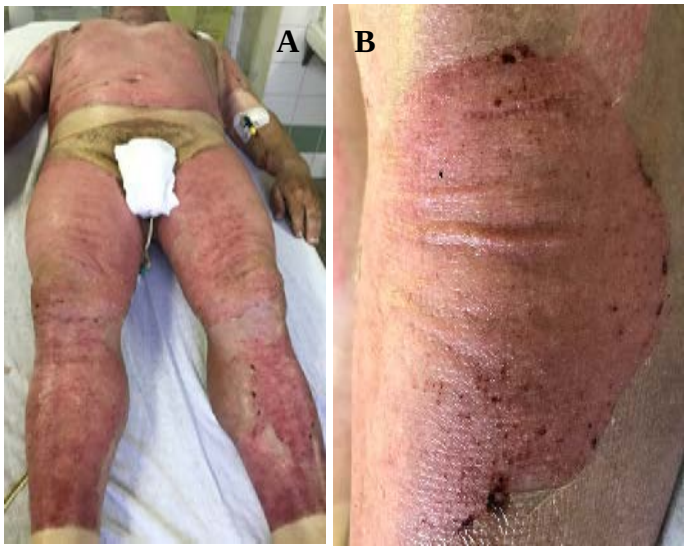

Fig. 5. View of II-IIIA degree burn wounds after the application of collagen on the 7th day: A, B, complete re-epithelialization

On days 7–12 of conventional treatment, fibrin deposits on the surface of burn wounds were noted, a thin scab had been formed in the area of initial ischemia, and only signs of the beginning of epithelialization in the form of islets were seen (Fig. 6). Re-epithelialization of wounds was completed only by the 10–20th day from the moment of injury.

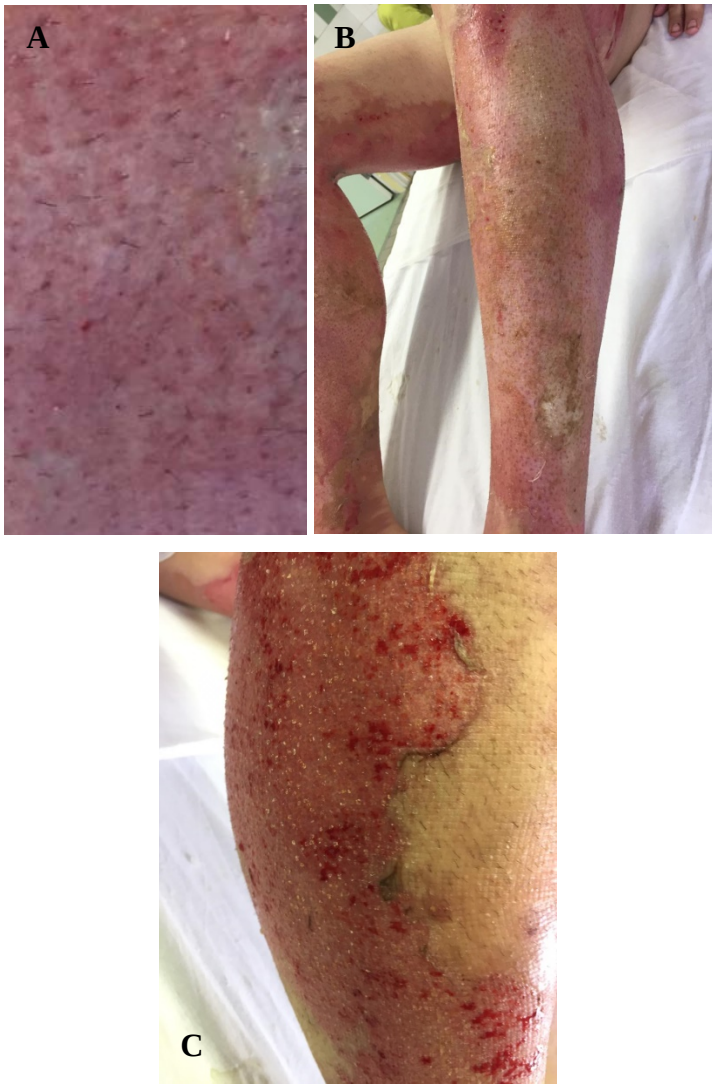

Fig. 6. View of II-IIIA degree burn wounds with conventional treatment on the 7th day: A, the II degree burn wound without signs of epithelialization; B, IIIA degree burn wound with areas of a thin scab; and C, islets of epithelialization

Treatment of donor site wounds

In the operating room, after taking a split skin flap using an electric dermatome with a gap of 0.2–0.4 mm, dry gauze napkins were applied to the inflicted donor site wounds. Bleeding, as a rule, stopped spontaneously within 5–10 minutes and did not require additional methods of hemostasis. Next, we removed the blood-soaked wipes and applied collagen dressings or dry gauze, depending on the method of treatment.

The application of collagen-based dressing on the donor site wounds is shown in Fig. 7.

A

B

Fig. 7. Application of collagen-based dressings on the donor site wounds: A, the donor site wound after harvesting the skin graft; B, collagen-based dressings were applied covering the donor site (the arrow indicates a strip of the donor site left uncovered between the collagen dressings for comparison)

Despite the fact that after applying collagen, we made the first dressing change on the donor site wounds on days 4–5, in several cases we performed it on the 2nd day after the operation (Fig. 8).

Fig. 8. The donor site under the degrading collagen on the 2nd day after its application; the view after the removal of the secondary gauze dressing

After 4–5 days, a blood scab formed on the wound of the donor site covered with collagen. The secondary gauze dressing did not stick to the wound during the change and was easily, painlessly removed.

In conventional treatment, the gauze dressing, soaked in blood, formed a gauze-blood scab soldered to the wound. While change, the dressing was cut off along the contour of the wound, the upper layers of gauze were taken off, the remaining layers were treated with an antiseptic agent and the dressing was left like tat until the wound was completely epithelialized.

At 8–10 days after the operation and collagen application, the secondary gauze dressing spontaneously separated from the wound, and the wound was completely covered with epithelium. Meanwhile, the donor site wound treated in a conventional mode remained at that time under a gauze-blood scab (Fig. 9). The re-epithelialization of the wound

took place under the dressing that removed spontaneously, as a rule, on the 10–12th day.

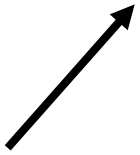

Fig. 9. Day 10 after harvesting the autodermal graft: at the top, there is a re-epithelialized wound of the donor site, on which collagen was applied (the area under the gauze-blood scab was left without collagen; indicated by an arrow); below there is a wound under a dry gauze-blood scab in the process of re-epithelialization

Thus, the period taken for complete epithelialization of II-IIIA degree burn wounds and the donor site wounds under a collagen dressing was statistically significantly shorter (by 1.8 and 1.2 times, respectively) than that in patients who received a conventional treatment (Table 3). Important to note that we observed no suppuration of donor site wounds, either in patients with collagen dressing use, nor in patients in conventional treatment group.

Table 3. Timing of complete epithelialization of superficial burns and donor sites

Type of wound	Timing of epithelialization depending on the use of collagen				p
	Collagen was applied		Collagen was not applied		
	n	Me (LQ;UQ), day	n	Me (LQ;UQ), day	
Superficial burns	234	10 (7;12)	102	18 (10;20)	<0.001
Donor sites	46	9 (8;10)	52	11 (10;12)	<0.001

The VAS assessments (Fig. 10) of pain intensity in the donor site wounds demonstrated the following: on the 1st day, the pain sensations was assessed as 2.5 (2;3) points by the patients who had collagen applied, and as 5 (5;6) points by the patients treated without collagen ($p<0.001$); on day 4, the assessments were 2 (1;2), and 3 (3;4) points ($p<0.001$); on day seven, pain sensations were assessed as 1 (1;1), and 2 (1;3) points in the patient groups, respectively ($p=0.003$) (all comparisons are statistically significant).

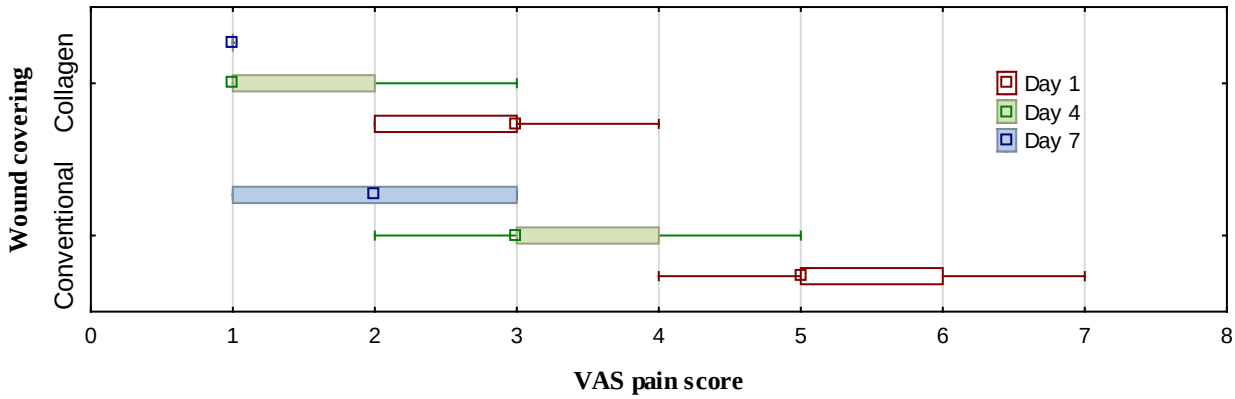

Fig. 10. Pain intensity in donor sites as assessed by the Visual Analogue Scale of pain, with regard of the treatment method

Thus, the patients whose donor site wounds were treated with collagen dressings experienced less pain from the first day after surgery, which allowed them to be more active in the postoperative period. At the

same time, the patients who received a conventional treatment of donor site wounds more often needed painkillers and a sparing regimen.

Discussion

Skin regeneration is the result of the interaction between different skin cells and the extracellular matrix.

In burns with damage to the basal layer of the epidermis, the source of keratinocytes are hair follicles, as well as sweat and sebaceous glands [10].

The extracellular matrix regulates cell proliferation, migration and differentiation [11]. The main structural protein of the human extracellular matrix is type I collagen [12]. The collagen matrix, even without growth factors, initiates the migration of dermal fibroblasts [13].

Treatment with collagen to stimulate re-epithelialization should be started within the first 48 hours after the injury or surgery. The goal is to reduce the intensity of inflammation and prevent the formation of hypertrophic scars. Rational use of time is required so to prevent the reactions causing and maintaining inflammation from reaching their peaks [14]. Therefore, type I allogeneic collagen dressings should be used no later than after 2 days for burns, and immediately after taking the flap for the treatment of the donor site wounds.

We have previously shown that the use of a collagen dressing with PDGF-BB reduced the healing time of IIIA degree burns to 7-9 days [9]. In this study, we used collagen without additional growth factors. The timing of wound epithelialization was almost identical.

In the treatment of deep burns, harvesting a split skin graft that consists of epidermal and dermal tissue creates a donor site wound that requires up to 2 weeks of pain relief therapy and care to heal [15]. A conventional treatment of donor site wounds is performed using gauze

dressings, being the most available means. The study conducted by B. Civelek et al. showed that the period of epithelialization of donor site wounds under a gauze dressing took 10.8 days [16], which is consistent with the epithelialization period in patients who receive the conventional treatment in our study. Meanwhile, the median time of wound healing in the donor sites where the collagen dressings were used was less and amounted to 9 days.

Many patients reported that pain sensations, itching, and discomfort were greater at the donor site than at the autograft site [17]. In the study by S.H. Ki et al., the VAS assessments of pain with conventional treatment made 4.5–6.33 on the 1st day, 2.55–4.33 on the 3rd day, and 1.5–2.5 on the 7th day [18], which is consistent with our findings in the conventional treatment group. In the cases of using collagen on the donor site wounds, the patients experienced lower pain sensations as assessed by VAS at all times after the operation.

The method we used for the treatment of II-IIIA degree burn wounds and the donor site wounds by using allogeneic type I collagen-based dressings without additional biostimulants made it possible to statistically significantly reduce the time taken for their epithelialization, and the pain intensity in the donor site wounds. Pain sensations, as assessed by VAS rating scale, were significantly lower in patients with collagen dressings from the first day of the postoperative period and became minimal from the 4th day, compared to the patients whose donor site wounds were treated in a conventional way.

The application of type I allogeneic collagen-based dressings is a more effective method of treating II-IIIA degree burns and donor site wounds than conventional methods.

Currently, the use of this type of collagen dressings is limited by the low availability of the starting material, and the still remaining

restrictions in legal documents governing the work of medical institutions in Russia involved in the study and use of cadaveric tissues in clinical practice.

Conclusions

1. The use of collagen dressings for the treatment of superficial burns and donor site wounds statistically significantly reduces the time taken for their re-epithelialization (by 1.8 and 1.2 times, respectively).

2. The use of collagen dressings on donor site wounds statistically significantly reduces the patient pain sensations (by 1.5–2 times, as assessed by the Visual Analogue Scale) compared to the conventional treatment in all periods of follow-up.

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5%, data collection according to the study design, documenting the primary results

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