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The Comparative Study of Efficiency of Hyaluronic Acid Based Dressings and Atraumatic Dressings in Local Treatment of Partial-Thickness Burns

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ABSTRACT Partial-thickness burns (II degree according to ICD 10) remain a significant problem in combustiology. New approaches to the treatment of burn patients are associated with a group of modern dressings or skin substitutes based on natural biopolymers. Hyaluronic acid (HA) based polymers which is a natural component of the extracellular matrix, are promising.

AIMS OF STUDY A comparative study of the effectiveness of an atraumatic wound dressing based on a polyamide mesh and hyaluronic acid based wound dressings in the treatment of partial-thickness burns.

MATERIAL AND METHODS The work is based on the observation of 215 patients who were hospitalized in the Burn Department of the Far Eastern Medical Center in 2014–2018. All patients underwent surgical treatment of burn wounds - dermabrasion on days 2–3. To close of the postoperative wound, two types of dressings were used: based on hyaluronic acid (HA), n=61 and atraumatic dressings (AD), n=154. The effectiveness of treatment was assessed in terms of the healing time of burns, the severity of the general and local inflammatory response, and the quality of the restored skin.

RESULTS In the treatment with HA based dressings, burns healed five days faster; the wound healing time up to 21 days was noted in 90.2% of cases, with the use of AD — only in 57.1% of cases. HA dressings required replacement half as often as AD. With the use of HA dressings, the local and general inflammatory response to the burn wound developed less frequently and was managed faster. Resistant microorganisms and colonies with abundant growth, were found in the main group one and a half times less often than in the comparison group. When using HA dressings, the restored skin is much less likely to suffer from hypertrophy and scarring.

CONCLUSIONS Treatment with HA-based wound dressings in patients with partial-thickness burns are more effective than treatment with traditional atraumatic dressing. Biopolymer skin substitutes is optimal for the treatment of partial-thickness burns in the postoperative period, since the frequency of dressings and the likelihood of secondary microbial contamination of wounds decreases, the degree of contamination of wounds with microflora decreases, and favorable conditions are created for the wound process.

Keywords: partial-thickness burns, wound dressings, hyaluronic acid, skin substitutes

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AD - atraumatic wound dressings
HBM - histoequivalent bioplastic material
HA - hyaluronic acid
BS - body surface
WD - wound dressings
EST - early surgical treatment

INTRODUCTION

In the structure of general injuries, burns are in 6th place (2.1–2.4%). Most of the victims are people of working age and children [1, 2]. A special place is occupied by second-degree burns (according to ICD-10), in which not only the epidermis, but also partly the dermis dies, and independent epithelialization is observed on the 18–21st day after the injury. Some authors continue to use the classification proposed at the 27th All-Union Congress of Surgeons (1960), and classify such burns as IIIa degree; in foreign literature, the term "*partial-thicknes sburns*". According to some authors, burns of such depth are correctly called boundary burns [3, 4]. Border burns remain a significant problem in combustiology, as the most common variant of burn injury and present significant diagnostic difficulties, in addition, they are prone to "deepening". Slowed down, more than three weeks, the terms of self-epithelialization of burn wounds are the cause of the formation of hypertrophic scars and cicatricial deformities, especially in childhood [5]. Most experts agree that with borderline burns, early necrectomy in the amount of dermabrasion is indicated, since the removal of dead tissues prevents the inflammatory process in the wound [6]. The standard option for covering wounds after primary surgical treatment is atraumatic wound dressings (AD). They have been used to treat borderline burns since the end of the 20th century and have proven effective compared to wet-drying ointment dressings [7]. With the conservative management of borderline burns using AD, it is far from always possible to achieve wound healing in the optimal time - up to 3 weeks.

Improving and searching for new ways and methods of local treatment of borderline burns remains an urgent task. New approaches to the treatment of burn patients are associated with a group of modern wound dressings (WD) based on natural biopolymers. WD create optimal conditions in the wound for the course of the wound process (moist environment) to maintain the viability of keratinocytes and skin fibroblasts, the migration of immunocompetent cells, and the activation of local defense mechanisms. The authors note that the structure of the material impervious to bacteria and high adhesion to the bottom of the wound of the inner surface prevents secondary infection of the wound. Removal of excess exudate from the wound inhibits the growth of microorganisms.

The main part of clinical and experimental work in this direction is devoted to the study of WD based on collagen and chitosan [8–14]. According to some authors, polymers based on hyaluronic acid (HA), a natural component of the extracellular matrix, are promising [15–21]. In the domestic literature, abstract works were found based on a small number of clinical observations of patients with borderline burns, in the treatment of which WD based on HA were used [21–25]. At the same time, these works do not provide a comparative assessment of the clinical efficacy of WD based on HA, the issue of their barrier properties against pathogenic microorganisms is poorly studied.

Purpose of the study: comparative study of the effectiveness of atraumatic WD based on polyamide mesh and wound dressing based on HA in the local treatment of borderline burns.

MATERIAL AND METHODS

The work is based on the observation of 215 patients who were hospitalized in the burn department of the Federal State Budgetary Healthcare Institution of the Far East Medical Center of the Federal Medical and Biological Agency of Russia (Vladivostok). The study was conducted from January 2013 to December 2015, the duration of observation of patients was from 15 to 35 days during inpatient treatment and 3, 6 and 12 months after discharge.

Criteria for inclusion of a patient in a clinical trial:

— predominance of II degree burns according to ICD-10 (current version);
— time of admission to the hospital less than 6 hours from the moment of injury;
— age from 18 to 60 years;
— the area of burn wounds is from 5 to 15% of the body surface (b.s.);
— burns localization: trunk, upper and lower extremities;
— informed consent of the patient.

Criteria for exclusion of patients from a clinical trial:

— localization of burns on the face, neck, perineum, burns of the rear of the hands and feet;
— the patient has burn shock, burns of the respiratory tract, uncompensated concomitant diseases;
— patient refusal to participate in the study.

In all cases, less than 6 hours have passed since the injury (M=3,2±1,9). The area of burns was determined according to the "rule of the palm" (the area of the palm of an adult is approximately 1% b.s.). Burn depth was diagnosed based on the nature of the thermal agent, characteristic changes in the wound, and diagnostic tests. Patients had burn wounds of various depths from I to III degrees, but II degree burns prevailed and occupied an average of 75.3% of the total area of all wounds.

From among the examined patients, two groups were formed: the main group - 61 people, in whose local treatment biopolymer wound dressing was used, histoequivalent bioplastic material based on HA (HBM), and the comparison group - 154 patients, in whom local treatment was carried out using atraumatic wound dressing based on fabric-based polyamide mesh (AP). Groups were formed by the method of sequential inclusion of incoming victims and those who met the inclusion criteria. Patients were randomized according to the day of admission (even/odd) using the random number method. No differences were found between the main and the comparison group (Table 1).

Table 1

Characteristics of the main and comparison groups

Parameter	Main group, n=61	Group of comparison, n=154	Significance level
Men Women	77,1% 22,9%	68,2% 31,8%	χ2=2,03 p=0,155
Age, years	36,9±10,5	40,8±7,0	t=0,31 p=0,936
Total area, % b.s.	7,9±2,3	8,5±2,5	t=0,18 p=0,859
Second degree burns, % b.s.	6,1±0,9	6,5±1,1	t=0,28 p=0,778
— flame — hot liquid — voltaic arc	49,2% 42,6% 8,2%	52,6% 40,2% 7,2%	χ2=0,33 p=0,568
EST terms, days	2,2±0,4	2,3±0,5	t=0,16 p=0,873

Notes: EST — early surgical treatment; BS — body surface.

The treatment of all patients was carried out in accordance with the clinical recommendations approved at the Congress of Combustiologists of Russia. All patients underwent primary necrectomy in the volume of dermabrasion. Areas of necrotic dermis and the formed scab were removed tangentially in layers to the “bloody dew”, adhering to precision surgical technique to maximize the preservation of viable tissues, leaving a reserve for self-epithelialization. HBM and AD were used to close the postoperative wound.

HBM is a two-layer lamellar nanostructured material consisting of a peptide complex and a HA polymer, the ratio is 9:1. WD has the form of an elastic film 65–350 μm thick with a nanorough surface relief. Under the conditions of the wound process, HBM is destroyed on its own within 7–8 days [15]. To conduct clinical trials, the manufacturer provided the Conclusion of the Federal State Budgetary Institution "CMIKEE" of Roszdravnadzor No. 072-725-684 / 1-14 of 01/27/2014. VOSKOPRAN™ without ointment was used as an AD (manufactured by New Dressing Materials LLC, RU No. FSR 2008/022013 dated 03/17/2015).

Further management of patients was carried out according to the generally accepted method. Dressings were performed every other day, while visually assessing the condition of the wound and coverage. The replacement of WD and AD was carried out as they became contaminated and wound exudate accumulated under them. If there were no signs of a local inflammatory reaction, the coatings were not removed until the wounds were completely healed.

The overall assessment of the effectiveness of local treatment of burns in two groups was carried out according to the most indicative parameter for clinical trials - the healing time (epithelialization) of burn wounds. The period of epithelialization of the burn wound was considered the time interval from the moment of the burn to the formation on most of the surface of the wound, at least 90% of the area, of a young pink epithelium. In the study, this was the duration of inpatient treatment.

To assess burn wounds, we used (supplemented by the criterion "formation of secondary scab sites") a scoring scale for assessing burn wounds of the Department of Thermal Injuries of the Research Institute for Emergency Medicine named after. I.I. Dzhanilidze. The nature of the discharge, the degree of exudation from the wounds, adhesion of the wound bottom to the RP, bleeding of the wound bottom, the presence of marginal (insular) epithelization were assessed. The severity of the inflammatory response was assessed by the number of points. At 12–15 points, it is considered that there is no inflammatory reaction in the wound and the wound process proceeds normally, a lower number of points indicates that the wound process is accompanied by an inflammatory reaction (Yu.V. Yurova, 2014).

To assess the overall inflammatory response of the body, the leukocyte formula was used.

Microbiological samples were taken from the surface of burn wounds in all the studied patients on days 1–14. A swab from the wound surface was carried out using a sterile swab and seeded on an extended set of differential diagnostic media. Species identification and antibiograms of isolated strains were obtained using a semi-automatic microbiological analyzer *Microscan AutoScan* 4 (*Siemens*) and 96 well panels *Rapid Breakpoint Combo Panel* by photoelectric colorimetry.

The quality of the restored skin was assessed using the Vancouver scale *VSS* (*T. Sullivan et al*., 1990) 3, 6, 12 months after the burn.

Statistical data processing was performed using programs *Microsoft Excel* 2016 and *SPSS Statistics* 17. The arithmetic mean was used to describe the data *(M)* and standard deviation *(SD)*, for non-parametric data - the median *(Me)* and quartiles (*Q*25; *Q*75). To assess the statistical significance of differences in the obtained data (p<0,05) used the Pearson criterion χ^2, unpaired Student's t-test, U– Mann–Whitney test.

RESULTS AND DISCUSSION

When evaluating the duration of inpatient treatment, it was found that in the main group, the burn healing period averaged 20 (16; 22) days, in the comparison group, the average wound healing period was 25 (20; 28) days. (U=2164, Z=-6,179, p=0,035). It was found that when using HBM, the healing period of burns was reduced by an average of 5 days (figure).

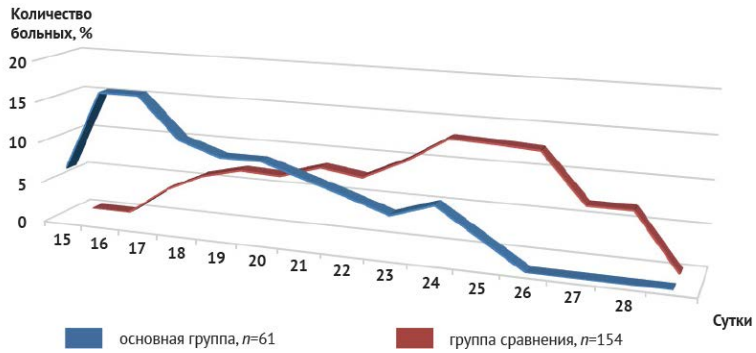

Figure. The terms of burns healing

In the study, 33.5% (n=72) of observations showed delayed wound healing. In 23.7% (n=51) of patients, wound epithelialization was delayed for more than three weeks, in 9.8% (n=21) autodermoplasty of residual wounds was required (Table 2).

Table 2

The terms of burns healing

Burn healing time *	Optimal time (up to 21 days)	Delayed time (more than 21 days)
Main group, n=61	n=55 (90,2%)	n=6 (9,8%)
Comparison group, n=154	n=88 (57,1%)	n=66 (42,9%)

Note: * χ2=23,571, p<0,001

In the main group, delayed wound healing occurs 4 times less than in the comparison group. For the entire course of local treatment, patients underwent from 2 to 12 WD replacements (on average, 6.9 ± 2.6). In the main group, on average, 3.6 ± 1.2 application coatings were performed (HBM formed a "biological scab"), in the comparison group 7.9±1. The local inflammatory reaction in its development corresponded to the stages of the course of the wound process of burn wounds (M.I. Kuzin, 1977). In both groups, by the 10–12th day, an increase in local signs of an inflammatory reaction was observed; on the 15–17th day, the severity of the reaction in the wounds decreased (t=2.15, p=0,033). In the main group, the signs of local inflammation were less pronounced (the number of points was higher) than in the compared group, the differences between the groups were significant (Table 3).

Table 3

Scoring of the local inflammatory response

Day	Main group, n=61	Comparison group, n=154	Level of significance
5–6	13.3±0,7	11.7±0,6	t=1.74 p=0.084
10–12	12.3±0,5	9.4±0,3	t=4.97 p<0.001
15–17	14.2±0,5	11.2±0,5	t=4.24 p<0.001

According to hematological parameters on the 1st–2nd day after the burn, there were no statistically significant differences between the main and the comparison group, the average values were within the age norm. On the 7th day in the main group, a slight increase in the number of leukocytes was noted, but they remained within the upper limit of the norm. (8,5±0,6·10^9/l). In the comparison group, an increase above the norm (12.8±0.8·10^9/l) was noted, which can be regarded as a reaction of the body to the infectious and inflammatory process in the burn wound. Differences between groups are statistically significant (t=3,94, p<0,001). On the 14th day in the main group, the indicator remained at the level of normal values 7.8±0.6·109/l; in the comparison group, it decreased to 11.4±0.7·109/l, but remained above the norm. Differences between groups remained statistically significant (t=4,31, p<0,001). Among the leukocytes, the predominance of neutrophils was noted. On the 7th day in the main group, the absolute number of neutrophils was 4.3±0.3·10^9/l; and in the comparison group — 7.9±0.8 10^9/l (differences are statistically significant, t=4,21, p<0,001). On the 14th day, the differences persisted: in the main group — the absolute number of neutrophils — 4.0±0.2 10^9/l, in the comparison group — 7.2±0.7 10^9/l (differences are statistically significant, t= 4.43, p<0.001). This indicates an ongoing acute inflammatory process in the comparison group.

Bacteriological examination was performed in 32 patients once, in 55 patients twice, in 81 patients three times, and in 47 patients four times. Particular attention was paid to the group of problematic microorganisms *ESKAPE*: mecitilin-resistant *S. aureus*, vancomycin-resistant *E. faecium*, fluoroquinolone-resistant *P. aeruginosa*, carbapenem-resistant *K. pneumoniae*, *A. baumannii* и *Enterobacteriaceae spp*. Given the significant pathogenetic role for burn hospitals, the group included mecitilin-resistant *S. Epidermidis*. In order to determine the share of microorganisms in the structure of microbiocenosis, an index of constancy based on the frequency of occurrence was used, which is a ratio expressed in %: $C=p\cdot100/P$, where p — number of samples containing the studied species; P — total number of samples (table. 4).

Table 4

Comparative characteristics of wounds microflora in patients

Indicator, %	Main group, n=61	Comparison group n=154	Significance level
Microflora growth detected	70,6±5,7	92,0±7,1	t=2,35 p=0,019
Abundant growth of colonies, CFU/ml >105	37,8±10,1	51,1±19,2	t=2,03 p=0,043
Group ESKAPE + S. Epidermidis	30,2±12,4	39,8±20,4	t=2,77 p=0,039

Microbiological studies showed that in the main group the level of microbial contamination of wounds was lower, a smaller number of colonies with abundant growth was found compared to the comparison group. Resistant opportunistic microorganisms of the *ESKAPE* group were also found less frequently in the main group than in the comparison group. Differences are statistically significant.

The formation of the epidermis under the HA-based RP occurred simultaneously in all areas of the burn; significantly less frequently than in the comparison group, zones with hypertrophic growth were recorded. All patients after discharge received standard therapy directed against scar formation (Contractubex gel, physiotherapy, compression stockings). Twelve months after the burn in patients of the main group, the total *VSS* score was 3 times lower than in the comparison group. The greatest difference was noted in terms of plasticity and height of scar tissue; in patients of the main group, it practically did not differ from normal skin indicators (Table 5).

Most researchers consider selective types of necrectomy and closure of burn wounds by various types of WD as the main direction in the search for new methods of treatment of borderline burns. The capabilities of modern technologies make it possible to create complex WDs based on natural polymers that provide prosthetics for skin functions and promote self-healing of defects in integumentary tissues with an acceptable cosmetic and functional result. [6–21].

The greatest experience in the use of WD based on HA *(Hyalomatrix®)* accumulated by Italian authors. The authors report that when using *Hyalomatrix™* in 83% of patients, deep dermal burns healed spontaneously by the 21st day, and post-burn scars that required correction formed only in 4% of patients [21].

In Russia, WD based on HA has been used in the treatment of burns in recent years, while a small amount of clinical material has been accumulated, we found 5 publications, mostly abstracts in conference proceedings, with 92 observations. In the works of Russian authors, it was noted that when using WD based on HA, marginal and insular epithelization accelerated by 5-6 days, and the frequency of purulent complications was 28% lower compared to traditional ointment dressings [16–20].

Our observations showed similar results. Comparing the obtained data with the results of the corresponding works of other authors, we were convinced that the best results were obtained when using collagen-based WD. This is the most expensive of the materials used, characterized by rapid biodegradation in the conditions of the wound process. WD based on chitosan polysaccharide is cheaper and more stable than collagen matrices, but somewhat behind in the rate of wound healing. WD based on HA is somewhat inferior to the latter, but in combination with dermabrasion, they provide epithelialization of borderline burns within an acceptable timeframe, up to three weeks (Table 6).

Table 5

Evaluation of the restored skin by the steady-state volume of distribution

Indicators	3 months *		6 months **		12 months ***	
	Main group, *n*=35	Comparison group, *n*=76	Main group, *n*=31	Comparison group, *n*=69	Main group, *n*=23	Comparison group, *n*=54
Vascularization	1,7±0,13	2,5±0,25	1,4±0,21	2,3±0,17	0,5±0,11	2,0±0,15
Pigmentation	1,5±0,16	1,9±0,23	1,2±0,19	1,8±0,27	1,5±0,11	0,7±0,13
Plasticity	1,3±0,23	1,9±0,17	0,9±0,11	2,3±0,19	0,1±0,01	2,1±0,16
Scar height	0,7±0,06	2,3±0,15	0,5±0,04	2,1±0,27	0,1±0,01	1,3±0,09
Sum of points	5,2±0,15	8,6±0,21	4,0±0,14	8,5±0,23	2,2±0,06	6,1±0,46

Notes: * – t=4.24, p<0,001; ** – t=4.24, p<0,001; *** – t=4.24, p<0,001

Table 6

Comparative characteristics of wound dressings in terms of the healing time of burns

Wound coating	The matrix	Terms of epithelialization of burns (days)	Авторы
Biobrane™	Collagen	11,8	*J.E. Greenwood*, *J. Clausen*, *S. Kavanagh* (2009) [14]
Carbosil-P + type I collagen	Collagen	7,0	M.Sh. Khubutia, S.V. Smirnov, V.B. Khvatov et al., 2012 [13]
COLLOST ™	Collagen	12,0–15,0	L.I. Budkevich, V.I. Kovalchuk et al., 2018 [12]
Biocol	Chitosan	9,0±1,6	K.Z. Salakhiddinov, A.A. Alekseev, 2013 [11]
Foliderm-Gel	Chitosan	14,0±1,5	S.F. Malakhov, B.A. Paramonov et al., 2006 [10]
Hitopran	Chitosan	10,0±2,0	A.V. Polyakov et al., 2019 K.A. Filimonov et al., 2017
Hyalomatrix™	Hyaluronic acid	11,9	*C. Longinotti*, 2009 [21].
G-Derm	Hyaluronic acid	15,0±6,2	A.A. Alekseev et al., 2016; N.K. Barova et al., 2016; V.S. Borisov et al., 2016; E.V. Zinoviev et al., 2016; V.S. Biktashev et al., 2017 [16–20]

CONCLUSION

The study showed that local treatment with the use of histoequivalent bioplastic material in patients with borderline burns is more effective than traditional atraumatic wound dressing. In the treatment of burns with the use of histoequivalent bioplastic material, the latter healed 5 days faster, the terms of wound healing up to 21 days were observed in 90.2% of cases, and when using an atraumatic wound dressing - only in 57.1% of cases. The histoequivalent bioplastic material required replacement 2 times less often than the atraumatic wound dressing. When using a histoequivalent bioplastic material, the local and general inflammatory reaction to the burn wound developed less frequently and stopped faster. Resistant microorganisms and colonies with abundant growth in the main group were found one and a half times less often than in the comparison group. When using a histoequivalent bioplastic material, the restored skin was much less likely to hypertrophy and scarring. Biopolymer wound dressing is optimal for the treatment of borderline burns in the postoperative period, as the frequency of dressings and the likelihood of secondary microbial contamination of wounds are reduced, the degree of contamination of wounds with microflora is reduced, and favorable conditions for the wound process are created.

FINDING

1. Local treatment using hyaluronic acid wound dressing in patients with borderline burns is more effective than traditional use of atraumatic dressings.

2. The use of wound coatings in patients with borderline burns is justified, since the likelihood of secondary microbial contamination of wounds decreases, the degree of contamination of wounds with microflora decreases, and favorable conditions for the wound process are created.

3. Coatings are best used after early surgical treatment, from 2–3 days of admission of the patient to the hospital.

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