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Improving the effectiveness of the skin integrity restoring after deep burns by platelet–enriched plasma application

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Підвищення ефективності відновлення цілісності шкіри при глибоких опіках шляхом використання плазми, збагаченої тромбоцитами

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Abstract

Objective. To study the effectiveness of platelet–enriched plasma application in patients with deep burns at the stage of wounds preparation for autodermoplasty.

Materials and methods. The study was performed on 23 patients with burns IIA, IIB and III degrees taking 25 – 40% of the body surface. Comprehensive local treatment of patients of the main group included injection of platelet–enriched plasma at the stage of preparation of postoperative wounds for autodermoplasty. In patients of the control group, local treatment was limited by dressings with antiseptic solution. Examination of patients included visual inspection of the damaged area, microbiological examination of wound contents and histological examination of damaged tissues.

Results. Applying the suggested method of burn wounds local treatment resulted in reducing time of wounds preparation for closure by autologous skin grafts, reducing of their healing period, decreasing of tissues inflammatory activity, blood flow improvement, and stimulating processes of tissue granulation, proliferation, epithelialization.

Conclusions. The application of the autologous platelet–enriched plasma can be considered as an effective biotechnology that can increase the effectiveness of the skin integrity restoring in patients with burns.

Keywords: burns; platelet–enriched plasma; wound healing; autodermoplasty.

Реферат

Мета. Вивчити ефективність використання плазми, збагаченої тромбоцитами, у хворих з глибокими опіками на етапі підготовки ран до аутодермопластики.

Матеріали і методи. Спостереження проведено щодо 23 пацієнтів з опіками IIA, IIБ, III ступеня 25 – 40% поверхні тіла. Комплексне місцеве лікування хворих основної групи на етапі підготовки післяопераційних опікових ран до аутодермопластики включало ін'єкційне введення плазми, збагаченої тромбоцитами. У пацієнтів контрольної групи місцеве лікування обмежувалось перев'язками з антисептичним розчином. Обстеження хворих передбачало візуальний огляд ушкодженої ділянки, мікробіологічне вивчення ранового вмісту, гістологічне дослідження ушкоджених тканин.

Результати. При застосуванні запропонованого методу місцевого лікування ран хворих з опіками спостерігали скорочення термінів підготовки ран до закриття аутологічними трансплантатами шкіри та періоду їх загоєння, зменшення активності запальної реакції в тканинах, покращення кровоплину, стимуляцію розвитку грануляційної тканини, процесів проліферації, епітелізації.

Висновки. Використання аутологічної плазми, збагаченої тромбоцитами, можна вважати ефективною біотехнологією, яка дозволяє підвищити ефективність відновлення цілісності шкірних покривів у хворих з опіками.

Ключові слова: опіки; плазма, збагачена тромбоцитами; загоєння ран; аутодермопластика.

Continuous progress in development of new methods for treatment of burns has led to improved care for patients with such injuries, resulting in a 2–fold reduction in the number of serious complications and mortality [1]. However, these achievements have not brought us closer to solve the problems of the care providing in the patients with a widespread, deep burns, which are life–threatening and require long–term complex systemic and local treatment [2]. One of the main stages of such treatment is active surgical tactics, consisting of early necrectomy (during the first days after injury), followed by closure of postoperative wounds with autodermotransplants or the wound dressings. Providing the maximum removal of necrotic tissue is essential to prevent the development of systemic inflammatory response, endotoxemia, sepsis and multiple organ dysfunction. A single step autotransplantation of the skin after early necrectomy is still debated, and it is used mainly and only, when the area of deep thermal damage is small. Application of allo-

geneic skin have sharply decreased recently or was banned in some countries, and xenomaterials, derived mainly from the pig skin, become more widely used [3]. In Ukraine, such xenomaterials are widely used, basing on the fundamental studies results and clinical implementation of domestic lyophilized xenodermoimplants by the team of "Institute of Biomedical Technologies" (Ternopil) [4].

The disadvantage of all these coatings is a temporary nature of their use in the deep burn injuries with the need for further staged surgical closure of granulating wounds. Today, a transplantation of the meshed skin grafts, which have both numerous advantages and serious limitations, especially when the process involves a large area of the body surface, constitutes a standard method of the skin defects repair. In particular, it was found, that in the patients with severe burns, the skin graft harvesting area should not exceed 8 – 12% of the body surface, guaranteeing, that, after preparing of the meshed skin grafts with a ratio of 1:4, the can close the wound, constituting 15 – 20% of the body surface, at best. [5]. Such aggressive tactics, associated with enhancement of the severe burns' wounds surface coverage, using a donor's material, adversely affects the patient's condition, increasing the risk of the anesthesia and postoperative complications. Advances in the cell technology may help to solve this problem. The potential of mesenchymal stem cells, as polypotent units with unique biological properties, cultured human skin fibroblasts, etc. were studied a lot [6].

In addition to high technical requirements, the price, the time, consuming preparation of materials, multi–staged character of interventions, high risk of complications, ambiguous results of use, a number of legal and ethical difficulties limit their application in clinical practice. In recent years, application of a platelet–rich plasma, an autologous product, containing a large number of platelets in a small volume of plasma, has become very popular. There was found, that these cells contain biologically active substances, involved in many physiological processes, including the ability to stimulate the tissue regeneration by releasing the growth factors from alpha granules [7]. Despite positive experience of this biological complex application in various fields of medicine, clear indications and recommendations for its use in patients with deep burns at different stages of treatment still were not developed.

The aim of the study: to assess the effectiveness of a platelet–enriched plasma in patients with deep burns while preparing the wounds for autodermoplasty.

Materials and methods

The study was performed on 23 patients with the IIA, IIB, III degrees fire burns with affection of 25 – 40% of the body surface. All the patients were treated at the Clinical Center for Thermal Trauma and Plastic Surgery of the Vinnytsia Regional Clinical Hospital named after MI Pirogov in the period from 2015 to 2020. The patients were subjected to general (infusion–transfusion, antibacterial, symptomatic therapy), local treatment and surgery (early necrectomy on the 2nd – 3rd day after the injury, xenodermoplasty with subsequent skin restoration in areas of the deep burns by autodermotransplantation).

Local treatment of 10 patients, with average age 48.13 (± 13.29) yrs old, after radical necrectomy and xenoplasty in preparation for autodermoplasty, have consisted of the wound surface processing with 0.02% solution of decamethoxine, followed by closing of the wound with a gauze, soaked in the same antiseptic (main group). On the 2nd – 3rd day after the operation, xenodermoimplants were removed from the area of deep lesions and from the 4th to the 5th day on the periphery and directly into the wound area with an interval of about 1 cm the autologous platelet–rich plasma (PRP) was injected – up to 30 injections of 0.2 – 0.3 ml. The remainder of the drug was applied to the wound defect, which was covered with a two–layer gauze, soaked in an antiseptic solution of decamethoxine at a dose of 0.2 mg / ml, and polyvinyl chloride film, which was fixed with adhesive tape and the gauze bandage.

In 13 patients with a mean age of 47.15 (± 14.75) yrs old, a local treatment of the wounds, regardless of xenocoating, was limited to dressings using the above–mentioned antiseptic solution (control group).

In both groups, dressings were performed daily.

To obtain the autologous PRP immediately before use, 18 ml of the venous blood was taken from a peripheral vein with a Vacutainer® Flashback device (Becton, Dickinson and Company, USA) with a needle size of 21 G in a 9 ml Vacutest® Plast tube (Vacutest Kima srl, Italy) and with sodium heparin 17 IU / ml, then gently stirred the contents in semicircular rotation 4 – 5 times. Subsequently, the blood centrifugation (ELMI CM–6M centrifuge, Latvia) was performed for 15 min at 1,500 rpm, after which 3 layers were formed in vitro: the upper layer of light yellow plasma, the intermediate layer of turbidity and the lower layer of intense red staining with a predominance of erythrocytes. Using a special pipette, the top layer was removed and filled with an insulin syringe, which was used to inject the drug immediately.

Examination of the patients have included a visual inspection of the damaged area with microbiological identification of the pathogen and its semi–quantitative analysis on the 3rd, 6th, 10th, 14th and 21st days after the injury. The approximate number of microorganisms (colony–forming units – CFU) in 1 ml of the wound exudate was determined by the well–known method of sectoral seeding, followed by conversion to decimal logarithms (lg). In addition, a sample of tissue was taken from the wound, 0,5 cm from the edge, for histological examination on the 4th, 8th and 10th day. The material was fixed in a 10% aqueous solution of neutral formalin for at least 48 h, then washed, dehydrated and embedded in paraffin in accordance to the standard scheme. The prepared sections, with a thickness of 5 – 7 μm, were stained with hematoxylin and eosin. Microscopy of histological specimens was performed using a light microscope OLYMPUS BX41 (Ministry of Health of Ukraine, State Reg-

istration Certificate No. 8120 / 2008, code 9011800000) at a magnification of 100 times. The image was visualized using the morphometric program Quickphoto micro 2.3 (license agreement No. 925113924), which allows quantitative analysis of the image by real colors in the image format of 3649 2737 pixels. During the microscopy of histological specimens and the study of digital images, the condition and composition of tissues in the wound, the presence and nature of pathological and reparative changes were evaluated.

The study was conducted in compliance with the patient's safety rules, a human rights law, moral and ethical standards in accordance with the basic provisions of Good Storage Practice (GSP, 1996), the Council of Europe Convention on Human Rights and Biomedicine of 04.04.1997, the Declaration of Helsinki World Medical Association on the ethical principles of conducting of scientific medical research with human participation (1964 – 2000) and the order of the Ministry of Health of Ukraine No. 281 of 01.11.2000, the Code of Ethics of Scientists of Ukraine (2009) and providing the informed consent of patients to participate in the study .

Results

Postoperative wounds on the 3rd day in patients of both groups have remained covered with xenodermoimplants with a moderate exudation of serous–hemorrhagic nature and the signs of inflammatory reaction, spreading to the surrounding intact tissues and accompanied by moderate redness and swelling. Subsequently, xenomaterial was rejected in the areas of deep damage, while the necrotized tissues and signs of inflammatory reaction have remained in the wound, progressively decreasing in dynamics, and the wound surface was filled with granulation tissue. In patients of the main group, the processes of the wound surface cleansing and granulation growth were more active with visually faster attenuation of inflammatory reaction. There were noticeable differences in the granulations structure, which in patients of the main group on the 10th day had a deep pink color, elastic consistency and were actively bleeding even after minor trauma. In patients of the control group, the appearance of granulation tissue had a flaccid consistency and pale pink color. The obvious advantage of injectable use of autologous PRP in the complex local treatment of patients of the main group was the earlier performance of free autodermoplasty with the mesh grafts – (10.4 ± 0.5) days, while in patients of the control group it was possible at (13.8 ± 0.3) days without differences in the rates of engraftment of the transplanted skin, which in both groups were not lower than 80 – 90%, with good fixation and without excessive exudation. Due to earlier performance of primary autodermoplasty, the duration of treatment in general of patients in the main group was reduced to (29.3 ± 0.9) days (*see table*).

The microbiology of the wound surface in patients of both groups on the 3rd day was characterized by a high level of colonization by opportunistic pathogens, which have averaged lg (7.4 ± 0.51) CFU / ml (main group) and lg (7.2 ± 0.43) CFU / ml (control group). No statistically significant differences in the species composition of the wound microbiota during this observation period were found. The species composition was represented by A. baumannii (60.9%), S. aureus (47.8%), P. aeruginosa (26.1%) in monoculture (56.5%) and in associations (45.5%). During the treatment, in accordance to the standard method, the persistence of microbial load in the wound on the 6th and 10th day to lg (6.5 ± 0.71) and (5.9 ± 0.87) CFU / ml, respectively, was noted.

In patients of the main group on the 6th day of treatment a microbial colonization was determined at the level of lg (5.6 ± 0.46) CFU / ml, which also exceeded its threshold level lg (5.0 CFU / ml), with marked gradual microbial decolonization of the wound on the 10th day lg (4.8 ± 0.86) CFU / ml. In the dynamics, a decrease in number of A. baumannii, S. aureus and P. aeruginosa was observed in both study groups.

After 14 days of treatment in the main group S.aureus was identified on the surface of the wounds of 2 patients, and in the control group – in 3 patients. A.baumannii have colonized the wounds in only 3 patients of the main group, while in the control one – in 6. The total microbial number in the main and the control group was lg (4.3 ± 0.91) and lg (5.3 ± 0.15) CFU / ml, respectively. The wound colonization by Corynebacterium spp. Have occurred in 3 patients of the main group – lg (1.4 ± 0.21) CFU / ml and in 1 patient of the control group – lg (1.5 ± 0.58) CFU / ml. The P. aeruginosa bacteria were isolated from 5 patients of the main group and 4 patients of the control group, but their number on the wound surface on the 14th day did not exceed lg (5.1 ± 0.24) and (5.4 ± 0.34) CFU / ml, respectively.

On the 21st day, the wound surfaces settlement of Corynebacterium spp. in the main group by 80%, in the control – by 43.5%, the microbial count of which was lg (1.5 ± 0.76) CFU / ml. In addition, patients in the main and control groups have retained colonization of P. aeruginosa at the level of lg (1.2 ± 0.68) and lg (1.1 ± 0.26) CFU / ml, respective-

Clinical criteria for the course of the wound process in patients of the studied groups

Groups	Terms of observation of clinical criteria, days					
	normalization of body temperaturea	subjective decrease in pain intensity	cleaning the wound from pathological layers	appearance of granulation tissue	performing primary autodermoplasty	wound healing
Main	5,9±0,7	7,1±0,5*	7,3±0,2*	5,2±0,2*	10,4±0,5*	29,3±0,9*
Control	8,4±0,9	10,9±0,3	10,5±0,4	7,1±0,3	13,8±0,3	35,5±0,8

Note. * - statistically significant difference between the indicators of patients in the study groups ($p \leq 0.05$).

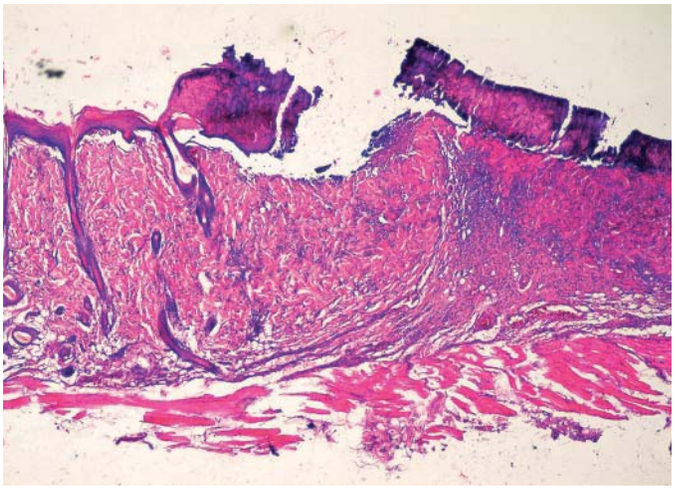

Fig. 1. Microphoto.
Microscopic changes in the skin of patients in the control group on the 4th day of observation.
Staining with hematoxylin and eosin. × 100.

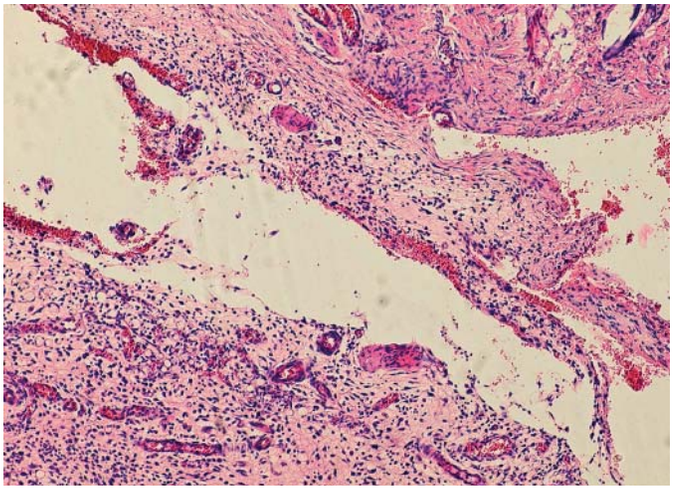

Fig. 2. Microphoto.
Microscopic changes of skin of patients of the main group on the 8th day of observation.
Staining with hematoxylin and eosin. ×100.

ly, and in 1 patient of the control group – even more, and with colonization of A. baumannii in the amount of lg (1.8 ± 0.35) CFU / ml. The rest of the patients did not show the growth of microorganisms during bacteriological examination of the material from the wound surface.

Histological examination on the 4th day in patients of both groups after removal of xenomaterial have revealed the tissues necrotized and sometimes a thin wound scab, as well as minor coagulation changes of the adjacent dermis, owing the skin appendages (hair follicles, sebaceous glands). There was a pronounced edema, defibering of collagen and elastin fibers of the deeper layers of the dermis, and the signs of moderate hypodermic edema. The inflammatory cell reaction was diffuse and was presented mainly by segmental leukocytes and lymphohistiocytic elements. The signs of the microhemocirculation disorder in the form of dilatation and stagnant plethora of vessels with signs of a sludge phenomenon of erythrocytes in some vessels were noted (*Fig. 1*).

On the 8th day in patients of the main group, whose local treatment have included application of autologous PRP, an intensive cleansing of postoperative wounds with subsequent development of granulation tissue was determined. Minor coagulation changes of the adjacent dermis, owing the skin appendages (hair follicles, sebaceous glands) persisted. Coagulation changes were not detected in the deeper layers of the dermis, instead there was a slight edema, defibering of collagen and elastin fibers of the deeper layers of the dermis, as well as the signs of moderate hypodermic edema. The inflammatory cell reaction was focal and was represented by lymphohistiocytic elements and a small number of segmental leukocytes mainly. Moderate microcirculatory disorders continued to be detected (*Fig. 2*).

At the same time, histological examination of damaged tissues in patients of the control group have shown, that the wounds cleaning process was slower, than in patients of the main group. Minor coagulation changes of the dermis in the form of a thin strip of necrotized tissues continued to be detected, while in the deeper layers of the dermis – a pronounced edema, defibering of collagen and elastin fibers, signs of moderate hypodermic edema. In patients of the control group, the inflammatory cell reaction was diffuse in nature and was manifested by a large number of segmental leukocytes and fewer lymphohistiocytic elements, compared with the results obtained in the main group. Microcirculatory disorders were pronounced: in the form of dilatation, stagnant plethora of blood vessels, and coordination of erythrocytes in the vessels (*Fig. 3*).

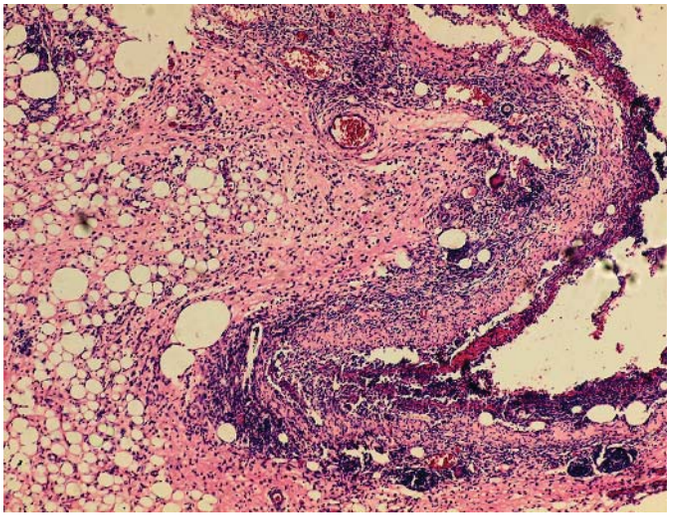

Fig. 3. Microphoto.
Microscopic changes in the skin of patients in the control group on the 8th day of observation.
Staining with hematoxylin and eosin. × 100.

Histological examination of the material in the main group of patients on the 10th day have shown the signs of positive course of the wound process, accompanied by further intensive development of young granulation tissue, somewhere matured with reduction of microcirculatory vessels and proliferation of young fibroblasts. In the deep-

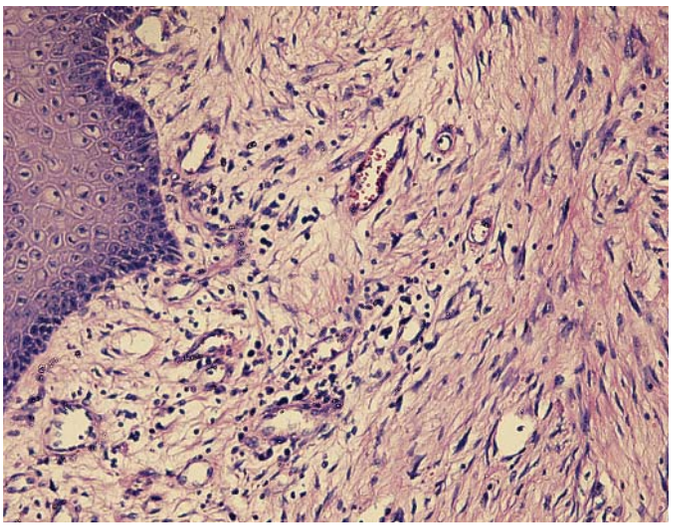

Fig. 4. Microphoto.
Microscopic changes in the skin of patients of the main group on the 10th day of observation.
Staining with hematoxylin and eosin. × 100..

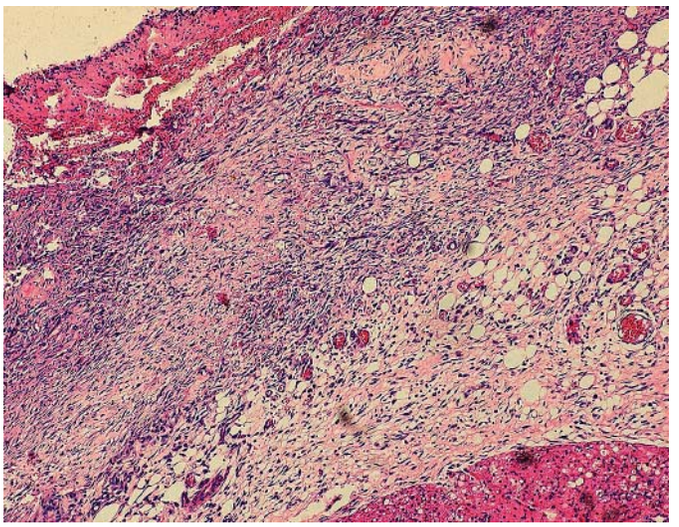

Fig. 5. Microphoto.
Microscopic changes in the skin of patients in the control group on the 10th day of observation.
Staining with hematoxylin and eosin. × 100.

er layers of the dermis, coagulation changes almost did not occur, only a slight edema with defibering of collagen and elastin fibers continued to be detected. At this time, the inflammatory cell response was manifested mainly by small number of lymphohistiocytic elements without signs of the segmental leukocytes presence. Minor microcirculatory disorders in the form of dilated and full–blooded vessels without signs of intravascular sludge phenomenon of erythrocytes have remained. Proliferation of young epidermis with its growth on the edge of the cleared granulating wound was observed on the periphery. The obtained results of histological analysis have confirmed the optimal period to perform autodermotransplantation (*Fig. 4*).

At the same time, in the tissues of the control group patients, who underwent a standard treatment, the process of formation of young granulation tissue was slower without signs of its transformation into a mature form. Reduction of the microcirculatory vessels number and proliferation of young forms of fibroblasts were not observed. There was also more intense swelling and defibering of collagen, elastin fibers of the deeper layers of the dermis, and hypodermic edema. The inflammatory cells reaction was manifested by significant number of lymphohistiocytic elements, with many segmental leukocytes remained. The signs of proliferation of young forms of fibroblasts and epidermis were not determined. In general, the histological picture have indicated incomplete readiness of the wounds for skin transplantation and the need for their further preparation (*Fig. 5*).

Discussion

The consequences of pandemic constraints and the shift in the priority of leading research towards the development of effective methods of prevention, diagnosis, treatment of new coronavirus infection SARS–CoV–2 (COVID–19) have caused a reorientation in the structure of modern medical problems [8]. However, the research in other fields of medicine does not stop. In particular, we are talking about the treatment of patients with deep burns on a large surface of the body [9]. On the basis of the Clinical Center of Thermal Trauma and Plastic Surgery of Vinnytsia region, as well as in other similar specialized hospitals of Ukraine and the world, since spring 2020 there is a steady decrease in the number of hospitalized patients with thermal injuries up to 50% compared to previous years. At the same time, the number of seriously ill patients who need resuscitation support remains unchanged, what indicates the urgency of this problem and the need to find the ways to solve it. Of interest is a new and widely available method of using of autologous plasma for treatment, which after simple processing of native blood by centrifugation contains a significant number of platelets, exceeding a normal level of these cells at least in 3 – 5 times [10]. Despite the relative novelty of the method, having uneven mechanisms of action, the convincing results of experimental studies have contributed to its rapid introduction into various fields of medicine with emphasis on repairing a damaged or lost tissues [11].

Naturally, among the various surgical areas, of particular interest was the possibility for application of such technology in combustiology, where the skin integrity restoration after the action of various aggressive thermal and other factors remains a priority. The results of a number of experimental studies have not made it possible to unambiguously establish the effectiveness of the use of a platelet–enriched plasma in the treatment of burns [10]. According to many researchers, the reason for this may be differences in the plasma preparation technology, way of administration, frequency and duration of use, features of application depending on each stage of the wound process [12]. To avoid these discrepancies, a similar study was performed, which have involved the injection of autologous PRP, obtained by one of the sim-

plest methods of single centrifugation without special tools in a group of patients with a certain area and depth of damage in preparation for primary autodermoplasty. The results of our own research have confirmed the effectiveness of this method in the local treatment of the wounds in patients with burns, as evidenced by reduction of time for preparation of the wounds for closure by autologous skin grafts, reducing the healing period and length of hospital stay.

Despite numerous reports of antimicrobial properties of autologous PRP due to presence of the immune complexes, leukocytes and platelets, which, according to the authors, sometimes not inferior to some antiseptics, in the study a statistically significant differences between qualitative and quantitative indicators of microbial environment were not established, although patients in the control group had relatively worse microbiological parameters. A possible reason for the differences between the obtained results of microbiological examination and the existing ones may be the systematic topical use of antiseptic solution, based on decamethoxine in daily dressings, which, despite increasing resistance among clinical strains of microorganisms, retains high antimicrobial properties with minimal cytotoxic action.

A convincing argument was the results of histological examination of tissues in the area of injury, which have objectively confirmed the ability of the injected autologous PRP to reduce the activity of inflammatory response, improve the blood flow, stimulate the granulation tissue, and at a later date – to promote proliferation of young fibroblasts and even epidermis.

In general, it is useless to believe that with the independent application of this method, despite its many advantages, you can solve the problem of treating patients with critical burns. Also questionable are the results of studies, which convince for potential possibilities of the autologous PRP application to restore a lost skin in dermal burns on a large area of the body surface, eliminating the need for standard autodermoplasty. It would be more correct to assume the expediency of using autologous PRP in deep burns only as a complementary effective stimulator of the processes of healing, engraftment and growth of the skin grafts. Due to the reduction of the duration of active inflammatory response in the wound, long–term results are also improved as it prevents pathological scar growth and neuropathic pain in these areas, which were described in other studies [14].

Conclusions

Application of autologous PRP may be considered an effective biotechnology that increases the effectiveness of the skin integrity restoration in patients with burns, especially with significant area and depth of damage, providing, in addition to standard tactics, early eradication of the wound infections (S. aureus, A. baumannii) to the level of lg (4.8 ± 0.86) CFU / ml, starting from the 10th day of treatment, further active colonization of the skin saprophytic normobiota (Corynebacterium spp.) up to 80% on the 21st day of treatment.

The substantiated advantages of this method, along with the simplicity of implementation, affordability and safety, confirms the prospects for its further study with widespread introduction into everyday clinical practice.

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Contribution of each author. Chornopyschuk RM – data collection, article writing; Nagaichuk VI – concept and design of research; Nazarchuk OA – editing the article; Zheliba MD – final approval of the article; Urvan OG – analysis and interpretation of data.

Conflict of interest. The authors declare no conflict of interest.

Consent to publication. All authors have agreed to publish this manuscript.

Ethical statement. All procedures performed in patient studies complied with the ethical standards of the Institutional and / or National Research Committee, as well as the 1964

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