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CLINICAL RESULTS OF APPLICATION OF INJECTABLE IMPLANT OF HYALURONIC ACID AND SODIUM SUCCINATE IN COMBUSTIOLOGY

Literary source data analysis indicates a direct impact of Extra Cellular Matrix (ECM) condition on tissue regeneration processes in case of injuries and surgical interventions. In particular, enhancement of fibroblast proliferative activity is accompanied by increased production of glycosaminoglycans (GAGs) - namely, hyaluronic acid (HA) and sodium succinate. That is providing optimal conditions of neocollagenogenesis locally determines the increase of tissue need in HA with specific biological properties. R. Donoff regards the functional significance of a GAG:

—as collagen biosynthesis monitoring;

—direct participation in the organization of fibrous network;

—providing stabilization of collagen fibres.

Thus, wound healing and scar formation process is directly dependent on the ability of tissues to synthesize the sulphate-containing GAGs [1-19]. Modern medical technologies enable realizing the mechanism of direct HA injection in tissues with high needs.

Study objective: assessment of efficacy and tolerability of injectable implant based on 1.5% hyaluronic acid and sodium succinate in pre-filled syringes manufactured by “Yuria-Pharm” LLC in burned patients with donor wounds after autodermoplasty with area of up to 5% of the body surface.

Study tasks:

—to study therapeutic efficacy of the study drug - injectable implant based on 1.5% hyaluronic acid and sodium succinate applicable in burned patients with donor wounds after autodermoplasty;

— to study tolerability and possible side effects/reactions in using the study drug;

— to compare treatment results received in the use of injectable implant based on 1.5% hyaluronic acid and sodium succinate and standard therapy to assess superior drug efficacy compared to standard therapy.

Injectable implant based on 1.5% hyaluronic acid and sodium succinate is a colourful, transparent, cohesive gel of non-stabilized hyaluronic acid of non-animal (bioenzymatic) origin, sterile, pyrogen-free, with a physiological pH. Hyaluronic acid is naturally occurring polysaccharide (glycosaminoglycan), an important structural element of skin and connective tissue. Sodium succinate provides powerful regenerative and antioxidant effect, enhances cellular and tissue respiration, ion transport, protein synthesis, as well as strong stimulation of energy production (ATP) and microcirculation enhancement.

Study design. This clinical study was conducted as open-label comparative single-group. The design assumed to enrol one group of patients (study drug and reference treatment were used in every patient simultaneously on the wound surface, conditionally divided into two equal parts).

This clinical study was conducted in accordance with the Law of Ukraine "On Medicines" and ethical principles of the Declaration of Helsinki. This study was initiated after approval of the clinical trial protocol by the Central Ethics Committee of the Ministry of Health of Ukraine. Patients, as potential study participants were informed of its nature, the study drug, as well as possible risk associated with drug administration. Every patient was presented with written

information about the conducted study, contained in "Patient information". All patients included in the study gave written consent to participate in the trial. Study sponsor provided clinical study insurance and compensation of damage in case of threat to life or health of a patient due to the study drug administration. Data were stored and processed with account of preserving confidentiality of information about patients.

Criteria for inclusion of patients in the study:

— men and women;

— age — 18–65 years;

— patients with donor wounds immediately following autodermoplasty in the treatment of skin burns of IIIA–IIIB degrees without burn disease;

— donor wound area not more than 5 % of skin surface;

— informed written consent of a patient to participate in the study;

— for women of childbearing age – a negative pregnancy test, adhering to adequate contraceptive measures.

Exclusion criteria:

— pregnancy, lactation;

— burn disease;

— known hypersensitivity to any component of the study drug;

— active inflammatory processes in the areas of intended administration;

— tendency to develop hypertrophic scars;

— coagulation failure;

— diabetes mellitus;

— thrombolytic or anticoagulant therapy within 2 weeks prior to the screening visit;

— decompensated concomitant diseases or acute conditions, the presence of which in the opinion of the investigator may affect the study results;

— the need to prescribe inadvisable drugs during conduction of the study;

— participation in any other clinical study.

Scheme of the study drug prescription. The treatment was initiated immediately after autodermoplasty. Donor wound was conditionally divided into two equal parts. Along the perimeter of a half of donor wound (zone A) 1-2 ml of the implant was injected intradermally (depending on the wound area). The drug is administered under the following scheme: 1-2 ml depending on the wound size (but not exceeding) immediately after surgery and after 3 days. Another half of donor wound (zone B) was treated according to a standard protocol: the entire wound surface was covered with a sterile gauze wad and dried with a fan heater till dry scab appeared. The treatment continued until complete wound defect epithelialization, the results of 14-day prescription were considered as the main criterion. At the end of the study the average time to complete healing of burn wounds using various treatments was taken into account. In case of complete epithelialization of the wound defect in less than 14 days the treatment should have been stopped and examination scheduled for the 14th day should have been conducted. During the study, patients could also receive drugs continually used to treat associated diseases. The dose of prescribed drugs should have remained unchanged throughout the whole study period. During the study prescription of agents that could significantly affect the result was not permitted.

To include patients in the study and assess therapeutic efficacy and tolerability of the study drug, patients underwent examination using clinical, instrumental and laboratory methods:

— physical examination: visual examination of a burn wound, burn wound area determination, donor wound area determination, assessment of signs of pathological scarring (intense skin itching, intensity of skin colour, inconsistency of skin surface), severity of inflammation, nature and extent of epithelialization;

— complete blood count (erythrocytes, haemoglobin, white blood cells, erythrocyte sedimentation rate (ESR), platelets);

— common urine analysis (pH, specific gravity, protein, sugar, epithelial cells, leukocytes, erythrocytes, cylinders);

— blood chemistry (alanine aminotransferase, aspartate aminotransferase, creatinine, glucose, total bilirubin);

— general examination: body temperature measurement, auscultation of heart and lungs, palpation and percussion of the abdomen, inspection of skin and visible mucous membranes; registration of subjective complaints;

— pregnancy test for women of reproductive age - before the start of the study;

During visual assessment of burn wound the following parameters were taken into account:

— wound surface area, in % of body surface;

— parameters characterizing reparation

process (severity of inflammatory changes, nature of epithelialization, a degree of epithelialization), expressed in points 0-3;

— parameters characterizing the process of pathological scarring (intense skin itching in the wound area, intensity of skin colour, inconsistency of skin surface), expressed in points 0-3.

The study included the following stages: screening, treatment period (until complete epithelialization of wound defect). During screening period preliminary assessment of patient compliance with criteria of inclusion/exclusion was conducted. Potential patient was presented with oral and written information about the study drug and conditions of the study conduction. Preliminary examination under this protocol was carried out after signing of the patient consent form. During **treatment period** patients received prescribed treatment and underwent examination on specific monitoring days.

Efficacy criteria:

— treatment duration (days) until complete healing of the donor wound.

Efficacy assessment:

— the drug is effective — complete epithelialization of the wound defect;

— the drug is not effective — partial epithelialization of the wound defect and/or presence of complications.

Analysis of the initial group homogeneity. The term "group" in this analysis is conditional, as the study design is single-group. The term "core group" implies the number of cases of the study drug (hyaluronic acid and sodium succinate) application, the term "control group" - the number of cases of the reference treatment application.

Analysis of the initial homogeneity of groups was carried out by clinical and demographic indicators and efficacy indicators.

1. Methods of descriptive statistics to describe the initial state of the core and control groups were used (for quantitative indicators - n, the arithmetical mean, median, standard deviation, minimum and maximum values; for qualitative indicators - rate and percentage, %).

2. For quantitative indicators normality of data distribution has been studied in the groups using Shapiro-Wilk criterion.

If the data in groups by certain indicators were normally distributed, the groups were compared by these indicators using Student's criterion for independent samples (after preliminary check of the homogeneity of group dispersions using Levene's criterion to select Student's criterion option). Otherwise (abnormally distributed data) a comparison of groups using the Mann-Whitney criterion was performed.

3. For categorical indicators groups were compared by Pearson chi-square criterion. If prerequisites of this criterion application are not met, Fisher's exact test was used for comparison.

4. Statistical conclusions about the homogeneity of initial groups on these variables were made.

Work with data was conducted in accordance with the basic principles of data management in order to ensure their integrity and validity. For this purpose data were input in pre-designed Excel spreadsheets, using the principle of "double-entry" and the subsequent cross-validation.

Obtained results and their analysis

The clinical study included 50 patients with burns of IIIA-IIIB degree with area of up to 5% of body surface, who gave written consent to participate in the study and met the inclusion criteria. All patients received a full course of treatment and were included in the analysis of efficacy and tolerability. All patients were hospitalized on the first day of the burn injury and received in-patient treatment in the clinic of the Department of Combustiology, Reconstructive and Plastic Surgery of the Kharkiv Medical Academy of Postgraduate Education on the basis of city hospital of emergency medical assistance named after prof. I. Meshchaninova.

The study group consisted of 32 (64%) men and 18 (36%) women aged 18 to 65 years. The mean age was 43.47 years. Distribution of the studied patients by age and sex is shown in Tab.1.

All patients were hospitalized for skin burns of IIIA-IIIB degree. All burns were localized, patients with burn disease were not included in the study. In part of patients in both groups combined lesions were determined (shin - foot, shoulder - forearm - wrist, etc.). By localization burns were distributed as follows (Tab.2).

Table 1. Patients distribution by age and sex (%)

Age, years	Men)	Women
18-25	8(16)	3(6)
26-35	7 (14)	6 (12)
46-55	11 (22)	5 (10)
56-65	6 (12)	4 (8)

Table 2. Patients distribution by burn localization

Burn localization	Number of patients (%)
Wrist	8 (16)
Forearm	8 (16)
Shoulder	10 (20)
Corpus	9 (18)
Thigh	9 (18)
Shin	6 (12)

Patients included in the study had thermal and chemical burns. Patients with concomitant trauma, blood loss, presence of symptoms of poisoning by combustion products, or burns of the upper respiratory tract were not included in the study.

Autodermoplasty on the area of 0.2 to 5% of body surface was performed in the study group. The average area of donor wound in group of patients was 1.93% of body surface. The largest percentage (86%) consisted of patients, whose donor wound area was up to 3% of body surface. Distribution of the studied patients by donor wound area is presented in Table 3.

During physical examination a slight increase in heart rate (HR) and blood pressure (BP), the lability of pulse and blood pressure, in some patients - a slight increase in temperature were revealed. Skin and mucous membranes outside the affected areas were clean, peripheral oedema were not observed. Daily diuresis in all patients was within normal limits. Also during examination patients with comorbidities requiring changes in treatment regimens or preventing further participation of patients in the study were not revealed. Initial results of assessment in group of patients according to physical examination using methods of descriptive statistics are presented in Table 4.

Table 3. Patient distribution by donor wound area

Donor wound area, % of skin surface	Number of patients (%)
Up to 1	15 (30)
1-2	16 (32)
2.1-3	12 (24)
3.1-4	5 (10)
4.1-5	2 (4)

Laboratory blood and urine tests conducted prior to the clinical study revealed in some patients increased erythrocyte sedimentation rate, white blood cell count. Data of laboratory tests are presented in Table 5-7.

Thus, the clinical study included 50 patients with donor wounds after autodermoplasty from 0.3 to 5% of the body surface, who met the inclusion criteria and gave written consent to participate in the study.

Data obtained during the study. In accordance with the protocol, treatment was initiated immediately after completion of autodermoplasty (see above). The treatment continued until complete wound defect epithelialization, the results of 14-day treatment were considered as the main criterion. Additionally, patients were prescribed infusion-transfusion therapy, if necessary - analgesics and symptomatic therapy agents.

Evaluation of donor wound condition in dynamics.

During the study, donor wound condition was observed on days 3, 7, 10 and 14. Clinically, in patient donor wound area different clinical picture was observed in compared zones starting with 7th day of treatment. Thus, on the 7th day of treatment the appearance of marginal epithelization was observed in zone A (implant injections), whereas dermal scab preservation was observed in zone B (standard therapy). Further, more pronounced wound defect epithelization was observed in zone A compared to zone B in all observation points. Quality of regenerated skin surface on the 14th day of treatment in zone A was different from the one in zone B: characteristics of vegetative activity peculiar to pathological scarring were significantly less pronounced in zone A. The results of donor

wound examination presented in categorical scale are shown in Tabs 8, 9.

Assessment of treatment duration (days) until complete healing of donor wound. Treatment continued until complete epithelization of donor wounds. Upon completion of the treatment course average duration of treatment in groups was assessed. Analysis of average treatment duration by descriptive statistics methods is presented in Tab.10.

Table 4. Initial assessment results according to the data of physical examination using descriptive statistics methods prior to treatment (n = 50)

Indicator	Arithmetical mean	Median	Standard deviation	Min.	Max.
Heart rate	86.9	86.0	9.765	70.0	104.0
Systolic blood pressure	129.1	124.0	12.408	95.0	150.0
Diastolic blood pressure	87.7	84.0	9.863	65.0	110.0
Body temperature	37.2	36.9	0.322	36.5	37.4

Table 5. Indicators of descriptive statistics for parameters of complete blood count (m = 50)

Indicator	Statistical indicators				
	Arithmetical mean	Median	Standard deviation	Min.	Max.
Erythrocytes	4.21	4.0	0.192	4.05	4.62
Haemoglobin	125.6	122.0	6.655	108.0	139
Leukocytes	9.39	8.7	0.445	5.9	15.3
Erythrocyte sedimentation rate	15.56	15.4	1.874	9.0	29.0

Table 6. Indicators of descriptive statistics for parameters of blood chemistry (n = 50)

Indicator	Statistical indicators				
	Arithmetical mean	Median	Standard deviation	Min.	Max.
ASAT	0.37	0.32	0.632	0.27	0.59
ALAT	0.32	0.30	0.526	0.22	0.49
Glucose	4.16	4.2	0.346	3.42	5.13
Creatinine	85.4	86.0	6.461	68.0	91.0

Tolerability assessment.

The results of physical examination data analysis

Physical examination of patients was performed on days 3, 7, 10, and 14 to assess treatment tolerability : examination of skin and visible mucous membranes, measurement of body temperature, heart rate and blood pressure, assessment of subjective complaints. During the study no negative changes in hemodynamic parameters were detected, initially increased heart rate and blood pressure in some studied patients

gradually decreased reaching normal values by the 3rd-4th day of treatment. Increased body temperature in some patients also normalized by the 2nd-3rd day of treatment. Analysis of hemodynamic parameters by descriptive statistics methods is presented in Tab.11.

During physical examination no pathological changes were detected in any case. During skin examination no negative changes associated with the study drug administration were detected. Patients did not report pain increase or burning in the wound or surrounding skin areas after injections of the study drug.

There were no reports of any unpredictable reactions, acute states or exacerbation of chronic diseases.

The results for each variable were converted into categorical scale with categories of "norm/pathology". Descriptive statistics indicators for variable conversion in each group and for every visit (rate and percentage, %) are presented in Tab.12.

The results of laboratory data analysis

Upon termination of treatment course, laboratory blood and urine tests were repeatedly performed. Good treatment tolerability was confirmed by laboratory findings. Changes in laboratory parameters corresponded to a normal course of wound process - there was a tendency to a decrease in white blood cells in the blood and ESR. No negative changes in laboratory parameters were observed. Assessment data of complete blood count dynamics in group of patients by descriptive statistics methods are presented in Tab.13.

The results for each variable were converted into categorical scale with categories of "norm", "above the norm", "below the norm". Descriptive statistics indicators for variable conversion in each group and for every visit (rate and percentage, %) are presented in Tab.14.

Table 7. Indicators of descriptive statistics for parameters of urinary test (n = 50)

Indicator	Statistical indicators				
	Arithmetical mean	Median	Standard deviation	Min.	Max.
Specific gravity	1020.3	1017.0	3.513	1014	1025
Protein	No				
Leukocytes	Single per field of view				
Erythrocytes	Single per field of view				
Cylinders	No				
Glucose	No				

Assessment data of blood chemistry dynamics in patient populations by descriptive statistics methods are presented in Tab. 15.

The results for each variable were converted into categorical scale with categories of "norm", "above the norm", "below the norm". Indicators of descriptive statistics for variable conversion in each group and for every visit (rate and percentage, %) are presented in Tab. 16.

Indicators of common urine analysis also did not undergo negative changes, being within the normal range. Results on each variable were converted into categorical scale with categories of "norm", "above the norm", "below the norm". Descriptive statistics indicators for variable conversion in each group and for every examination (rate and percentage, %) are presented in Tab. 17.

In order to select criterion to evaluate the significance of differences in laboratory parameters for $T_{day\ 1}$ compared to $T_{day\ 14}$, the normality of distribution $dT = T_{day\ 1} - T_{day\ 14}$ was checked using Shapiro-Wilk criterion.

As the differences were normally distributed, comparison of values for $T_{day\ 1}$ and $T_{day\ 14}$ was performed using paired Student t-test (Tab. 18).

Conclusion: for most laboratory parameters there are no significant differences between visits. There are statistically significant differences between visits only in terms of "white blood" and "ESR" indicators.

Table 8. Result distribution in zone A (n=50) according to assessment of donor wound condition, expressed in categorical scale

Indicator	Sign pronouncement	Rate, absolute number				
		Day 1	Day 3	Day 7	Day 10	Day 14
Degree of wound epithelialization	0 — complete epithelialization	-	-	12	39	50
	1 — more than 50 % of	-	-	15	11	-
	2 — from 25 to 50 % of	-	-	23	-	-
	3 — less than 25 % of	50	50	-	-	-
Nature of epithelialization	0 — entire	-	-	12	36	50
	1 — marginal and insular	-	-	30	14	-
	2 — marginal	-	50	8	-	-
	3 — no epithelialization	50	-	-	-	-
Inflammatory changes in the wound and surrounding tissues	0 — no	-	-	12	19	27
	1 — insignificant	-	10	15	28	22
	2 — moderate	35	36	23	3	1
	3 — pronounced	15	4	-	-	-
Skin itching in the wound area	0 — no	-	-	-	-	-
	1 — insignificant					41
	2 — moderate					9
	3 — pronounced					-
Inconsistency of skin surface in the wound area	0 — no	50	-			21
	1 — insignificant	-				25
	2 — moderate	-				4
	3 — pronounced	-				-
Intensity of skin colour in the wound area	0 — normal skin colour	-	-	-	-	-
	1 — moderate hyperemia	-				40
	2 — pronounced hyperemia	50				10
	3 — purple-blue colour	-				-

Table 9. Result distribution in zone B (n=50) according to assessment of donor wound condition,expressed in categorical scale

Indicator	Sign pronouncement	Rate, absolute number				
		Day 1	Day 3	Day 7	Day 10	Day 14
Degree of wound epithelialization	0 — complete epithelialization	-	-	-	3	21
	1 — more than 50 % of surface	-	-	2	29	24
	2 — from 25 to 50 % of surface	-	-	22	16	5
	3 — less than 25 % of surface	50	50	26	2	-
Nature of epithelialization	0 — entire	-	-	-	3	21
	1 — marginal and insular	-	-	6	16	29
	2 — marginal	-	31	44	31	-
	3 — no epithelialization	50	19	-	-	-
Inflammatory changes in the wound and surrounding tissues	0 — no	-	-	5	12	19
	1 — insignificant	-	6	15	21	20
	2 — moderate	35	38	30	17	11
	3 — pronounced	15	6	-	-	-
Skin itching in the wound area	0 — no	-	-	-	-	-
	1 — insignificant					24
	2 — moderate					22
	3 — pronounced					4

Inconsistency of skin surface in the wound area	0 — no	50	-			11
	1 — insignificant	-				23
	2 — moderate	-				16
	3 — pronounced	-				-
Intensity of skin colour in the wound area	0 — normal skin colour	-	-	-	-	-
	1 — moderate hyperemia	-				23
	2 — pronounced hyperemia	50				23
	3 — purple-blue colour	-				4

Table 10. Analysis of average treatment duration by descriptive statistics methods

Indicator	Group	Arithmetical mean	Median	Standard deviation	Min.	Max.
Duration of treatment, days	Zone A (n=50)	11.68	12	2.307	7	14
	Zone B (n=50)	15.22	16	2.349	10	19

Table 11. Results of physical examination data analysis in patient population in the study dynamics by descriptive statistics methods (n=50)

Indicator	Time	Arithmetical mean	Median	Standard deviation	Min.	Max.
Heart rate	Day 1	86.9	86	9.765	70.0	104.0
	Day 3	79.6	82	9.524	60.0	94.0
	Day 7	78.5	80	8.988	64.0	92.0
	Day 10	76.2	78	7.779	62.0	90.0
	Day 14	77.3	80	8.156	60.0	92.0
Systolic blood pressure	Day 1	129.1	124	12.408	95.0	150.0
	Day 3	125.6	122	11.578	90.0	145.0
	Day 7	123.8	126	12.580	95.0	145.0
	Day 10	125.7	128	11.167	95.0	150.0
	Day 14	126.0	122	11.654	90.0	150.0
Diastolic blood pressure	Day 1	87.7	84	9.863	65.0	110.0
	Day 3	85.5	82	8.099	60.0	90.0
	Day 7	84.6	85	9.087	65.0	95.0
	Day 10	83.1	87	7.877	65.0	90.0
	Day 14	84.3	86	8.015	70.0	95.0
Body temperature	Day 1	37.2	36.9	0.322	36.5	37.4
	Day 3	37.0	36.8	0.247	36.6	37.2
	Day 7	36.8	36.9	0.239	36.6	37.0
	Day 10	36.7	36.7	0.215	36.5	36.9
	Day 14	36.7	36.6	0.193	36.4	36.8

***Table 12.* Descriptive statistics indicators for the results of abdominal palpation and percussion, skin and mucous membranes examination (rate and percentage, %)**

Indicator	Category	Zone A (n=50)		Zone B (n=50)	
		Day 1	Day 14	Day 1	Day 14
Auscultation of heart and lungs	Norm	50 (100)	50 (100)	50 (100)	50 (100)
	Pathology	0 (0)	0 (0)	0 (0)	0 (0)
Examination of skin and mucous membranes	Norm	50 (100)	50 (100)	50 (100)	50 (100)
	Pathology	0 (0)	0 (0)	0 (0)	0 (0)
Abdominal palpation	Norm	50 (100)	50 (100)	50 (100)	50 (100)
	Pathology	0 (0)	0 (0)	0 (0)	0 (0)

Table 13. **Assessment results of complete blood count dynamics in study group by descriptive statistics methods (n=50)**

Indicator	Time	Arithmetical mean	Median	Standard deviation	Min.	Max.
Erythrocytes	Day 1	4.21	4.0	0.192	4.05	4.62
	Day 14	4.28	4.4	0.425	4.11	4.71
Haemoglobin	Day 1	125.6	122.0	6.655	108	139
	Day 14	128.9	132.0	4.986	116	148
Leukocytes	Day 1	9.39	8.7	0.445	5.9	15.3
	Day 14	7.04	9.2	1.239	4.4	9.7
Erythrocytes sedimentation rate	Day 1	15.56	15.4	1.874	9.0	29.0
	Day 14	9.25	10.3	2.235	5.0	18.0

Table 14. **Distribution by categorical scale for results of complete blood count of patients in dynamics (rate and percentage, %)**

Indicator Category		Day 1	Day 14
Erythrocytes	Above the norm	0 (0)	0 (0)
	Norm	50 (100)	50 (100)
	Below the norm	0 (0)	0 (0)
Haemoglobin	Above the norm	0 (0)	0 (0)
	Norm	50 (100)	50 (100)
	Below the norm	0 (0)	0 (0)
Leukocytes	Above the norm	16 (32)	4 (8)
	Norm	34(68)	46 (92)
	Below the norm	0 (0)	0 (0)
Erythrocyte sedimentation rate	Above the norm	21 (42)	5 (10)
	Norm	29 (58)	45 (90)
	Below the norm	0 (0)	0 (0)

Table 15. Assessment results of blood chemistry dynamics in the core group by descriptive statistics methods (n=50)

Indicator	Time	Arithmetical mean	Median	Standard deviation	Min.	Max.
ASAT	Day 1	0.36	0.37	3.115	0.25	0.53
	Day 14	0.32	0.30	3.137	0.24	0.51
ALAT	Day 1	0.33	0.38	2.931	0.24	0.47
	Day 14	0.29	0.35	2.874	0.21	0.44
Glucose	Day 1	4.03	4.2	0.266	3.50	5.02
	Day 14	4.04	4.10	0.236	3.50	5.14
Creatinine	Day 1	82.8	85.0	6.871	62.0	94.0
	Day 14	79.7	82.5	7.369	57.0	85.0

Information on adverse reactions. During the clinical study no adverse reactions that could be associated with the study drug prescription were reported.

Comparison of tolerability in groups. Thus, tolerability of the study drug was estimated as good in all cases (Tab. 19).

Conclusions:

1. Injectable implant based on 1.5% hyaluronic acid and sodium succinate in pre-filled syringes manufactured by "Yuria-Pharm" LLC exceeds the standard treatment of donor wounds after autodermoplasty in efficacy. Efficacy of treatment when using the study drug on the combination of the studied parameters was 100%, the efficacy of reference treatment - 58%.

Table 16. Distribution by categorical scale for results of blood chemistry in dynamics (rate and percentage, %)

Indicator	Category	Day 1	Day 14
ASAT	Above the norm	0 (0)	0 (0)
	Norm	50 (100)	50 (100)
	Below the norm	0 (0)	0 (0)
ALAT	Above the norm	0 (0)	0 (0)
	Norm	50 (100)	50 (100)
	Below the norm	0 (0)	0 (0)
Glucose	Above the norm	0 (0)	0 (0)
	Norm	50 (100)	50 (100)
	Below the norm	0 (0)	0 (0)
Creatinine	Above the norm	0 (0)	0 (0)
	Norm	50 (100)	50 (100)
	Below the norm	0 (0)	0 (0)

Table 17. Descriptive statistics indicators for urine analysis results (rate and percentage, %)

Indicator	Category	Day 1	Day 14
Specific gravity	Above the norm	0 (0)	0 (0)
	Norm	50 (100)	50 (100)
	Below the norm	0 (0)	0 (0)
Protein	Yes	0 (0)	0 (0)
	No	50 (100)	50 (100)
Glucose	Yes	0 (0)	0 (0)
	No	50 (100)	50 (100)
Leukocytes	Above the norm	0 (0)	0 (0)
	Norm	50 (100)	50 (100)
Erythrocytes	Above the norm	0 (0)	0 (0)
	Norm	50 (100)	50 (100)
Cylinders	Yes	0 (0)	0 (0)
	No	50 (100)	50 (100)
Epithelial cells	Yes	0 (0)	0 (0)
	No	50 (100)	50 (100)

Table 18. The results of laboratory parameters comparison using paired Student t-test

Parameter	t-statistics	P-value (bilateral)	Statistically significant differences*
Erythrocytes	1.121	0.267	No
Haemoglobin	1.379	0.154	No
Leukocytes	5.663	0.000	Yes
Erythrocyte sedimentation rate	17.054	0.000	Yes
ASAT	0.234	0.815	No
ALAT	0.432	0.667	No
Glucose	0.232	0.817	No
Creatinine	1.401	0.118	No

Notes: * — conclusion at significance level 0.05; t_{critic} = 2.0095 at df = 49.

Table 19. Results of the study drug tolerability assessment

Tolerability	Zone A		Zone B	
	Frequency	Percentage, %	Frequency	Percentage, %
Good	50	100.0	50	100.0
Satisfactory	0	0.0	0	0.0
Unsatisfactory	0	0.0	0	0.0

2. Prescription of injectable implant based on 1.5% hyaluronic acid and sodium succinate contributed to reduction of period of the wound defect epithelialization after autodermoplasty Treatment duration until complete healing of the donor wound in application zone of the study drug was 11.68 days, what was far less than in comparison zones - 15.22 days.

3. Prescription of injectable implant based on 1.5% hyaluronic acid and sodium succinate contributed to decrease of vegetative activity of regenerated tissues peculiar to pathological scarring. Pronouncement of pathological scarring indicators (skin itching, intensity of skin colour, inconsistency of skin surface) in zone of the study drug application was significantly less by all indicators compared to control zone.

4. The study drug - injectable implant based on 1.5% hyaluronic acid and sodium succinate in pre-filled syringes manufactured by "Yuria-Pharm" LLC - is well-tolerated by patients and does not cause side effects in case of intradermal administration along the perimeter of donor wound.

5. Injectable implant based on 1.5% hyaluronic acid and sodium succinate in pre-filled syringes manufactured by "Yuria-Pharm" LLC may be recommended for medical use as a product optimizing the treatment of wound defects at levels of papillary and reticular dermis layers with area of up to 5% of the body surface.

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