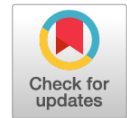


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Morphological aspects of bedsore healing against high-frequency electrical stimulation in patients with severe brain damage

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ABSTRACT

BACKGROUND: Bedsores or decubital ulcers are significant medical and social problems in patients with serious brain damage. The majority of local treatments are ineffective and do not ensure their healing. Therefore, the search for nondrug methods as part of the complex treatment of decubital ulcers is extremely relevant.

AIM: To assess the morphological picture of bedsores against the background of an improved method of treatment using high-frequency electrical stimulation with pulsed currents in chronically immobilised patients who survived a cerebral catastrophe.

MATERIALS AND METHODS: Biopsies of bedsores were examined in 12 patients with severe neurological disorders that developed after a cerebral catastrophe. The initial status of all patients was a 'chronic critical condition' (CCC). In all patients, the bedsore defect was located in the sacral region, with a length of 7–25 cm². The depth of the bedsore corresponded to grade III according to the classification of the Agency for Health Care Policy and Research. Two groups of patients were formed: the main group of five patients (three men + two women), with an average age of 49.0 years, who were subjected to electrical stimulation with pulsed currents of the radiofrequency range. A control group of seven patients (three men + four women), with an average age of 60.1 years, who underwent traditional treatment. The duration of the chronic wound process ranged from 2 months to 1.5 years. The immediate cause of CCC was more often a massive ischemic stroke (8), less often a severe traumatic brain injury (3) and radical operations to remove brain tumours (1) of various prescriptions from 3 months to 1.5 years. Morphological studies were conducted in both groups to assess the complicated wound process.

RESULTS: The complex morphological study revealed that in the presence of high-frequency electrical stimulation, an earlier appearance of foci of fibroblastic proliferation, an increase in the regenerative potential of tissues due to increased production of type I and III collagens, and myofibroblastic and endothelial growth factors were noted.

CONCLUSION: In the case of CCC of cerebral genesis, the wound process in bedsores inevitably becomes complicated and, according to morphological research, is characterised by severe endothelial dysfunction, deep microcirculation disorders, depletion of the potential of myofibroblastic cells and deficiency of their growth factors. Local high-frequency electrical stimulation in patients with severe brain damage and decubital ulcers as a component of complex ulcer therapy significantly optimises cellular and tissue reactions in the area of bedsores.

Keywords: electrostimulation of wounds; bedsores; decubital ulcers; wound process; bedsore ulcers.

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Морфологические аспекты заживления пролежней на фоне высокочастотной электростимуляции у пациентов с тяжёлым поражением головного мозга

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АННОТАЦИЯ

Обоснование. Одной из значимых медико-социальных проблем у лиц, перенёвших тяжёлое повреждение головного мозга, являются пролежни или декубитальные язвы. Большинство средств местного лечения малоэффективны, не обеспечивают их заживления. В связи с этим поиск немедикаментозных методов терапии пролежней как составной части комплексного лечения декубитальных язв чрезвычайно актуален.

Цель исследования — оценка морфологической картины пролежней на фоне усовершенствованного способа лечения — высокочастотной электростимуляции импульсными токами — у длительно иммобилизованных пациентов, переживших церебральную катастрофу.

Материалы и методы. Исследованы биоптаты пролежней у 12 пациентов с грубыми неврологическими нарушениями, развившимися после церебральной катастрофы, и с исходным статусом «хроническое критическое состояние» (ХКС). У всех пациентов пролежневый дефект протяжённостью от 7 до 25 см² располагался в крестцовой области. Глубина пролежня соответствовала III степени по классификации Agency For Health Care Policy and Research.

Сформированы 2 группы: основная ($n=5$), состоящая из трёх мужчин и двух женщин (средний возраст — 49,0 года), у которых применяли электростимуляцию импульсными токами радиочастотного диапазона; контрольная ($n=7$) из трёх мужчин и четырёх женщин (средний возраст — 60,1 года), которым проводили традиционное лечение. Длительность хронического раневого процесса составила от 2 мес до 1,5 лет. Непосредственной причиной ХКС чаще был обширный ишемический инсульт (8), реже — тяжёлая черепно-мозговая травма (3) и радикальные операции по удалению новообразований головного мозга (1) различной давности (от 3 мес до 1,5 лет).

Для оценки осложнённого раневого процесса в обеих группах проведены морфологические исследования.

Результаты. По данным комплексного морфологического исследования на фоне высокочастотной электростимуляции отмечено более раннее появление очагов фибробластической пролиферации, повышение регенераторного потенциала тканей за счёт усиленной выработки коллагенов I и III типов, а также миофибробластических и эндотелиальных факторов роста.

Заключение. На фоне ХКС церебрального генеза раневой процесс в пролежнях неизбежно становится осложнённым и по данным морфологического исследования характеризуется тяжёлой эндотелиальной дисфункцией, глубокими нарушениями микроциркуляции, истощением потенциала клеток миофибробластического ряда и дефицитом факторов их роста. Применение методики локальной высокочастотной электростимуляции у пациентов с тяжёлым поражением головного мозга и декубитальными язвами в качестве компонента комплексной терапии этих язв заметно оптимизирует клеточно-тканевые реакции в зоне пролежней.

Ключевые слова: электростимуляция ран; пролежни; декубитальные язвы; раневой процесс; пролежневые язвы.

Как цитировать

Шулутко А.М., Османов Э.Г., Алтухов Е.Л., Яковлев А.А., Боблак Ю.А., Гандыбина Е.Г., Горбачёва А.В., Паталова А.Р., Хмырова С.Е., Хусаинова Н.Р. Морфологические аспекты заживления пролежней на фоне высокочастотной электростимуляции у пациентов с тяжёлым поражением головного мозга // Российский медицинский журнал. 2024. Т. 30, № 1. С. 7–14. DOI: <https://doi.org/10.17816/medjrf472099>

BACKGROUND

Pressure ulcers are a special form of chronic, long-term nonhealing wounds with various pathogenetic triggers [1]. They accompany many severe post-traumatic conditions and systemic diseases, such as massive stroke, infarction, diabetes mellitus, Parkinson's disease, paraplegia, and inanition [2–4]. The increase in the number of man-made disasters and the globalization of armed conflicts using new weapons cause a snowballing increase in the number of wounded and victims with severe damage to the spinal cord and brain. In the latter, a severe neurodystrophic process inevitably results in the development of multiple pressure ulcers or decubital ulcers (DU) resistant to local therapy [5–8]. Several studies have shown that starting from stage 2, DUs become the main source of surgical infection with a high risk of dystrophic and septic conditions. Mortality among such patients varies widely (21.0%–88.1%) [9, 10].

Local treatment of pressure ulcers takes time and often does not produce tangible results. Most modern physicochemical technologies and means of “hardware” acceleration of the reparative process (RP) have questionable efficiency because of the lack of clear morphological data [11, 12]. The above fully applies to the treatment of pressure ulcers in patients with an aggravated neurological status.

This study aimed to assess the morphological presentation of pressure ulcers in the course of high-frequency electrical stimulation (HFES) with pulsed currents in chronically immobilized patients who survived a cerebral accident.

METHODS

Study design

In this interventional, single-center, prospective, controlled, unblinded, non-randomized study, randomization was performed using the “envelope method.”

Compliance criteria

The study included patients in chronic critical condition (CCC) with persistent neurological deficits that arose after severe brain damage and pressure ulcers in the sacral area. The depth of the pressure ulcers corresponded to grade III according to the classification of the Agency for Health Care Policy and Research (1992). This grade is characterized by a loss of thickness of the integumentary tissue in the zone of constant compression no deeper than the native fascia.

Conditions

A comprehensive morphological assessment of the efficiency of HFES for a complicated wound was performed by a group of researchers, including employees of Sechenov University and the Federal Scientific and Clinical Center for Reanimatology and Rehabilitation.

Study duration

The results were assessed for the period from November 2021 to March 2022. The study is currently ongoing.

Description of the medical intervention

In all cases, local treatment was started with treatment of the DU to remove fibrin plaque, exudates, and necrotic tissues (debriding). Patients were blindly randomized into two groups. In the control group ($n=7$), treatment was performed according to the traditional regimen using conventional antiseptics and polyethylene oxide-based ointments. In the main group ($n=5$), the HFES procedure for pressure ulcers was also performed using a certified electrosurgical device EHVCh-250 (KiKMedimaster, Russia), generating alternating currents in the radio frequency range (0.3–3.0 MHz) with power of 4 W and 4 s of exposure (Fig. 1).

The stimulation session of pressure ulcers was performed using a monopolar needle electrode (0.3 mm in diameter) inserted into the tissue to a depth of 4 mm in appropriate zones: healthy skin around the DU and granulating areas in the bottom of the pressure wound in a checkerboard pattern, at a distance of 0.8–1.0 cm (Fig. 1).

HFES was performed after preliminary sanitation of the DU surface once every 3 days or earlier (according to indications), followed by covering the wound with a non-absorbent bandage.

To assess the complicated wound healing process in both groups, morphological studies were performed before the start of treatment and on days 14 and 28 of treatment. Tissue biopsies from the edges and bottom of the wound (one sample from each zone) were fixed in a 10% formalin solution and then embedded in paraffin. Sections (thickness of 3–4 μm) were stained with hematoxylin and eosin before viewing. For a more detailed characterization of RP activity against exposure to “high” currents, biopsy sample microscopy was supplemented with immunohistochemical (IHC) analysis in three cases. Monoclonal antibodies at a dilution of 1:100 (Santa Cruz Biotechnology, USA) and universal polymer systems N-Histofine® Simple Stain MAX PO (MULTI)



Fig. 1. Stage of high-frequency electrical stimulation of the bedsore.

(Nichirei, Japan) were used. During the IHC analysis, the dynamics of the following RP markers were studied:

- Collagen types I and III.
- Vascular endothelial growth factor (VEGF).
- Smooth muscle actin (SMA) as a biochemical marker expressed by vascular smooth muscle elements and myofibroblasts.

Main outcome of research

The main outcome was the emergence of morphological signs of RPs, namely, neoangiogenesis, polymorphonuclear leukocytes of the interstitial tissue, and fibroblast proliferation.

Additional outcomes of research

Additional outcomes were the results of cytological examination, wound reinfection, and results of IHC analysis.

Methods of outcome registration

An increase in the level of the above indicators was considered a reliable criterion for increasing RPs in a pressure wound. A semiquantitative assessment of the intensity of marker expression was performed by collagen scores (from 0 to 6), and the percentage of stained cell units per 300 wound stromal cells was calculated (for VEGF and SMA).

Ethical considerations

The study was approved by the Local Ethics Committee of the Federal Scientific and Clinical Center for Reanimatology and Rehabilitation (extract from Protocol No. 1/21/5 of March 17, 2021).

Statistical analysis

The sample size was not previously calculated. Statistical analysis was performed using Statistica 10.0 (StatSoft Inc., USA) and Microsoft Office Excel.

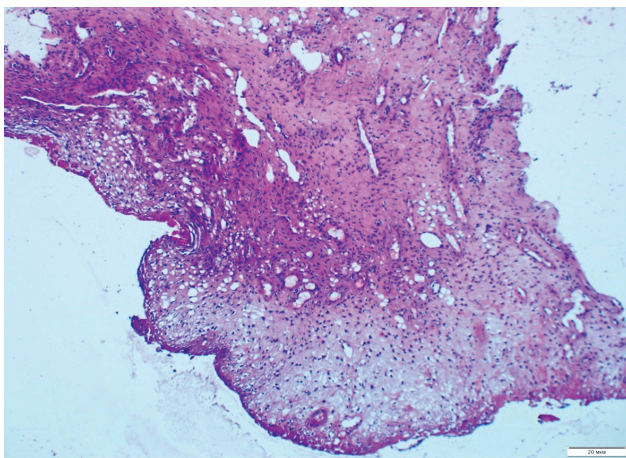


Fig. 2. Biopsy of the bottom tissue of the bedsore before treatment. Stained with hematoxylin and eosin.

RESULTS

Study participants

The study included 12 patients, namely, 7 men and 5 women (average age, 47.5 years; age range, 38–67 years). The distribution according to demographic criteria was asymmetrical. In the initial assessment, all patients had a CCC, which was characterized by protein-energy deficiency, persistent immobilization, infectious and septic complications (chronic pyelonephritis, chronic bronchitis, pneumonia, etc.), spastic syndrome, degenerative changes in the joints, and the need to use prosthetic invasive systems. The immediate cause of the CCC was more often extensive ischemic stroke (8) and less often severe traumatic brain injury (3) and radical surgeries to remove brain tumors (1) of varying duration (3 months to 1.5 years).

In all patients, the pressure ulcer was located in the sacral region and measured 7–25 cm² long (average, 18.6 cm²).

Main research results

Initially, all pressure ulcers appeared as open, chronic nonhealing ulcerative–necrotic defects with pronounced inflammation and obvious signs of RP stagnation, such as fibrin deposits, foci of necrosis, rare loci of flaccid granulation, edematous rigid edges, lack of marginal epithelization, exudation. Histological examination of biopsy specimens of the wound edges from both groups revealed a zone of fibrinoid–necrotic changes with an underlying layer of slightly pronounced granulation tissue, interstitial tissue edema, scattered infiltration of polymorphonuclear leukocytes with an admixture of eosinophils (Fig. 2).

No newly formed capillary-type vessels were noted.

On day 14 in the main group, microscopy revealed signs of RP activation. In the zone of fibrinoid–necrotic changes, neoangiogenesis in the form of granulation tissue fragments was detected, and elements of polymorphonuclear leukocytes of the interstitial tissue were visible (Fig. 3).

In the control group, the histological presentation of the lesion was almost unchanged over the same period. Fibroblast proliferation was extremely weak, and fibrinoid–necrotic changes persisted and were comparable with baseline.

On day 28 of HFES therapy, sites with maturing granulation tissues and mature connective tissues clearly dominated the DU biopsy samples. Pronounced regenerative changes in the integumentary multilayered squamous epithelium were observed (mainly at the edges) with acanthosis and increased neoangiogenesis of the capillaries (Fig. 4).

Maturing granulation tissue replaced the foci of fibrinoid–necrotic changes. In the control group, during standard therapy, the morphological presentation proceeded slowly and gradually into the structuration phase, where granulations were visible, but more sluggish and scanty than in the main group. Very weak marginal epithelialization was noted, and sites of necrosis and microcirculatory disorders remained (Fig. 5).

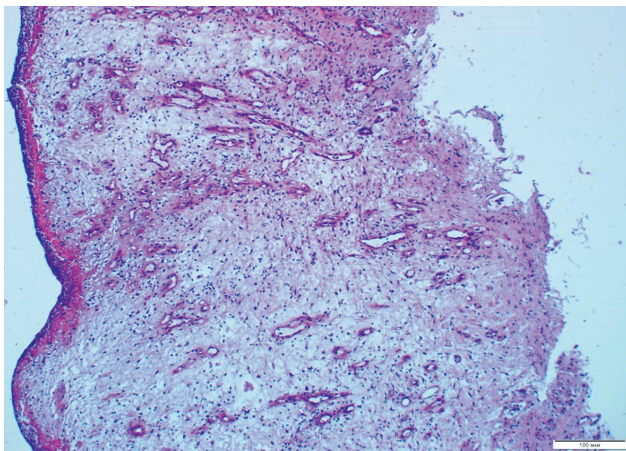


Fig. 3. Biopsy of the bottom of the bedsore on day 14 of treatment using high-frequency electrical stimulation. Stained with hematoxylin and eosin.

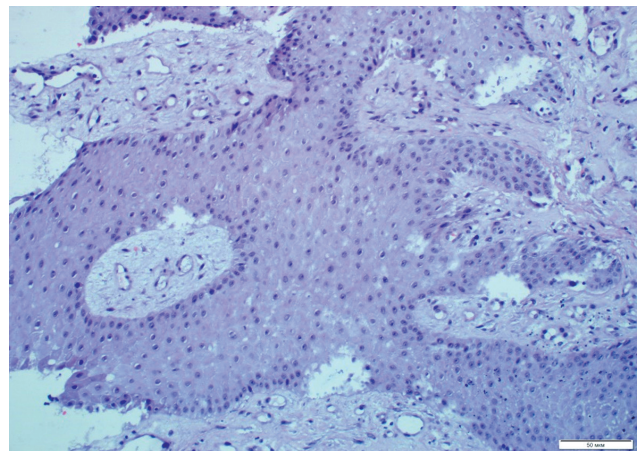


Fig. 4. Biopsy specimen of the bottom of the bedsore on day 28 of treatment using high-frequency electrical stimulation. Stained with hematoxylin and eosin.

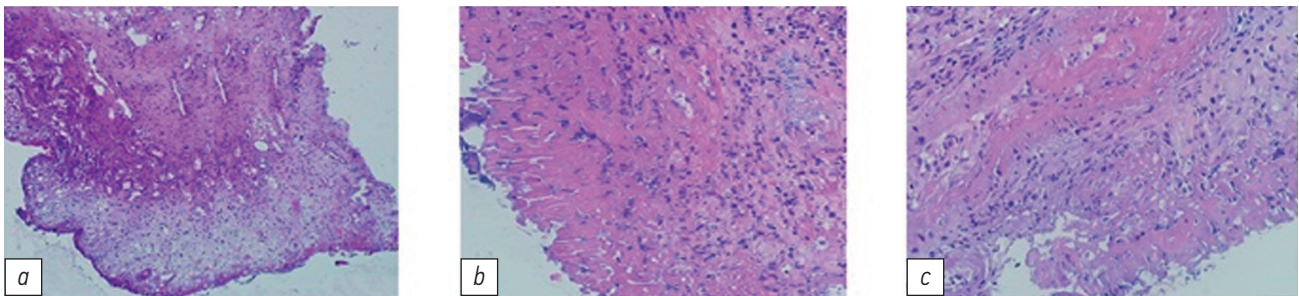


Fig. 5. Histology of the edge of the decubital ulcer (control group): *a* — day 1, $\times 300$; *b* — day 14, $\times 400$; *c* — day 28, $\times 400$.

In IHC analysis of RP markers before treatment, collagen types I and III in the bottom and edges of the pressure ulcer were found in the extracellular matrix only as minor deposits of amorphous structures without fiber formation. The minimal expression of VEGF in the endothelium of a few vessels (up to 15% of pressure wound stromal cells) and SMA was typical.

On day 14 of HFES therapy, the amount of collagen types I and III (up to 4 points each) increased moderately at the bottom and edges of the pressure ulcer, which formed clear fibrous structures in the extracellular matrix. Moreover, higher collagen contents were registered in DU edges than at the bottom. At the bottom and edges of the wound, the expression level of VEGF was increased compared with the expression at the initial stage, particularly in the endothelium of capillaries, that is, the number of stromal cells in the wound increased by 30%. The amount of SMA also increased compared with that before treatment (60% of wound stromal cells). The highest expression of this marker was noted in the intermediate stage.

On day 28, in the biopsy samples of the bottom and edges of the pressure ulcer of the main group, the amount of collagens increased moderately (up to 6 points each), which formed clear fibrous structures in the extracellular matrix. The collagen content was noticeably higher at the edges of the pressure ulcer than at the bottom. The collagen

content was comparable to that at day 14 of treatment. VEGF expression in the endothelium of the vessels at the bottom and edges of a pressure ulcer was higher than at day 14 of treatment (70% of wound stromal cells). The number of capillaries also increased. The dynamics of SMA expression were also positive compared with the baseline but somewhat worse than that at the intermediate period (day 14 of therapy) (30% of wound stromal cells).

The dynamics of RP markers in the control group were not assessed.

Adverse events

No adverse events were recorded.

DISCUSSION

Pressure ulcers are a great challenge for patients with severe neurological disorders. The systemic neurodystrophic process inhibits RP, with greatly extended phases [7, 8]. "Aging," depletion of regenerative cells, presence of severe microcirculatory disorders, often extending beyond the paravulnar zone, and poor healing dynamics against traditional therapy are noticeable. During examination, necrotic and granulation tissues are often observed [13, 14]. In patients on a serious condition, prolonged wound exhaustion often leads to sepsis with a lethal outcome [2].

The hypothesis of “wound exhaustion” was confirmed in the morphological study of the control group, where increased granulation tissue formation and sluggish epithelialization were noted.

In the main group receiving HFES therapy, accelerated normalization of the microvasculature and more pronounced growth and maturation of granulation tissue with the formation of collagen types I and III were observed, and more pronounced accumulation was noted at the edges of the pressure ulcer. A pronounced activation effect was noted from day 14 to day 28 of treatment. This treatment also stimulates neoangiogenesis, as the most pronounced expression of VEGF by the vascular endothelium was noted on day 28. Higher quantities of myofibroblastic elements (SMA) in tissues accumulate 2 weeks after the start of combined local treatment of DUs, which correlates with the acceleration of RPs and marginal epithelialization according to morphological data in the main group.

Nowadays, various therapeutic measures are available for the local treatment of DUs, including the use of special dressings, antiseptics, ointments, multicomponent wound covering, and physicochemical technologies. However, the efficiency of these methods does not always correspond to clinical tasks, and their high cost and laboriousness do not bear practical value to them. Thus, the search for non-drug methods of treating pressure ulcers as an integral part of the complex treatment of DUs is extremely relevant. One of the promising non-drug methods on a complicated wound, and in particular on DUs, is the activation of RP in the tissues of the defect area through interstitial exposure to electric currents of various frequencies. Previous studies have noted the important role of interstitial cold plasma discharges initiated by radio frequency current using a specialized device. According to A.I. Pshelenskaya (2014), in patients with purulent wounds of the perineum and sacrococcygeal zone, HFES stimulated metabolic processes and local immunity [15]. In addition, electrical stimulation “revives” the complicated process, stimulates the growth of young cellular elements of the fibroblastic series and their migration from the paravulnar zones (the so-called galvanotaxis), and increases the collagen-synthetic activity of cells over the entire area of

the DU, and the epithelialization of defects [16–18]. In this study, we examined the morphological patterns of RP activation by dosed exposure to radiofrequency current, which enabled us to identify an increase in the regenerative potential of tissues caused by the increased production of collagen types I and III by fibroblasts and cellular and endothelial growth factors throughout the DU.

Study limitations

The RP course can be significantly influenced by the following:

- Acute conditions (sepsis, septic shock, bleeding of any location, and wound reinfection).
- Systemic diseases with metabolic disorders.
- Local or systemic circulation disorders.

CONCLUSIONS

In the case of a CCC of cerebral origin, the healing process of pressure ulcers inevitably becomes complicated. According to a morphological study, it is characterized by severe endothelial dysfunction, profound microcirculation disorders, depletion of the potential of myofibroblastic cells, and deficiency of growth factors. The use of local HFES as a component of complex therapy for DUs can significantly improve RPs by optimizing its main phases.

ADDITIONAL INFORMATION

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Competing interests. The authors declare that they have no competing interests.

Authors' contribution. A.M. Shulutko — formation of the strategy and design of scientific work; E.G. Osmanov — writing the text of the article and final editing; E.L. Altukhov, A.A. Yakovlev, Yu.A. Boblak, E.G. Gandibina, A.V. Gorbacheva, A.R. Patalova, S.E. Khmirova, N.R. Khusainova — search for literary sources on the subject of the work, their translation from English, treatment of patients and collection of clinical material, formation of an electronic database.

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