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Research Article

Topical control of wound healing by nanocerium in carcinogenesis

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Abstract

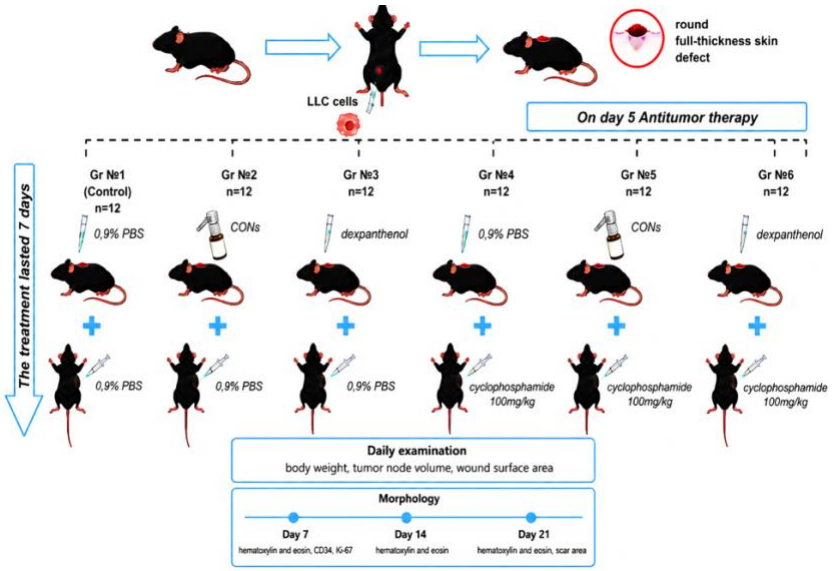
Introduction: Skin wound healing in cancer patients is a complex issue, influenced by both the tumor process itself and the effects of antitumor therapy. This study assessed the efficacy of various skin wound treatment regimens in mice with transplanted Lewis lung carcinoma (LLC).

Materials and Methods: 72 C57BL/6 mice were divided into six groups, including control, topical application of 1% cerium nanoparticles colloidal solution, 5% dexpanthenol spray, 100 mg/kg cyclophosphamide solution, and a combination of these.

Results and Discussion: It was found that topical application of cerium nanoparticles without chemotherapeutic treatment significantly shortened the time of wound regeneration to 16.5±1.0 days ($p \leq 0.05$) and reduces a postoperative scar (6±0.3 mm², $p \leq 0.0001$). Systemic chemotherapy treatment increased the healing time (22.5±1.0 days) and scar area (55.0±0.7 mm²), while reducing a tumor volume by 34% comparing to such in the control group. Combination therapy by dexpanthenol and cyclophosphamide promoted an antitumor effect and accelerated a tissue repair (16.3 ± 0.8 days). At the same time, local application of cerium nanoparticles did not alter regeneration (21.5 ± 1.0 days); however, the scar area was smaller (10.0 ± 0.7 mm²). Histological analysis revealed that the highest vascular density and maturity of granulation tissue in a wound were observed when treated cerium nanoparticles, while epithelial cell proliferation was reduced by cyclophosphamide.

Conclusion: The obtained data indicate the potential of topical application daily for 7 days of 1% nanocerium to accelerate wound regeneration in cancer patients without chemotherapy, and 5% dexpanthenol to accelerate skin regeneration in cancer patients receiving chemotherapy.

Graphical Abstract



Keywords

Lewis lung carcinoma; mice; nanocerium; dexpanthenol; cyclophosphamide; regeneration; wound healing

Introduction

Cancer is one of the leading causes of death worldwide. The International Agency for Research on Cancer (IARC) has estimated the global burden of malignant diseases, reporting 12.7 million new cancer cases annually, with cancer being the cause of over 7.6 million deaths worldwide each year (Nwosu et al. 2024). Regeneration of a skin wound in oncology patients represents a complex challenge influenced not only by the tumor process itself but also by the effects of anticancer therapy (Deptuła et al. 2018). Chemotherapy, targeting rapidly dividing cells, suppresses keratinocyte proliferation and immune cell migration, thereby delaying healing and disrupting skin homeostasis (Slonimska et al. 2024). In addition, modern targeted therapies, despite their molecular driver specificity, often impacts healthy tissues expressing target molecules in the skin layers. For example, epidermal growth factor receptor (EGFR) inhibition impairs normal epidermal renewal, while angiogenesis inhibitors disrupt vascular regeneration, which is critical for oxygen and nutrient delivery to wound sites (Zawrzykraj et al. 2024).

Current approaches incorporate adjunctive treatments such as antioxidants and regenerative agents (Fadilah et al. 2023). One of the widely discussed options is cerium nanoformulations. Notably, cerium oxide nanoparticles demonstrate promising reparative properties through antioxidant mechanisms (Nelson et al. 2016), while dexpanthenol is widely used to accelerate wound healing.

This study aims to evaluate the efficacy of topical wound treatment by cerium oxide nanoparticles and dexpanthenol in a Lewis lung carcinoma mouse model in dependence of antitumor therapy. The study focuses on the effects of these interventions on tumor growth dynamics, wound healing rate and quality, and histomorphological tissue changes, thereby advancing understanding of the interplay between anticancer therapy and cutaneous tissue repair.

Materials and Methods

Animals and ethics

The animal study was performed on 72 C57BL/6 mice of both sexes weighing 18–20 g. The animals were obtained from the SPF Pushchino Animals Breeding Facility (Russia) and were

kept under natural daylight conditions, standard room temperature and humidity, with free access to food and water. The study protocol met all the requirements of good laboratory practice (GLP) and the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes. The protocol was approved by the Local ethics committee of National Research Nuclear University MEPHI (Moscow, Russia), Reg. No. 12-24, 16.01.2026. The study was financially supported by the grant of the Russian Science Foundation (agreement No. 25-25-0094, 2026).

Preparation of cerium oxide nanoparticles (CONs)

The CONs were prepared by femtosecond laser ablation in liquid followed by laser fragmentation. A TETA-20 laser system (Avesta, Belarus) was used. The laser parameters for the ablation regime were as follows: λ = 1030 nm, pulse duration = 270 fs, repetition rate = 200 kHz, pulse energy = 50 μJ; for fragmentation regime: λ = 1030 nm, pulse duration = 270 fs, repetition rate = 100 kHz, pulse energy = 100 μJ.

Spectral properties of CONs were evaluated with the spectrometer MC122 UV-VIS (SOL instruments, Belarus) in a range from 350 to1100 nm. Figure 1a shows the UV-Vis spectrum of CONs colloidal solution. The UV region of the spectrum (<350 nm) shows strong absorption, while the higher wavelengths exhibit low absorption values. Size distribution of nanoparticles was measured by the Dynamic Light Scattering (DLS) method using Zetasizer Nano ZS (Malvern Panalytical, Switzerland) (Fig. 1b).

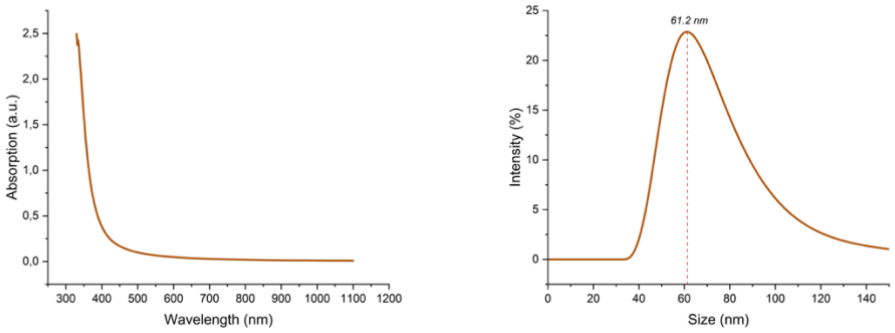


Figure 1. (**a**) UV-Vis spectrum and (**b**) size distribution of CONs.

Murine models of cancer and wound. Experimental groups and treatment regimens

A syngeneic Lewis lung carcinoma (LLC) cells were used to model the murine tumor. The tumor cells were provided by the BioBank of Institute of Experimental Oncology, Blokhin National Medical Research Center of Oncology (Moscow, Russia). A tumor cells suspension containing 1 × 106 cells / 100 μL was prepared in Hanks' solution (Biolot, Russia) and injected subcutaneously into the left thigh region.

On the 5th day after LLC cells transplantation, a topical defect was created. Under general anesthesia (Zoletil, 20 mg/kg), hair on the withers was removed and a round full-thickness skin defect including subcutaneous fat was cut using preformed template with an area of 40 mm². Wound treatment and anti-tumor therapy were started the same day.

The animals were randomly divided into 6 groups of 12 animals in each. Control animals (group 1) were treated both topically and IV with 0.9% saline daily for 7 days. Animals from the second group were administered 0.9% saline IV, and the wound surface was sprinkled with a 1% CONs solution. In the third group, dexpanthenol was applied topically, while 0.9% saline was injected IV. Group 4 included animals received 100 mg/kg cyclophosphamide (98.85%, Pharmasyntez, Russia) as anti-tumor therapy in combination with a topical wound treatment with 0.9% saline. In group 5, IV cyclophosphamide at the same dose was combined with a topical application of a 2% CONs solution to the wound. In group 6, cyclophosphamide was combined with a topical dexpanthenol treatment. The duration of the experiment was 21 days. The antitumor and wound-healing effects were evaluated using both morphological and quantitative parameters.

Tumor growth and wound healing assessment

The animals' body weight and tumor node volume were recorded every day. Wound healing time was assessed. The wound surface area was measured using digital images processed with ImageJ software (National Institutes of Health, USA) with a consequent relative wound closure percentage.

Four randomly assigned animals from each group were euthanized under isoflurane anesthesia on the 7th, 14th and 21st days. Tumor nodes and wound tissues were collected, processed, and 4 μm slices were made for a morphological examination (H&E staining) with a light microscope (Olympus CX23, Japan).

On the 21st day, tumor nodes were additionally assessed for a pathomorphological regression using the Miller–Payne scale: grade 1 (the absence of cell's loss), grade 2 (minimal cell's loss), grade 3 (cell's loss of 30% to 90%), and grade 4 (more than 90% of dead cells) and grade 5 (no invasive tumor cells) (Miller et al. 2002).

Wound tissue microstructure was assessed with a subsequent inflammatory changes scoring on the third day (integral scale according to Shekhter et al. (2020): 0 – absent, 1 – singular immune cells, 2 – focuses of infiltration, 3 – moderate infiltration, 4 – massive infiltration).

Immunohistochemistry

The density of newly formed vessels in the wound granulation tissue was evaluated immunohistochemically using mouse monoclonal anti-CD34 antibodies (clone QBEnd/10, Ventana, USA). Wound cells proliferation was analyzed using rabbit recombinant monoclonal anti-Ki-67 antibodies (clone SP6, Abcam) staining.

A quantitative assessment of vascular density was performed over an area of 0.73 mm² at ×200 (three fields of view were assessed, and then the median and quartile ranges were calculated) (Matsuyama et al. 1998; Bosari et al. 1992).

Statistical analysis

The data were represented as median with interquartile interval (in case of scale's data analysis). After assessment of the distribution pattern of continuous variables by Shapiro-Wilk method, intergroup differences were analyzed using ANOVA followed by post-hoc Dunnett's test for normally distributed continuous variables or Kruskal-Wallis test for nonparametric datasets. All data were recorded in an electronic spreadsheet and subsequently processed statistically using SPSS software package (USA). We used 95% significance level for the data analysis.

Results

Weight dynamics and final tumor volume

The body weight among the experimental groups showed a slight decrease until the 5th day of observations (Fig. 2a), which might be attributed to post-surgical stress. The same pattern of the weight dynamics was observed in the control group with a gradual mass decrease during the first five days of observation followed by a remediation of a positive dynamics from Day 6 (22.7 ± 0.7 grams) up to Day 21 (23.2 ± 1.5 grams) (Fig. 2a).

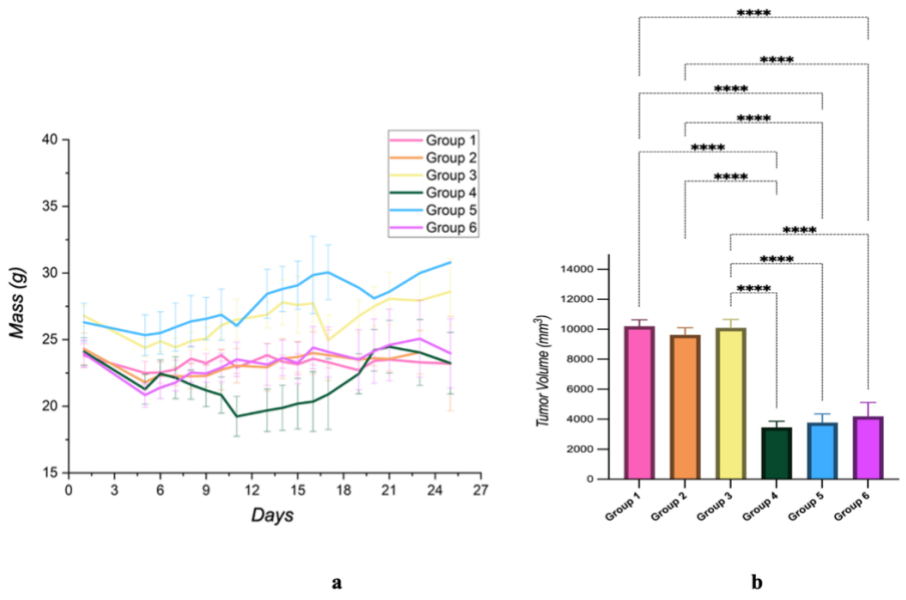


Figure 2. (**a**) animal body weight dynamics and (**b**) final tumor node volume among the studied groups (****p ≤ 0.0001). Groups: 1 – wound treatment by 0.9% PBS, 2 – 1% CONs, 3 – 5% dexpanthenol, 4 – 0.9% PBS + cyclophosphamide, 5 – 1% CONs + cyclophosphamide, 6 – 5% dexpanthenol+ cyclophosphamide.

The tumor volume in the control group continuously increased, and by the 21th day it was 10206,7 ± 427,2 mm^3 (Fig. 2b). Both parameters, body weight and tumor node volume in the experimental groups that received only local treatment, showed a similar pattern.

IV cyclophosphamide resulted in a decrease in the weight of animals from day 6 to day 11. However, the tumor node volume was 34% lower than in the control group ($p < 0.001$). Starting from day 12, an increase in body weight was recorded, but it did not reach the initial values.

Complex treatment with cyclophosphamide and local application of either CONs or dexpanthenol to the wound area demonstrated the following patterns: an increase of the body weight during the first 17 days of observation (Fig. 2a), while the final tumor volume was lower compared to such in groups 1, 2 and 3 (Fig. 2b).

Full repair of a skin defect in the control group was completed within 18.1 ± 1.3 days with the scar area of 15 ± 1 mm². Local application of the CONs spray (Group 2) in absence of chemotherapy accelerated wound healing to 16.5 ± 1.0 days ($p \leq 0.05$) with a barely noticeable postoperative scar (6 ± 0.3 mm², $p \leq 0.0001$).

Local application of dexpanthenol (Group 3) prolonged the time of wound remodeling to 21.0 ± 1.1 days, and the scar area was larger compared to such in Group 2 (14±1.4 mm² $p \leq 0.0001$) (Figs 3 and 4).

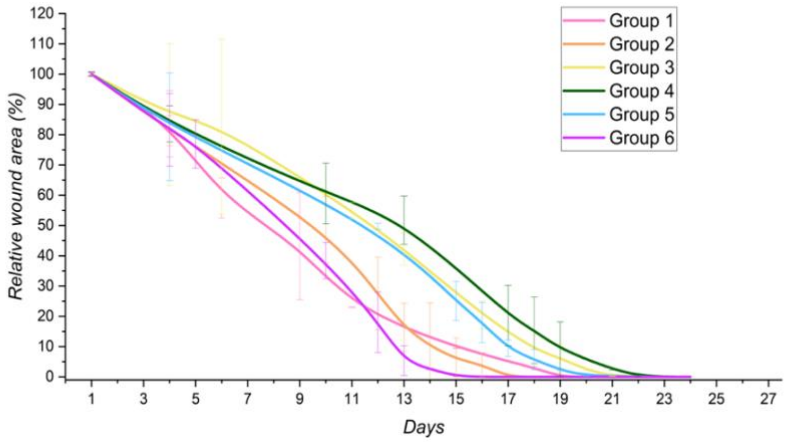


Figure 3. Relative wound closure dynamics (as % from the initial size). Groups: 1 – wound treatment by 0.9% PBS, 2 – 1% CONs, 3 – 5% dexpanthenol, 4 – 0.9% PBS + cyclophosphamide, 5 – 1% CONs + cyclophosphamide, 6 – 5% dexpanthenol+ cyclophosphamide.

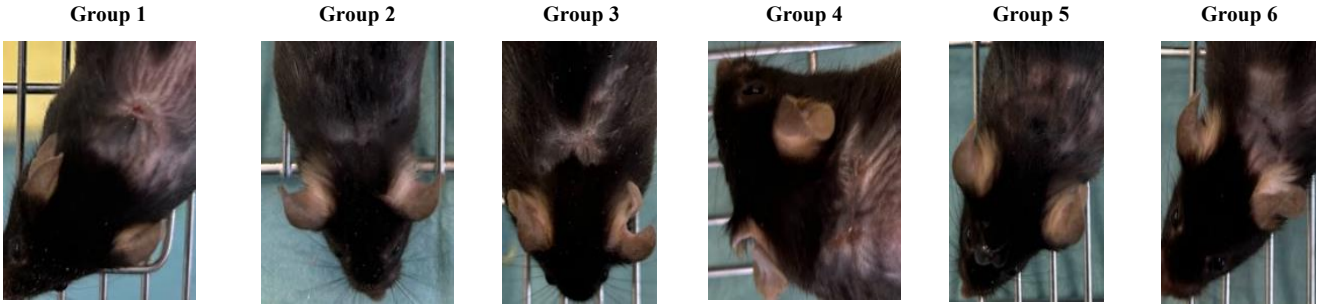


Figure 4. The murine wound status on Day 21 of the experiment. Groups: 1 – wound treatment by 0.9% PBS, 2 – 1% CONs, 3 – 5% dexpanthenol, 4 – 0.9% PBS + cyclophosphamide, 5 – 1% CONs + cyclophosphamide, 6 – 5% dexpanthenol+ cyclophosphamide.

Cyclophosphamide treatment restrained wound healing for Groups 4, 5, 6. Time to complete wound closure (Group 4) was the longest (22.5±1.0 days). The postoperative scar was 55.0±0.7 mm² ($p \leq 0.001$). Decreased hair growth was also noted in the surgical area (Figs 3 and 4).

Dexpanthenol accelerated the wound regeneration in the group of animals receiving cyclophosphamide (Group 6) to 16.3 ± 0.8 days, ($p > 0.05$ with the control group), and scar area was 14±1.4 mm² ($p \leq 0.0001$) At the same time, local application of CONs spray (Group 5) did not alter regeneration (wound closure at 21.5 ± 1.0 days); however, the scar area was smaller than in either Group 4 or 6 (10.0 ± 0.7 mm² $p \leq 0.0001$, $p \leq 0.001$, respectively) (Figs 3 and 4).

Histological quantification

HE staining of tumors revealed typical neoplastic morphological changes without signs of LLC pathomorphological regression (Groups 1-3) (Fig. 5). In Groups 4, 5 and 6, foci of necrosis and fibrosis were noticeable, occupying up to 40% of the tumor area. Some tumor cells also exhibited autolytic changes. The degree of pathomorphological tumor regression, according to G.A. Lavnikova scale, was grade II (moderate effect).

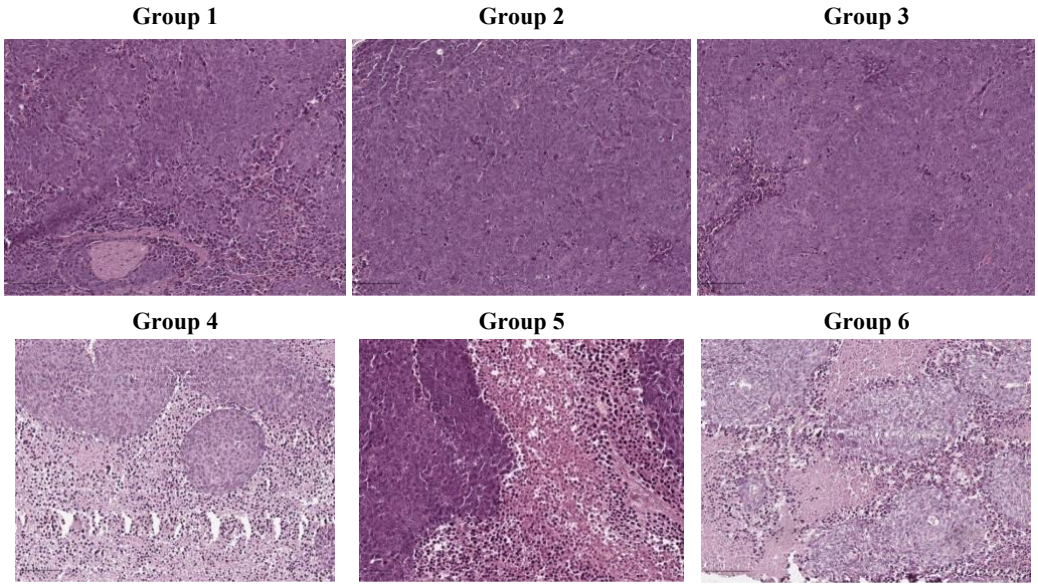
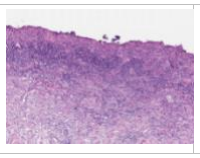
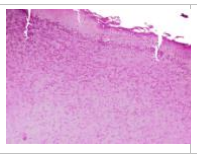
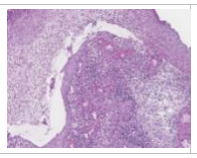
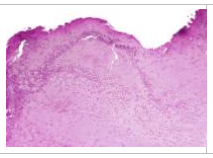
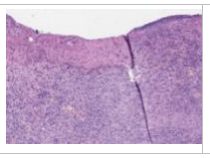
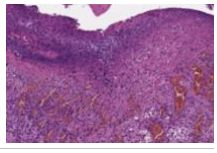


Figure 5. LLC specimens on Day 21 of the experiment, hematoxylin and eosin, x200. Groups: 1 – wound treatment by 0.9% PBS, 2 – 1% CONs, 3 – 5% dexpanthenol, 4 – 0.9% PBS + cyclophosphamide, 5 – 1% CONs + cyclophosphamide, 6 – 5% dexpanthenol+ cyclophosphamide.

A histological examination of the wound was performed in all groups of animals on Days 7, 14 and 21.

By day 7, in the control group the wound bottom contained foci of necrosis and well-defined granulation tissue with prominent infiltration by neutrophils, lymphocytes, plasma cells, and macrophages as well as moderate fibroblast proliferation. In Group 2, the base and margins of wound bottom were filled by granulation tissue with small foci of necrosis, abundant fibroblasts, moderate infiltration by neutrophils, lymphocytes, plasma cells, and macrophages, fibroblast proliferation, and pronounced angiogenesis. In Groups 3, 5, and 6, the wound bottom contained foci of necrosis and well-defined granulation tissue with less pronounced fibroblast proliferation and angiogenesis and moderate inflammatory infiltration. In Group 4, the wound bottom was filled by necrotic debris and immature granulation tissue, with weak infiltration by lymphocytes, plasma cells, macrophages, and neutrophils, and no fibroblast proliferation. The severity of inflammatory infiltration in the wound bottom in Groups 1-6 is shown in Table 1.

Table 1. The severity of inflammatory infiltration in the wound bottom on the 7th day

Hematoxylin and eosin, x200					
					
Inflammatory infiltration, point					
3.8±0.8	2.6±0.5	3±0.8	2.4±0.5	2.6±0.5	2.8±0.8
Group 1	Group 2	Group 3	Group 4	Group 5	Group 6

To determine the vascular density of newly formed vessels in granulation tissue ICH with anti-CD34 antibodies was performed. It was demonstrated that in Group 2 there was the highest vascular density in the wound bottom, results in Groups 3, 5, and 6 demonstrated

moderate vascular density, while Groups 1 and 4 showed the lowest vascular density (Fig. 6a).

To determine the proliferation activity of keratinocytes, we stained the wound slices with anti-Ki-67 antibodies, and then proliferation index was calculated. The proliferation index was reduced in keratinocytes from animals treated with cyclophosphamide (Fig. 6b).

By day 21, the wound bottom area in Group 2 had completely regenerated without fibrosis. In Groups 1, 3, 5, and 6, wound bottom regeneration occurred with mild to moderate fibrosis. In Group 4, a scar was visible, consisting of bundles of dense collagen in the dermis with a few scattered fibroblasts and myofibroblasts. No skin appendages were visible.

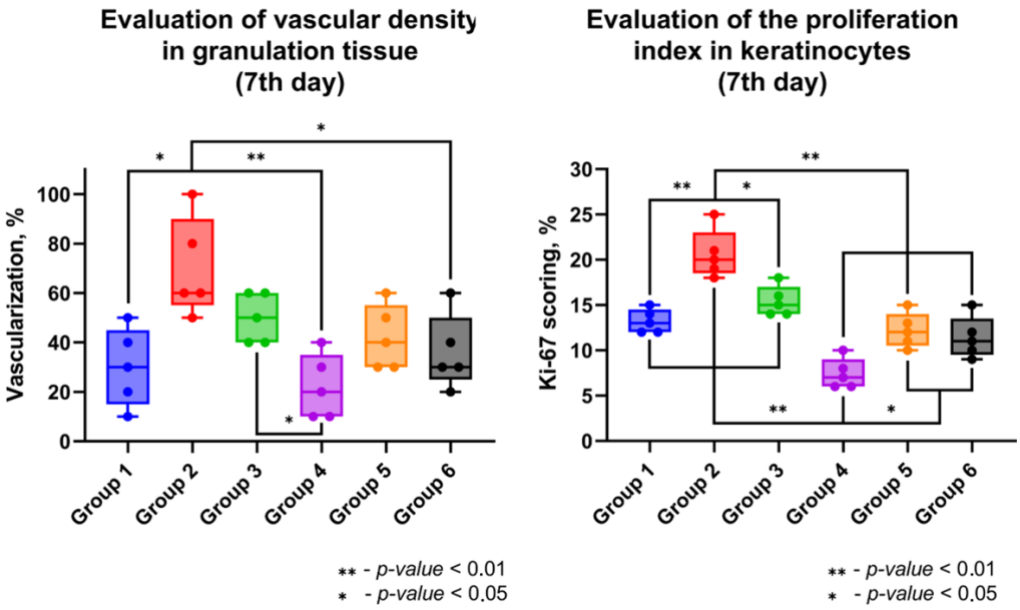


Figure 6. Vascular density in granulation tissue (**a**) and keratinocytes proliferation index (**b**) in wound tissue of experimental animals: * p = 0.05 in comparison with the control group; ** p < 0.01. Groups: 1 – wound treatment by 0.9% PBS, 2 – 1% CONs, 3 – 5% dexpanthenol, 4 – 0.9% PBS + cyclophosphamide, 5 – 1% CONs + cyclophosphamide, 6 – 5% dexpanthenol + cyclophosphamide.

Discussion

Rapid restoration of skin integrity is an essential for maintaining homeostasis of living organisms, and its disruption leads to high risk of pathogen invasion and homeostatic imbalance (Sundaram et al. 2018). The wound healing process in the cancer patients is complicated by the systemic influence of the tumor process, the patient's direct condition, and concomitant diseases (Payne et al. 2008). This applies not only to postoperative wounds but also to abrasions and ulcerative-necrotic changes (Kuo et al. 2025). The multimodal approach in treating cancer patients also leads not only to a decrease in the activity of reparative processes but also to alterations in the properties of the surrounding tissues (Payne et al. 2002; Behranvand et al. 2022).

Chemotherapy, as one of the main treatment options for cancer, exerts systemic cytostatic and cytotoxic effects, transforming the microenvironment of damaged tissue into a chronic inflammatory environment incapable for proper regeneration (Behranvand et al. 2022). This effect extends not only to rapidly dividing tumor cells but also to healthy tissues, significantly compromising tissue repair processes (Levra et al. 2024). In the context of wound healing, chemotherapeutic agents disrupt the key phases of this process: fibroblast proliferation, collagen synthesis, and angiogenesis (Payne et al. 2002; Behranvand et al. 2022). Specifically, chemotherapeutic drugs such as doxorubicin and cisplatin inhibit epithelial cell migration and reduce the rate of granulation tissue formation, leading to delayed wound closure. Chemotherapy also causes immunosuppression through the recruitment of myeloid-derived suppressor cells, increasing the risk of infectious complications, while systemic inflammation and oxidative stress induced by treatment create an unfavorable metabolic background for regeneration (Zafaryab et al. 2025). Consequently, cancer patients receiving chemotherapy exhibit a higher rate of postoperative complications and wound chronicity, necessitating a specific approach to managing such conditions. Current strategies aimed at mitigating these effects include the use of

local delivery systems of growth factors and anti-inflammatory agents capable to stimulate repair during ongoing systemic treatment (Payne et al. 2008; Zafaryab and Vig 2025).

For the last years, particular attention has been drawn to CONs due to their wide range of potential applications. These nanoparticles are characterized by high stability, biocompatibility, and low toxicity (Carvalho et al. 2018). The key advantage of these nanoparticles is their ability to donate electrons and act as a reducing agent which allows conducting a therapy of a wide range of diseases associated with oxidative stress (Zhou et al. 2022). CONs represent a multifunctional nanomaterial impacting all stages of wound healing.

Our study demonstrated that velocity of paracancerous wound reparation in the group of local application of the CONs spray was higher (16.5±1.0 days, $p \leq 0.05$) than in the control group (18.1 ± 1.3 days), with a barely noticeable postoperative scar (6±0.3 mm², $p = 0.001$).

Their therapeutic potential stems from the known antioxidant activity (the ability to mimic superoxide dismutase and catalase enzymes, neutralizing excess reactive oxygen species and reducing oxidative stress), anti-inflammatory action (suppression of pro-inflammatory cytokines and mediators), antibacterial properties (via membrane damage and ROS generation), and the ability to stimulate angiogenesis (through modulation of HIF-1α and growth factors) of cerium nanoparticles (Nosrati and Heydari, 2023).

In our study, CONs significantly increased vascular density in newly developing granulation tissue, which exceeded the level of angiogenesis in the control group and cyclophosphamide group, confirmed by the results of immunohistochemical studies.

Beyond direct antioxidant protection, CONs help to reduce the expression of pro-inflammatory cytokines and inflammatory cell infiltration, creating a favorable environment for fibroblast and endothelial cell proliferation, which plays a part in angiogenesis (evidenced by increased expression of VEGF and Bcl-2) and accelerates extracellular matrix remodeling by enhancing collagen synthesis. Due to their low toxicity and ability to act as effective carriers for therapeutic molecules (e.g., microRNA-146a), cerium oxide nanoparticles are considered as a promising component for creating combination drugs aimed at the comprehensive correction of healing disorders (Dewberry et al. 2022). For effective and safe delivery of CONs to the wound area, they are incorporated into various scaffolds and wound dressings created by electrospinning, 3D printing, or as hydrogels. Preclinical in vivo studies demonstrate that such nanocomposite systems significantly accelerate wound closure, improve re-epithelization, stimulate new blood vessel formation, and increase collagen deposition, making CONs an extremely promising tool for treating chronic and infected wounds (Nosrati and Heydari 2023; Dewberry et al. 2022; Erokhina et al. 2025; Chen et al. 2024).

A review of experimental studies on animal models (rats, mice) shows that incorporating CeO_2 nanoparticles into hydrogels, wound dressings, or solutions significantly accelerates wound closure, improves the histological characteristics of regenerating tissue (ordered collagen deposition, skin appendage formation), and aids in restoring its biomechanical properties (Zhou et al. 2022; Zafaryab and Vig 2025; Erokhina et al. 2025). However, it is noted that the ultimate therapeutic effect of applying various forms of cerium oxide nanoparticles depends on factors such as the primary tumor origin, surgical approach, and chemotherapy regimen (Payne et al. 2008; Behranvand et al. 2022).

Thus, the application of cerium oxide nanoparticles is considered a promising direction in the development of wound healing therapies, capable of accelerating regeneration and improving healing quality. However, transitioning to clinical practice requires further study of the properties and effects of this agent under conditions closely mimicking the real clinical scenario (Erokhina et al. 2025; Chen et al. 2024). Therefore, the aim of our study was to investigate the efficacy of topical application of CeO2 nanoparticles on wound healing in vivo in laboratory animals by modeling the course of the wound process against the background of various types of systemic chemotherapy and without it.

Conclusion

The process of skin wound regeneration in cancer patients is complicated not only by the presence of the tumor, but also by the side effects of antitumor treatment. The obtained results demonstrate that in the absence of anti-tumor therapy, topical application of cerium nanoparticles significantly accelerate wound healing and reduced scarring compared to the control group. As expected, cyclophosphamide slowed tissue repair and increased scar area, but reduced tumor volume. Combination therapy by dexpanthenol and cyclophosphamide promoted an antitumor effect and accelerated a tissue repair (16.3 ± 0.8 days). At the same time, local application of cerium nanoparticles did not alter regeneration (21.5 ± 1.0 days); however, the scar area was smaller (10.0 ± 0.7 mm²). Histological analysis revealed that the highest vascular density and

mature granulation tissue were observed with topical application of nanocerium, while epithelial cell proliferation was reduced by cyclophosphamide. Thus, the study highlights the importance of developing new approaches to wound management in cancer patients, given the negative impact of chemotherapy on tissue regeneration.

Additional Information

Conflict of interest

The authors declare that they have no conflicts of interest.

Funding

The study was financially supported by the grant of the Russian Science Foundation (agreement No. 25-25-0094, 2026).

Ethics statement

The work with the animals was carried out in accordance with the Local ethics committee of National Research Nuclear University MEPHI (Moscow, Russia), Reg. No. 12-24, 16.01.2026

Data availability

All of the data that support the findings of this study are available in the main text.

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