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Evaluating wound-healing effect of silicon-zinc-boron-containing glycerohydrogel and its effect on mammary glands of high producing dairy cows

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ABSTRACT

Cow's milk quality, which may deteriorate due to inflammatory processes in the mammary glands, remains one of the important problems of dairy farming and requires effective, safe and affordable therapeutic agents. Nanocomposite silicon-zinc-boron-containing glycerohydrogel (Si-Zn-B-gel) may become a very good solution to the issue. The paper demonstrates wound-healing effect of the glycerohydrogel and confirms its effectiveness for teat hyperkeratosis treatment in dairy cows. Results of a rat-burn model – based experiment suggest that Si-Zn-B-gel is a promising wound healing agent for topical use. Thus, on Day 9 complete re-epithelialization of the burn surface was observed, with fibrous structures prevailing in the granulation tissue of the dermal layer, on Day 19 a mature scar was formed with a longitudinal alignment of collagen fibers. The production tests conducted in high producing dairy cows have demonstrated good therapeutic effect of the Si-Zn-B gel for teat-end hyperkeratosis and confirmed its long-term effect, which helps to longer maintain the results achieved during treatment. After a 7-day treatment physiological structure of up to 27.8% teats improved, on Day 14 of the experiment, no severe hyperkeratotic lesions were observed and the number of teats that correspond to the physiological norm was 72.2%. Analysis of the data collected shows that the Si-Zn-B-gel is effective for teat-end hyperkeratosis treatment, thus, it prevents mastitis in animals and improves the milk quality.

Keywords: silicon-zinc-boron-containing glycerohydrogel, 10% methyluracyl ointment, wound healing effect, long-term effect, high producing dairy cows, mammary glands, mastitis, teat-end hyperkeratosis, milk quality

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Оценка ранозаживляющего эффекта кремнийцинкборсодержащего глицерогидрогеля и влияние его на молочную железу высокопродуктивных коров

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РЕЗЮМЕ

Качество получаемого коровьего молока, снижающееся прежде всего за счет наличия у животных воспалительных процессов в молочной железе, остается одной из важных проблем молочного животноводства, что требует разработки высокоэффективных, безопасных и доступных терапевтических средств. Большим потенциалом для решения данного вопроса обладает нанокомпозитный кремнийцинкборсодержащий глицерогидрогель (Si-Zn-B-гель). В работе представлены данные, подтверждающие наличие ранозаживляющей активности глицерогидрогеля и эффективность его использования в схемах лечения гиперкератоза сосков молочной железы коров. Результаты исследования, проведенного на экспериментальной модели термического ожога кожи крыс, свидетельствуют о том, что Si-Zn-B-гель является перспективным ранозаживляющим средством для местного применения. Так, на 9-е сут была зафиксирована полная эпителизация ожоговой поверхности, при этом в грануляционной ткани дермального слоя кожи преобладали волокнистые структуры, к 19-м сут формировался зрелый рубец с продольно ориентированными коллагеновыми волокнами. Проведенные производственные исследования на высокопродуктивных коровах показали терапевтическую эффективность применения Si-Zn-B-геля в лечении гиперкератоза сосков у коров и наличие пролонгированного действия, что увеличивает сроки результативности проведенной терапии. Через 7 дней лечения установлено увеличение количества сосков с физиологической структурой до 27,8%, на 14-е сут после опытного периода зафиксировали отсутствие поражений сосков тяжелой формой гиперкератоза, при этом количество сосков, соответствующих физиологической норме, составило 72,2%. Анализ данных, полученных в результате исследований, показывает, что применение Si-Zn-B-геля позволяет производить эффективное лечение гиперкератоза сосков молочной железы, тем самым обеспечивать профилактику мастита у животных и повышать качество получаемого молока.

Ключевые слова: кремнийцинкборсодержащий глицерогидрогель, 10%-я метилурациловая мазь, ранозаживляющая активность, пролонгированное действие, высокопродуктивные коровы, молочная железа, мастит, гиперкератоз сосков, качество молока

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INTRODUCTION

Production of high quality and competitive dairy products is a top priority for the Russian Federation. The solution to the task is a matter of special importance for the national economy, when health promotion improves the quality of life and maximizes competitive advantages of producers and regions and ensures food security [1, 2, 3, 4]. Today, our country is one of the world's largest producers of milk and dairy products. It is now ranked number four in the world, at the same time quality improvement remains one of the primary tasks of the domestic livestock industry [3, 5]. The mammary gland of high producing dairy cows becomes overactive during lactation, which may result in such diseases as mastitis that affects milk production, safety and quality [1, 3, 6, 7, 8].

Teat-end hyperkeratosis is a risk factor for clinical mastitis in cows as it disrupts the teat canal barrier function, thus, significantly increasing the risk of penetration of opportunistic and pathogenic microflora into the mammary gland resulting in its damage and inflammation [5, 9, 10, 11, 12, 13, 14]. The current regimens implemented worldwide to treat and prevent diseases of mammary glands in animals offer a wide variety of medicinal products containing cosmetic, antiseptic, probiotic and emollient components, however, the agricultural holdings with milk yield more than 8000 kg per cow, see no stable or long-lasting positive effect of these therapeutic measures [7, 11, 15]. Therefore, modern practical science shall search for new, more effective approaches to treat teat-end hyperkeratosis and prevent mastitis in cows [7, 11]. Nanocomposite silicon-zinc-boron-containing glycerohydrogel (Si-Zn-B-gel), developed by I. Ya. Postovsky Institute of Organic Synthesis, Ural Branch of Russian Academy of Sciences [16], may become a very good solution to the issue.

The gel chemical formula is:

$$3Si(C_3H_7O_3)_4 \times ZnC_3H_6O_3 \times 2HB(C_3H_6O_3)_2 \times 15C_3H_8O_3 \times 70H_2O.$$

At the molecular level, the developed substance contains silicon, zinc and boron atoms, has a gel-like consistency and pronounced wound-healing, regenerating, antibacterial and fungicidal effect [16, 17]. Consequently, it is an urgent task to study its therapeutic effectiveness for treatment of teat-end hyperkeratosis in cows and to confirm its prolonged effect.

The goal of the experiment is to study effectiveness of the Si–Zn-B-gel for treatment of teat-end hyperkeratosis in high producing dairy cows.

The following tasks need to be addressed to achieve this goal.

1. Evaluate specific wound-healing effect of Si-Zn-B-gel in comparison with 10% methyluracyl ointment using a rat thermal burn model.

2. Study clinical efficacy of the developed glycerohydrogel in comparison with 10% methyluracyl ointment in experimental groups of cows with teat-end hyperkeratosis.

MATERIALS AND METHODS

The experiment involved white mongrel rats at the age of 10 weeks; high producing black-and-white cows at the age

of 4–6 lactation with an average annual milk yield per cow of more than 8000 kg.

Preclinical experiments were carried out using an experimental rat thermal burn model to evaluate the specific wound-healing effect of the Si-Zn-B-gel in comparison with 10% methyluracyl ointment. II–IIIa degree thermal burns were caused by heated metal devices (at a temperature of 98–100 °C) applied directly to the skin of an individual for 40 seconds [18]. The treatment course was assessed at the final stage of the wound healing and was characterized by primary intention resulting from the use of Si-Zn-B-gel (19 days). During this period, healing was reported in three groups of rats: control group – a burn without treatment; Experimental Group 1 – a burn treated with 10% methyluracyl ointment; Experimental Group 2 – a burn treated with Si-Zn-B-gel. The number of animals in each group was 10.

All tests in animals were carried out in strict compliance with intergovernmental standards on laboratory animal keeping and handling adopted by the Intergovernmental Council for Standardization, Metrology and Certification as well as in accordance with Directive 2010/63/EU of the European Parliament and of the Council of the European Union of 22 September 2010 on the protection of animals used for scientific purposes.

Histomorphological tests were carried out to confirm the wound healing effect. Pieces of burn-affected skin from experimental rats were used as the biomaterial. At the first stage, the material was fixed in a 10% buffered formalin. The material was then dehydrated and soaked in the embedding medium. Paraffin medium "Histomix" (LLC "BioVitrum", Russia) was used for subsequent three-time soaking and embedding the material. Next, rotary microtome Leica RM 2255 (Leica Microsystems, Germany) was used to prepare 6 µm-thin sections of paraffin-embedded specimen. The micro-preparations were stained with hematoxylin and eosin and using Weigert – Van Gieson stain method. Histological changes were photographed on a "Micros" microscope (Austria).

Field trials. The clinical efficacy of glycerohydrogel was assessed on a farm of the Sysertsky Raion of the Sverdlovsk Oblast. For this purpose, two groups of cows (9 animals in each) were formed. All the animals were diagnosed with teat-end hyperkeratosis of different levels. The experimental animals were treated with Si-Zn-B-gel applied to the teats 2 times a day for 7 days. The control group was treated with 10% methyluracil ointment following the same scheme.

Conventional methods were used to *clinically test* the teat-ends [19]. The level of teat-end hyperkeratosis was assessed using an upgraded diagnostic scale, represented by a panel of 18 photographs [9]. The mammary gland was tested for clinical mastitis by palpation and strip-cup test, subclinical mastitis was diagnosed using rapid test Keno™test (CID LINES, Belgium).

Ultrasound scanning of the mammary glands was performed using the veterinary ultrasound scanner Ecoson 900V (West Medica Produktions- und Handels-GmbH, Austria). Two types of multi-frequency transducers (convex and linear) were used to test mammary gland parenchyma of cows. The teat cistern was examined with a 7.5 MHz linear scanner. Scanning in segmental and frontal planes was used. Teat-end condition was assessed using a plastic teat dip cup with a water buffer (water 38 °C) and a multi-frequency probe attached to it. The resulting echograms were processed using software provided by an ultrasound scanner [5, 20].

The milk was centrifuged in order to remove blood, if detected. To do this, a pooled sample of the residual milk (40–50 mL) was put into a plastic container, then heated up to 20–22 °C; after that 5–7 mL of milk was poured into the test tube and centrifuged for 10 minutes at 1000 rpm. A red ring sediment at the bottom of the tube suggested there was blood in the tested milk. The milk quality was tested using "Lactan 1–4 M" analyzer (Sibagropribor, Russia).

RESULTS AND DISCUSSION

The preclinical trials carried out to assess the specific wound healing effect on the experimental rat-burn model revealed that the percentage of incomplete healing associated with the application of Si-Zn-B-gel and 10% methyluracyl ointment was 0.12 and 3%, respectively. Thus, it demonstrates good prospects for the gel use. Following application of the soft dosage forms, in addition to the accelerated healing of the damaged skin, tissue crusts were formed on Day 3 of treatment. Complete crust detachment was observed on Day 9 and hair regrowth together with primary intention was observed on the new tissue at the end of the experimental application of Si-Zn-B-gel (Table 1).

Additionally, histomorphological tests were performed to study the wound healing effect, the test results are given in Figures 1–5. Necrotic epidermis with lymphocytic infiltration was found in the control group (that received no treatment) on Day 9 post the thermal burn. Granulation tissue (represented by functionally active fibroblasts and forming sinusoidal capillaries) was formed in the underlying dermis. The tissue was diffusely infiltrated with lymphoid elements (Fig. 1).

Weigert and Van Gieson stain method demonstrated that the scar area had collagen fibers of different maturity and different diameter, while the elastic fibers were identical (Fig. 2*a*). On Day 19 of the experiment, re-epithelization of the largest part of the skin defect was observed. The dermal scar was represented by functionally active

Table 1
Dynamics of rat skin regeneration in a thermal burn

Group of animals	Day 2	Day 9	Day 19	% incomplete healing
Control	40 × 20 mm (800 mm^2)	35 × 18 mm (630 mm^2)	20 × 10 mm (200 mm^2)	25
Experimental 1	40 × 20 mm (800 mm^2)	25 × 12 mm (300 mm^2)	7 × 3 mm (21 mm^2)	3
Experimental 2	40 × 20 mm (800 mm^2)	13 × 6 mm (78 mm^2)	3 × 0.3 mm (0.9 mm^2)	0.12

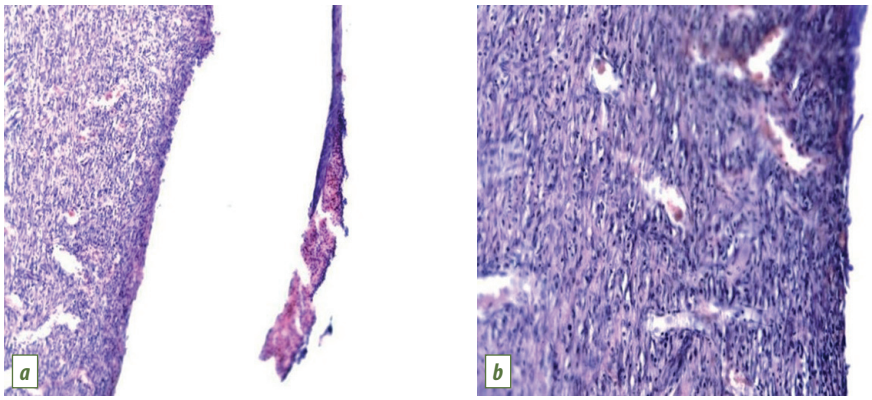

Fig. 1. Epidermis on Day 9 of the experiment (without treatment):
a) thermal burn on rat skin; stained with hematoxylin and eosin, magnification 100×;
b) granulation tissue formed after the burn;
stained with hematoxylin and eosin, magnification 200×

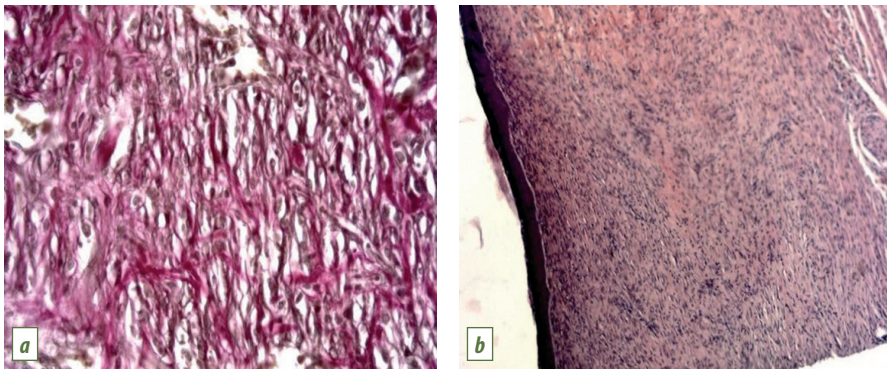

Fig. 2. Control group (without treatment):
a) collagen fibers formed in granulation tissue on Day 9 of the experiment;
Weigert and Van Gieson stain, magnification 400×;
b) forming dermal scar in the projection of the thermal burn on Day 19 of the experiment;
stained with hematoxylin and eosin, magnification 100×

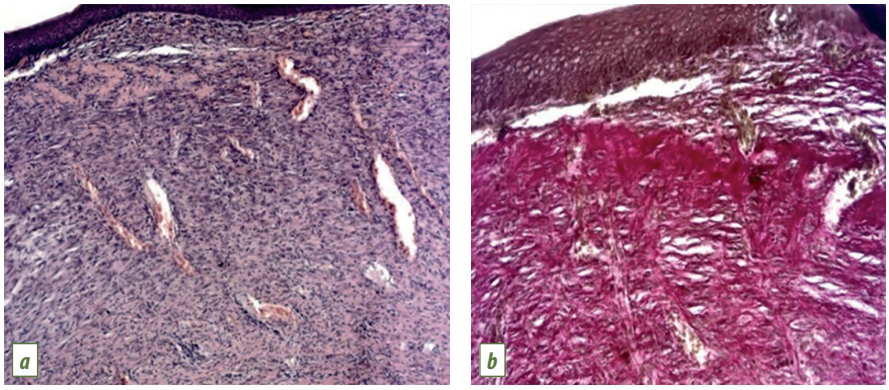

Fig. 3. Experimental Group 1 (10% methyluracyl ointment used for treatment) on Day 9 of the experiment:
a) a scar forming in the dermal layer in the projection of a thermal burn;
stained with hematoxylin and eosin, magnification of 100×;
b) scar of the dermal layer in the projection of a thermal burn;
Weigert and Van Gieson staining, magnification 100×

fibroblasts formed by randomly oriented collagen fibers. There were sporadic vessels, lymphoid infiltration was minimal (Fig. 2*b*).

On Day 9 of the experiment Experimental Group 1, where methyluracil was applied topically, demonstrated complete re-epithalization of the defect. The dermal scar is represented mainly by fibroblast cells formed by collagen fibers and sinusoidal vessels. Lymphoid infiltration was minimal (Fig. 3*a*). Weigert and Van Gieson stain method demonstrated that the scar area was represented by collagen fibers of different maturity degree and different diameter. Elastic fibers were sporadic (Fig. 3*b*).

On Day 19 after exposure, the group that was treated with 10% methyluracyl ointment demonstrated complete re-epithelization of the defect, acanthosis foci were reported with simultaneous formation of keratinous cysts. A dermal scar was formed with collagen fibers. Angiomatosis was sporadic, vessels – with collapsed walls. Lymphoid elements in the area of the scar were sporadic (Fig. 4*a*). Weigert and Van Gieson stain method demonstrated that the scar area in the dermal layer had mature dense collagen fibers similar in diameter (Fig. 4*b*).

On Day 9 of the experiment, Experimental Group 2, that received Si-Zn-B-gel treatment, demonstrated complete re-epithelization of the defect in the burn area. Granulation tissue was formed in the dermal layer from functionally active fibroblasts, sinusoidal capillaries, infiltrated with lymphoid elements (Fig. 5*a*). On Day 19 of the experiment, a mature scar was formed with a longitudinal alignment of collagen fibers; complete re-epithelization of the defect was observed with a fibrous scar in the dermal layer (Fig. 5*b*).

Thus, on Day 9 of the experiment, the control group (received no treatment) demonstrated longer burn healing with signs of exudative inflammation. On Day 19, the exudation phase was followed by the proliferation phase characterized by regeneration and replacement of the damaged tissues due to the influx of fibrinogen molecules to the defect region resulting in fibrin formation. At the same time, functionally active fibroblasts and mature randomly oriented collagen fibers form scar tissue, which becomes a dermal scar on Day 19 of the experiment.

In Experimental Group 1, where 10% methyluracyl ointment was topically applied, on Day 9 of the experiment complete re-epithelialization and dermal scar formation were observed, represented mainly by granulation tissue infiltrated by lymphocytes and granulocytes. By Day 19, the epidermis in the defect area got thicker; the scar tissue was formed mainly with collagen fibers and granulation tissue.

In Experimental Group 2, where Si-Zn-B-gel was used, on Day 9 of the experiment, the burn wounds fully re-epithelized, with fibrous structures prevailing in the granulation tissue of dermis, and on Day 19 a mature scar with longitudinally oriented collagen fibers was formed. The results of burn treatment with 10% methyluracyl ointment (Fig. 3*a*) and Si-Zn-B-gel (Fig. 5*a*) compared on Day 9, demonstrate that the developed hydrogel effectively triggers granulation process resulting in formation of young connective tissue, which stimulates the healing process; whereas, application of methyluracil immediately leads to scarring.

Experiments conducted in high producing dairy cows to study effectiveness of Si-Zn-B-gel for teat-end hyperkeratosis treatment showed a decrease in the number of udder quarters with pronounced changes in the teat ends.

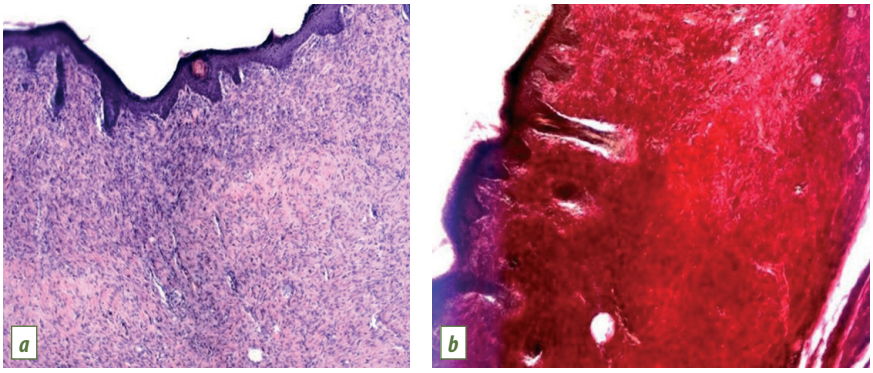

Fig. 4. Experimental group 1 (10% methyluracyl ointment used for treatment) on Day 19 of the experiment:
a) scar of the dermal layer in the projection of the thermal burn;
staining with hematoxylin and eosin, magnification of 100×;
b) scar of the dermal layer; Weigert and Van Gieson staining, magnification 100×

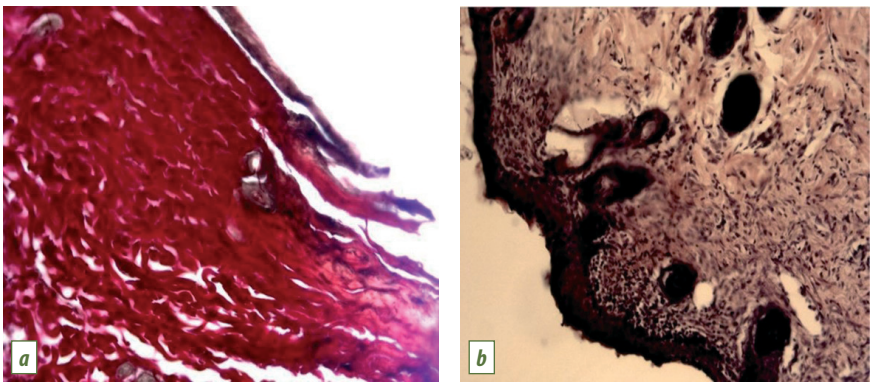

Fig. 5. Experimental Group 2 (treatment with Si-Zn-B-gel):
a) burn area on Day 9 of the experiment; staining with hematoxylin and eosin, magnification 100×;
b) fibrous scar in the dermal layer on Day 19 of the experiment; Weigert and Van Gieson staining, magnification of 200×

At the end of the experimental period (which took 7 days), the group of animals who received the hydrogel demonstrated regeneration of the teat-end epidermis, the number of teat-ends with a physiologically normal structure increased to 27.8%. On Day 14 after application of Si-Zn-B-gel, no severe hyperkeratosis-associated lesions of teat-ends were reported, at the same time the number of physiologically normal teat-ends grew up to 72.2%. On Day 21 after the end of the experiment, a diagnostic test for hyperkeratosis revealed that teat-end condition remained at the achieved level with a tendency to improve (Fig. 6*a*).

The experiment results showed that the number of teat-ends with radial cracks decreased by 2.7 times in the control group treated with 10% methyluracyl ointment, and physiologically normal teat-ends accounted for 38.9%. On Day 14 after the treatment period with 10% methyluracyl ointment, no complications in animals were detected following and the number of physiologically normal teat-ends accounted for 84.1%. The teat-end examination done after the treatment course (on Day 21 after the end of the treatment) reflected a deterioration, which is most likely caused by the negative factors of milking process and animal husbandry. Thus, the number of healthy teat-ends decreased by 15.5%, and the number of teat-ends with hyperkeratosis increased by 2 times – up to 31.4% (Fig. 6*b*). While the experimental group of animals kept under the same conditions showed improvement of the teat-ends condition, so, the number of teat-ends with hyperkeratosis decreased to 13.9%, and the number of physiologically normal teat-ends accounted for 86.1%. These changes may suggest Si-Zn-B-gel has a more a prolonged effect and is more effective in comparison with 10% methyluracyl ointment.

Diameter of teat-end callosities measured during the experiment suggests that both medicines gradually reduce the callosity size. In the experimental and control groups the mean callosity diameter decreased by 1.6 times. Therefore, at the beginning and at the end of the experiment, the callosity size in the experimental group was 7.8 and 4.8 mm, respectively, in the control group at the beginning of the experiment the mean diameter was 7.9 mm, by the end of the experiment it decreased to 4.9 mm.

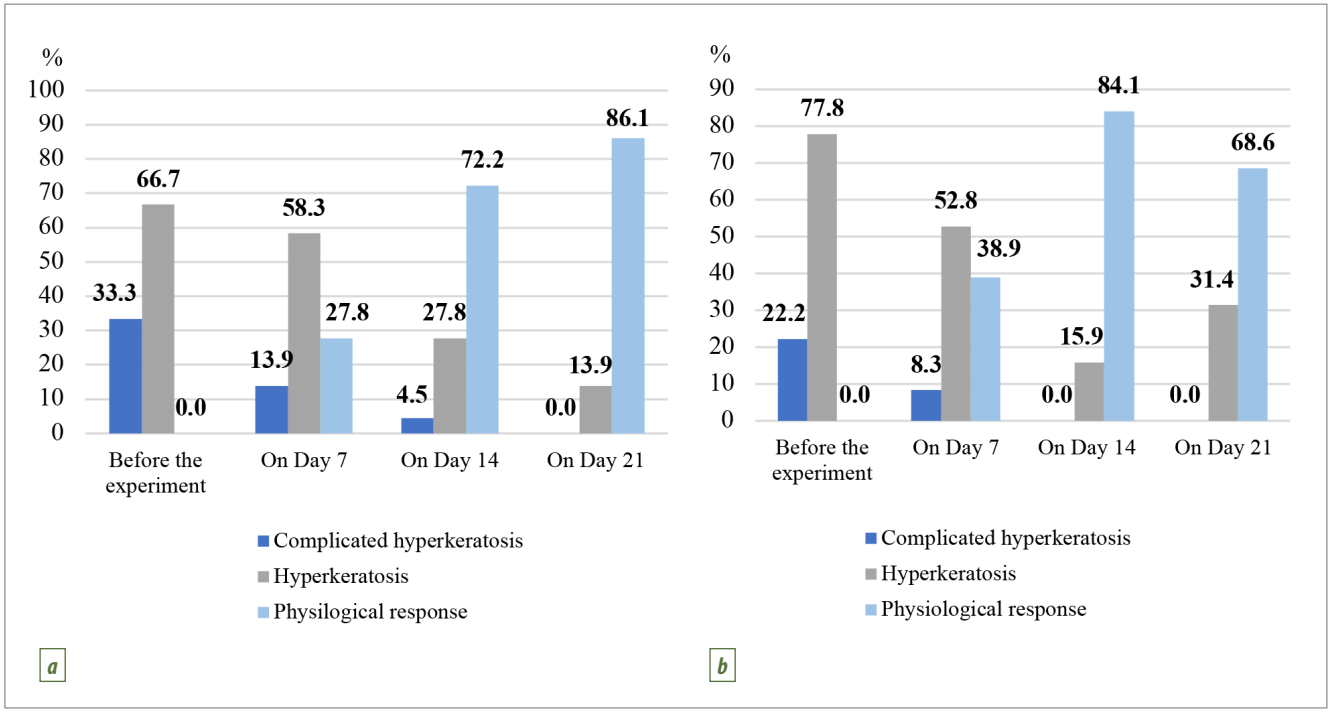

Fig. 6. Results of the cows' teats examination during the treatment process:
a) experimental group – use of Si-Zn-B-gel; b) control group – use of 10% methyluracyl ointment

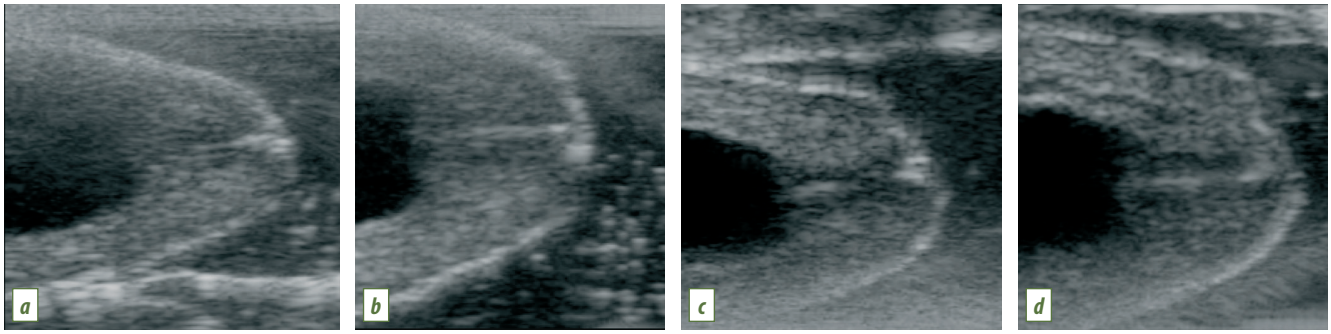

Fig. 7. Ultrasound examination of the teat canal: a) before the use of Si-Zn-B-gel; b) after the use of Si-Zn-B-gel; c) on Day 7 after the use ; d) on Day 14 after the use

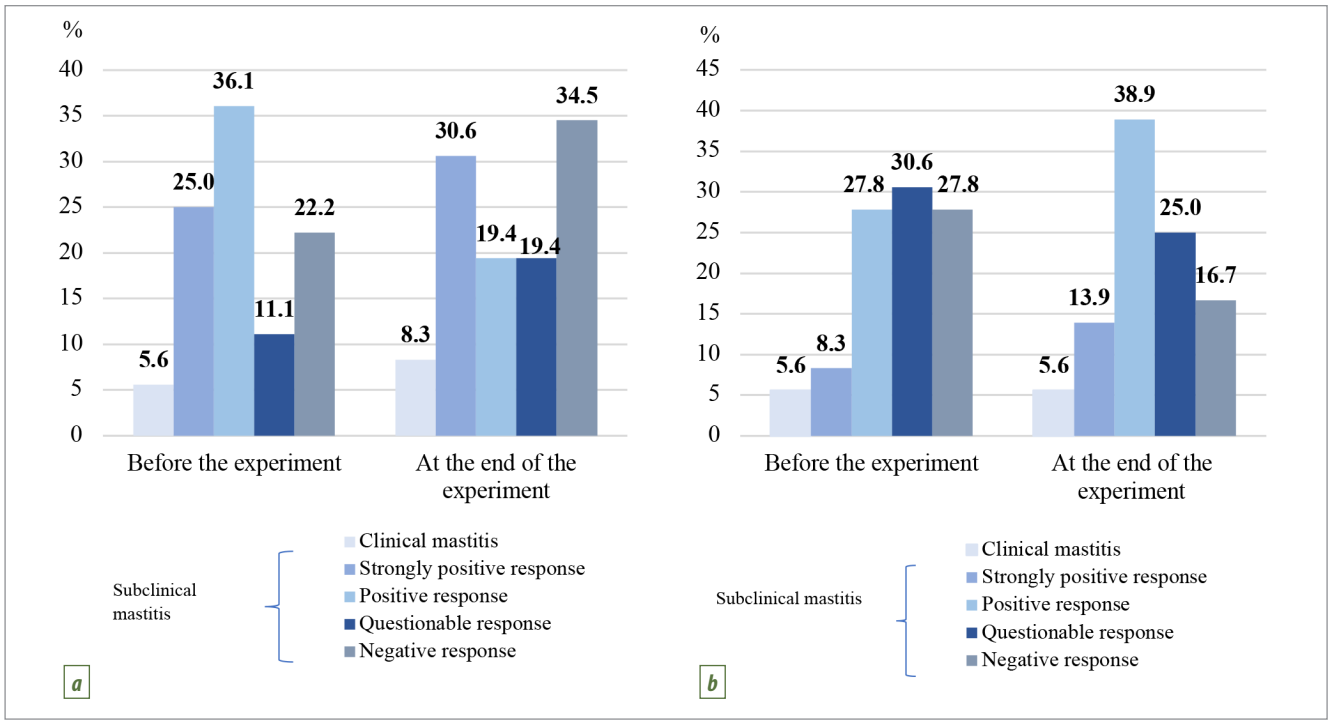

Fig. 8. Mastitis incidence rate during the treatment:
a) experimental group – use of Si-Zn-B-gel; b) control group – use of 10% methyluracyl ointment

Ultrasound examination detected changes in the teat canals associated with a decrease in the volume of the affected tissue around the external teat orifice, as it can be seen in hyperechoic tissue in the picture; with the final recovery on Day 14 after the therapy (Fig. 7).

The condition of the mammary gland was assessed by examining each quarter of the udder for clinical and subclinical mastitis. As a result, latent inflammation (strongly positive and positive response) was reported in 61.1% of quarters. At the end of the experimental period, the number of quarters with a questionable and negative response to subclinical mastitis increased by 8.3 and 12.6%, respectively. There was a 16.7% decrease in positive response to latent mastitis, at the same time, there was a slight (2.7%) increase in clinical mastitis, which most likely results from faulty milking techniques and had nothing to do with the effectiveness of the developed glycerohydrogel (Fig. 8*a*). In the control group, the proportion of diagnosed clinical mastitis before and after the therapy was 5.6%, however, there was a decrease in the number of udder quarters with questionable and negative response to subclinical mastitis by 5.6 and 11.1%, respectively (Fig. 8*b*).

At the beginning of the experiment, 33% of milk samples from the animals of the experimental group had a weakly positive reaction to blood impurities, whereas all milk samples from the control group gave a negative result. At the end of the experimental period, milk samples from the cows of the experimental group showed a negative result, one positive result was detected in the control group.

Estimating solids-not-fat, protein, fat and density in milk from animals of both groups revealed no significant differences between the groups (Table 2).

CONCLUSION

Evaluation of the specific wound-healing effect of the two medicines showed that by the end of the experiment, the group of rats that received Si-Zn-B-gel to treat thermal burn had a mature scar with longitudinally oriented collagen fibers, and the group of animals treated with 10% methyluracyl ointment (applied topically) demonstrated thickening of the epidermis and the scar tissue included collagen fibers and foci of granulation tissue. The overall duration of the treatment in both experimental groups was the same (the same number of days); however, the use of Si-Zn-B-gel resulted in improved morphostructural indicators, which offers great potential for the product application.

The data obtained for cows treated with Si-Zn-B-gel confirm its therapeutic efficacy. Thus, there was an increase in the number of udder quarters not affected

Table 2
Milk quality assessment in experimental and control groups

Group of animals	Fat, %	Protein, %	Solids-not-fat, %	Density,°A
Control	4.68 ± 3.10	3.02 ± 0.49	7.90 ± 1.23	26.25 ± 6.03
Experimental group	3.95 ± 3.14	3.05 ± 0.40	7.99 ± 0.83	27.16 ± 5.03

$P \leq 0.05$.

by the inflammatory process; an increase in the number of teats without hyperkeratosis; the teat-end callosity diameter decreased. The newly developed product had a positive effect on the tissues of the teat-ends of cows, as confirmed by the ultrasound examination, which showed a decrease in the volume of the affected tissue around the external teat orifice.

A comparative assessment of the Si-Zn-B-gel and 10% methyluracyl ointment revealed the prolonged action of the former resulting from its longer therapeutic effect. Thus, there was a decrease in the diagnosed teat-end hyperkeratosis in the experimental group during the whole observation period, however, in the control group, first, there was a decrease in the number of animals with teat-end hyperkeratosis, and then followed by an increase. Similar data were received when diagnosing latent inflammatory diseases in the bovine mammary glands. The results obtained show effectiveness of the developed Si-Zn-B-gel due to its pronounced wound-healing, regenerating, antibacterial, fungicidal activity and prolonged action, which makes it possible to recommend it as a medicine to treat teat-end diseases in lactating cows.

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