Original Article

Investigation of Pharmacological and Wound-Healing Properties of Zinc Oxide Nanoparticles

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Abstract

A comparative analysis of the specific pharmacological activity and wound-healing properties of zinc oxide nanoparticles (ZnO-NPs) was carried out. It has been shown that ZnO-NP forms reduce the severity of formalin paw edema in mice and the exudative reaction in "felt" granuloma in rats. Notably, the effectiveness of the ointment form exceeded the effectiveness of the gel form. The ability of ointment and gel based on ZnO-NPs has been shown to significantly reduce the recovery time of hemorrhagic soft tissue injuries in rats and, unlike medicinal forms of heparin, to increase the blood clotting time of rabbits by 1.25 times and 1.19 times, respectively. Thus, ointment and gel containing ZnO-NPs are potential medicines with anti-inflammatory, anticoagulant properties and the property of shortening the recovery time of hemorrhagic soft tissue injuries. It is concluded that the therapeutic effect of samples containing ZnO-NPs, due to the ability of these nanoparticles to penetrate the skin epithelium, providing regenerating and fibrinolytic activity, blocking the activity of inflammatory mediators and providing, including the systemic effect on blood clotting.

Keywords: ZnO-NPs, Apoptosis, Anti-inflammatory activity, Anticoagulation, Wound healing

Introduction

Modern medicine pays increasing attention to the creation of new highly effective and safe medicines [1]. For the most part, the use of drugs presented as products of chemical synthesis, as well as animal or plant origin, is accompanied by side effects, which often limits their clinical use [2-4]. The problem of finding new potential medicines, including those based on natural raw materials, remains urgent. At the same time, it is important to search for drugs that exhibit a multifaceted effect (including anti-inflammatory, wound healing, anti-burn, antihemorrhagic, and anti-clotting) when applied to the skin for the treatment of injuries [5-7].

Currently, zinc oxide nanoparticles (ZnO-NPs) are widely used in various fields due to their special physico-chemical properties: diverse morphology, large surface area to volume ratio, powerful antibacterial activity, excellent biocompatibility, environmental friendliness, cost-effectiveness and low toxicity [8-11]. ZnO-NPs have unique optical, chemical, semiconductor, photocatalytic, electrically conductive, and piezoelectric properties [12-15]. They are widely used to treat various skin conditions, have wound-healing activity, anti-cancer properties, and exhibit antimicrobial activity against various microorganisms [16-21].

Therefore, there is a scientific and practical interest in the application of ZnO-NPs in formulations of modern drugs with multifaceted pharmacological and wound-healing properties. Thus, this study aimed to evaluate the prospects for the development of drugs based on ZnO-NPs in the case of skin application.

Materials and Methods

The experiments were carried out on 100 white non-harmless mice weighing 20.2±0.4 g, 240 white non-harmless rats weighing 210±4 g, and 20 rabbits weighing 3000±10 g. The

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studies were conducted following the rules of high-quality laboratory practice in conducting preclinical studies in the Russian Federation. *In vivo* experiments were performed in compliance with national and international requirements for the maintenance and humane treatment of animals [22]. The objects of the study were ZnO-NPs produced by the Institute of General Physics (Moscow, Russia), as well as "Fastum" ointment and gel for external use (Biopharm, Moscow, Russia).

In the work, the doses of the studied ointment and gel were determined taking into account the interspecific recalculation of doses from humans (4g/70kg = 57.1 mg/kg) per mouse (1:11), rat (1:7) and rabbit (1:3.2) [23]. The resulting doses amounted to 630 mg/kg for mice, 400 mg/kg for rats, and 183 mg/kg for rabbits. ZnO-NPs were used in the same doses as a 1% solution with 0.9% NaCl. Diclofenac gel (Biopharm, Moscow, Russia) and Heparin ointment (BioProtect, Gomel, Belarus) were used as controls and applied to animals at the same doses.

Anti-inflammatory activity was evaluated on a model of formalin paw edema in mice with subplantar injection of 0.1 mL of 2% aqueous formalin solution into the hind paw [24]. The experimental animals applied the studied samples to the sole of the paw with light rubbing daily for 10 days. The control group was given an isotonic sodium chloride solution. The severity of edema was assessed by measuring the thickness of the foot before and 4 hours after the administration of formalin [25-27]. The evaluation of anti-inflammatory activity was also carried out on a model of "felt" granuloma in rats [28]. Chronic proliferative inflammation was caused by the implantation of sterilized felt pieces weighing 40±2 mg under the skin of the medial part of the back [29, 30]. The studied samples were applied daily to the trimmed area with light rubbing. On the 8th day after the operation, pieces of felt with granulation tissue formed around them were removed, weighed, and dried to a constant mass. The proliferative and exudative reactions were calculated and expressed in % [31].

The therapeutic effect in hemorrhagic lesions was evaluated on non-harmless white rats. In experimental animals, the hair covering on a part of the skin of the back was removed. Hemorrhagic soft tissue injuries using local anesthesia (lidocaine) were caused by applying a standard blunt blow of fixed force [32, 33]. The examined samples were applied to rats daily for 6 days with light rubbing until the hematomas completely disappeared.

The wound healing effect was studied on white nonlinear rats. Previously, the hair covering a part of the skin of the back with an area of 3x3 cm^2 was removed from the experimental animals. Layered skin wounds were applied using a 225 mm^2 stencil using local anesthesia (lidocaine) [34]. The tested samples were applied daily to the skin of experimental animals until complete healing.

The anticoagulation effect was evaluated on rabbits when applied to experimental animals for 10 days with light rubbing of the test samples onto a skin area with a hairline removed with an area of 4x4 cm^2 [35]. Before the experiment and 10 days later, blood was taken from the marginal vein of the ear to record the time of blood clotting according to the hemocoagulation analysis using AGCM 1-01 device (Lumex, St. Petersburg, Russia).

Statistical data processing was performed using the software package Microsoft Office EXCEL 2010 and STATISTICA 12. The presence of a normal distribution of data was checked using the Kolmogorov–Smirnov criterion. The parameters of the normal distributions of features in the samples were described in the format M±m (mean value ± standard error of the mean). The statistical reliability of the differences in research results between the groups was checked by the Student's t-test.

Results and Discussion

With subplantar administration of 0.1 mL of 2% formalin solution, experimental mice develop pronounced paw edema, as evidenced by a significant increase in its volume. 4 hours after the injection of formalin, the paw volume in the experimental animals of the control group increased by 72.1 ± 2.8%. With the skin application of ZnO-NPs, there was a decrease in the severity of formalin-induced paw edema in mice to 52.28±4.60%, which is 1.38 times ($p<0.05$) less than in the control. The severity of the anti-inflammatory effect of 1% of the ointment with ZnO-NPs corresponded to the activity of aqueous extraction of ZnO-NPs, whereas the gel with ZnO-NPs acted weaker **(Figure 1)**. This was also manifested in relation to the activities of the ointment and diclofenac gel.

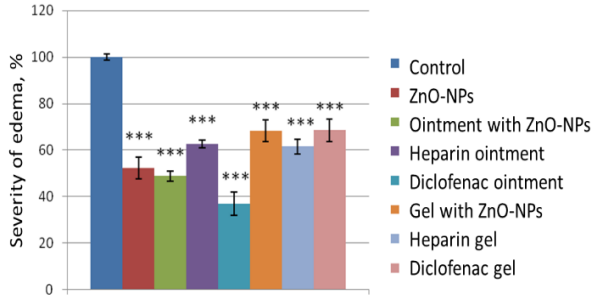

Figure 1. The effect of control and experimental substances on the severity of formalin edema of the paws of mice. Note: *, ** and *** – the differences with the control are significant at $p<0.05$, 0.01 and 0.001, respectively

Thus, diclofenac ointment showed the greatest effect on decongestant action (63.22±4.96%), 1.64 times more pronounced ($p<0.05$) than diclofenac gel (38.5±4.8%). ZnO-NPs and ZnO-NPs-based ointment also showed a fairly high reliable effect, amounting to 47.72±4.6% and 51.3±2.2%, respectively, against 31.74±4.6% for a ZnO-NPs-based gel,

1.6 times more pronounced than for a gel. The smallest but reliable effect was found for heparin ointment and gel, amounting to 37.5±1.7% versus 38.5.5±3.18%.

On day 8, the exudative and proliferative reactions in "felt" granuloma in rats amounted to 66.1±3.3% and 9.4±0.8%, respectively. When evaluating the proliferative reaction in "felt" granuloma in rats, there were no significant differences from the control group on day 8. At the same time, for the exudative reaction, a significant decrease was revealed when using ZnO-NPs substance, ZnO-NPs ointment, heparin ointment, and diclofenac ointment with 66.1±3.3% in the control to 52.5±2.0 %, 57.5±4.1 %, 56.6±2.7 % and 42.9±4.6%, respectively. For the gel based on ZnO-NPs, heparin gel, and diclofenac gel, there was only a tendency to decrease this indicator **(Figure 2)**.

Thus, an analysis of the results of an experimental study of anti-inflammatory activity showed that when ZnO-NPs were applied to a model of felt granuloma in rats, there was a decrease in the severity of the exudative reaction without affecting the proliferative one.

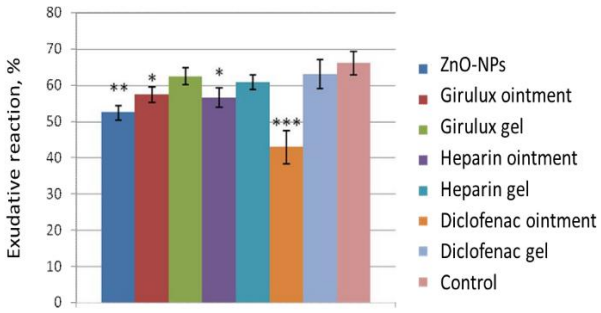

Figure 2. The effect of control and experimental substances on the severity of the exudative reaction in "felt" granuloma in rats.

When evaluating the therapeutic effect of the studied samples for hemorrhagic soft tissue injuries in rats, it was found that the time of resorption of hematomas using ZnO-NPs significantly decreased by an average of 1.22 times, and the gel with ZnO-NPs – by 1.16 times. The data presented in **Table 1** indicate that ZnO-NPs in free and gel forms lead to a significant reduction in the recovery time of hemorrhagic soft tissue injuries in rats [36-38].

Table 1. The effect of Girulux gel and ZnO-NPs on the course of hemorrhagic soft tissue injuries in rats

Sample	Terms of tissue recovery after hemorrhagic damage, days	
	Results	Total change, %
ZnO-NPs	3.6±0.2*	-18.2±4.5*
Gel with ZnO-NPs	3.8±0.2*	-13.6±4.5*
Heparin Gel	3.9±0.3	-11.4±6.8
Control	4.4±0.2	-0.0±4.5

Notably, there were no significant differences in the healing rate of skin wounds under the action of ZnO-NPs and ointment with leech extract, but there was a tendency to accelerate the healing process by 0.4 days (4.8%) and 0.3 days (3.6%), respectively.

Skin application of ZnO-NPs to rabbits leads to a significant increase in the blood clotting time of experimental animals by an average of 40%, ointment with ZnO-NPs by 25%, and when using gel with ZnO-NPs by 19%. At the same time, heparin preparations proved ineffective in this setting of the experiment **(Figure 3)**.

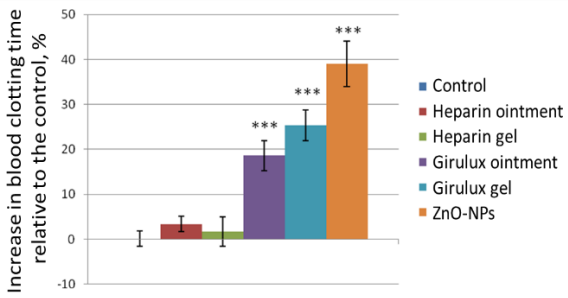

Figure 3. Effect of substance, ointment, gel with ZnO-NPs, and heparin on blood clotting time in rabbits.

Thus, ZnO-NPs, as well as Girulux gel and Girulux ointment showed anti-inflammatory, anticoagulant properties and the ability to accelerate the resorption of hemorrhagic soft tissue injuries. The results obtained are in line with recent data reported by other researchers [39-41].

Taking into account the fact that earlier it was shown that the acceleration of healing of burn wounds in rats when applying ZnO-NPs was on average 1.2 times faster than in the control with a significant (3 times) acceleration of the rate of epithelization of burn wounds from 5 days after injury [42-46]. Probably, the therapeutic effect of samples containing ZnO-NPs, due to the ability of these nanoparticles to penetrate the skin epithelium, providing regenerating and fibrinolytic activity, blocking the activity of inflammatory mediators and providing, including the systemic effect on blood clotting [47-50].

Conclusion

ZnO-NPs, when applied to mice in a dose of 630 mg/kg, inhibit paw edema with the introduction of formalin. Moreover, diclofenac ointments with ZnO-NPs and heparin exceed the activity of similar gels in terms of the effectiveness of inflammation suppression. In the model of felt granuloma in rats, the ZnO-NPs substance reduces the exudative reaction during course application. ZnO-NPs and ZnO-NPs gel, unlike heparin gel, significantly reduce the tissue recovery time for hemorrhagic lesions in rats. Daily for 10 days, course skin application of ZnO-NPs ointment to rabbits at a dose of 183 mg/kg leads to an increase in the blood clotting time of

experimental animals by an average of 1.25 times, and when using gel by 1.2 times, unlike heparin preparations. Ointment and gel with ZnO-NPs when applied on the skin of experimental animals have a complex anti-inflammatory effect, accelerate tissue repair after hemorrhagic damage, reduce the rate of blood clotting, and are potential medicines.

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ETHICS STATEMENT: All studies were performed following the Guidelines for the preclinical study of medicines of the Russian Federation and approved by the Ethics Commission (Protocol 3 dated by Aug 3, 2024).

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