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Research Article

Systemic Effect of the Antioxidant Gel in Experimental Dermatologic Pathology

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Abstract

Many dermatological diseases are accompanied by oxidative stress and natural antioxidants are used in dermatology and cosmetology. The efforts to use synthetic antioxidants for skin care and treatment are practically absent. That is why we select for this investigation new topical formulation of ethylmethylhydroxypyridine succinate (EMHPS), a synthetic antioxidant. The objective is to study the status of lipid peroxidation and antioxidant protection in the blood of animals with experimental dermatologic pathology under the influence of the EMHPS gel topical use. There were three series of experiments on 125 adults male Wistar rats with chemical depilation, acute ultraviolet skin damage and psoriatic-like dermatitis. The 5% EMHPS gel was applied to the skin in a dose of 125 mg/kg. The duration of treatment was 21 days after chemical depilation, 3 days after ultraviolet irradiation, and 6 days after the induction of imiquimod dermatitis. The animals were euthanized in different moments of the experiments and the malondialdehyde (MDA) concentration, superoxide dismutase (SOD) and catalase activities were determined in the blood. The data were statistically processed by ANOVA method with a post-hoc Tukey test. Obtained results confirmed that local pathological processes of an inflammatory nature in the skin of laboratory animals, modeled as chemical depilation, ultraviolet irradiation, and psoriatic-like dermatitis, are accompanied by oxidative stress at the level of the whole organism with the manifestation in the blood. In the recovering period after chemical depilation, the EMHPS gel reduced the MDA concentration in the blood and increased the SOD and catalase activity in 3, 9 and 21 days after depilation. On the background of ultraviolet irradiation, the studied gel inhibited the MDA accumulation in the blood 2 and 3 days after and reduced the SOD activity 1 day after the exposure. In the developed imiquimod-induced dermatitis, the EMHPS gel lowered the MDA concentration in the blood and enhanced the catalase activity to the end of treatment. Therefore, the 5% EMHPS gel used topically, produced an antioxidant effect at the systemic level, which, given neuro- and organoprotective properties and low toxicity of EMHPS, is a positive aspect of experimental therapy for dermatological pathology.

Keywords: *Oxidative Stress; Antioxidant; Ethylmethylhydroxypyridine Succinate; Gel; Skin Disease Animal Model; Systemic Effect*

Abbreviations

b.w.: Body Weight; DNA: Deoxyribo Nucleic Acid; EMHPS: Ethyl Methyl Hydroxy Pyridine Succinate; LPO: Lipid Per Oxidation; MDA: Malon Di Aldehyde; ROS: Reactive Oxygen Species; SOD: Super Oxide Dismutase; TRIS: TRIS(hydroxymethyl)aminomethane; UV: Ultra Violet

Introduction

It is known that the skin faces numerous environmental influences that generate reactive oxygen species (ROS) and has a powerful antioxidant defense [1] and many dermatological diseases are accompanied by oxidative stress [2]. Two main possible mechanisms underlie oxidative stress-induced skin cellular senescence, inflammation, and cancer. One mechanism is that ROS directly degrade

biological macromolecules, including proteins, DNA, and lipids; another one is that ROS mediate signaling pathways affecting cytokine release and enzyme expression [3]. These ideas are the basis for the use of antioxidants in dermatology and cosmetology [4,5]. The following compounds have been tested as antioxidants in dermal pathology: alpha-tocopherol, ubiquinone, L-ascorbic acid, alpha-lipoic acid, lycopene, plant polyphenols, etc [4]. Majority of studies are devoted to natural antioxidant products [6], efforts to use synthetic antioxidants for skin care and treatment are practically absent. That is why we select for this investigation new topical formulation of ethylmethylhydroxypyridine succinate (EMHPS), a synthetic antioxidant of heterocyclic structure which can have dermatologic action according to computer prognosis [7]. This substance is characterized by wide spectrum of pharmacodynamic activity, including sedative, nootropic, cerebroprotective, cardioprotective, renoprotective and oculoprotective effects [8]. In Ukraine, it is approved for clinical use in neurology and cardiology [9].

Objective of the Study

The objective is to study the status of lipid peroxidation (LPO) and antioxidant protection in the blood of animals with experimental dermatologic pathology under the influence of topical use of the EMHPS gel.

Materials and Methods

Materials

The EMHPS substance was obtained from the manufacturer (NVF Microchem TOV, Ukraine). The gel contained 5.0g of EMHPS, 0.5g of sodium metabisulfite, 1.0g of polyvinyl alcohol, 2.0g of carbomer 940, 2.8g of tris(hydroxymethyl)aminomethane (TRIS) and distilled water to 100,0g. It was made by laboratory technology: EMHPS substance and sodium metabisulfite were dissolved in water, polyvinyl alcohol was separately dissolved in water by heating and the resulting solutions were mixed; carbomer 940 and TRIS were added in small portions with constant stirring until a gel was formed.

In this study, the 2% solution of minoxidil (Industrial Pharmaceutics Cantabria, S.A., Spain), 5% ointment of panthenol (Khemofarm AD, Serbia), and 0.5% ointment of prednisolone (Chervona Zirka PAT Khimzavod, Ukraine) were used as reference preparations in different series of experiments. 5% imiquimod cream (Keravort) (Glenmark Pharmaceuticals Ltd, India) served as an inductive agent in the model of psoriatic-like skin inflammation.

Model pathology and experimental therapy

There were three series of experiments with design of chemical depilation (series I), acute ultraviolet (UV) damage of the skin (series II), and psoriatic-like dermatitis (series III). 125 adult male Wistar rats (age 122-126 days, weight 185-215g) were used in the experiments which have been performed in accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986) and the European Union Directive 2010/10/63 EU. The research protocols were approved by the Commission on Ethical Issues and Bioethics of the Poltava State Medical University (No. 197, September 23, 2021).

In the series I, pathology was modeled by chemical depilation of the backs of animals, for which the dorsal skin was treated with a commercial depilatory product based on potassium thioglycolate during 10 minutes [10]. The EMHPS gel was applied to the skin of the test area in a dose of 125 mg/kg body weight (b.w.) (an average of 0.5 ml for a rat weighing 200g). The minoxidil solution as a reference preparation (30 mg/kg b.w., or an average 0.3 ml per rat) was used in the same manner. The treatment was carried out daily during 3, 9 and 21 days.

In the series II, a 5 cm^2 area of the dorsal skin was depilated with a commercial cosmetic product with 3 min exposure a day before UV irradiation. Rats were irradiated with a Cleo Compact Isolde UV lamp (Philips, Germany). A dose of UV A was 3.75 J/cm^2 and a dose of UV B was 0.05 J/cm^2 [11]. The affected skin was lubricated with 5% EMHPS gel (125 mg/kg b.w., once a day). 5% panthenol ointment, a reference preparation, was applied similarly at the same dose. The duration of treatment was 1, 2, or 3 days.

In the series III, rats' hair on the back was cut with scissors and finally removed with a commercial depilatory agent. The skin of the test area was treated with 5% imiquimod cream at 125 mg daily for 6 days for induction of psoriatic-like dermatitis [12]. After the development of dermal lesions (day 7), the topical therapy with studied EMHPS gel (125 mg/kg b.w. per day) or 0.5% prednisolone ointment as a reference preparation began. It lasted for 6 days.

In all series, control groups of animals were treated with an indifferent gel base as a vehicle. The animals were removed from the experiment by terminal blood loss [13] under general anesthesia with thiopental sodium (50 mg/kg b.w.) (Kyivmedpreparat, Ukraine). Blood samples were collected from the heart and used for biochemical investigation.

Biochemical assays

The content of malondialdehyde (MDA) in the blood was determined by a method based on the MDA ability to react with 1-methyl-2-phenyl-indole [14]. The activity of superoxide dismutase (SOD) was measured by the kinetics of epinephrine autoxidation [15]. The activity of catalase was studied by the molybdate colorimetric assay [16]. The optical density measurements were performed on a Ulab 101 spectrophotometer (China).

Statistical analysis

The digital data were presented as a mean and a standard error of the mean (M ± SEM). They were statistically processed by ANOVA method with a post-hoc Tukey test. The difference between groups considered probable at $p < 0.05$.

Results

Oxidative stress biomarkers in the therapy of chemical depilation

Changes in the MDA content were recorded in the blood of animals with chemical depilation: it was increased after 3 days ($p < 0.001$) and 21 days ($p < 0.001$) and was at the level of the intact rats 9 days after hair removal (Figure 1A). Minoxidil reduced these indicators in all periods of observation: after 3 days - by 1.2 times ($p < 0.001$), after 9 days - by 1.2 times ($p < 0.001$) and after 21 days - by 1.1 times ($p < 0.001$) in comparison with the control. The new EMHPS gel acted similarly, reducing the concentration of MDA in the blood after 3 days by 1.5 times ($p < 0.001$), after 9 days - by 1.5 times ($p < 0.001$), after 21 days - by 1.3 times ($p < 0.001$) as compared to control. In all periods of observation, this decrease was probably more pronounced than that under the influence of the reference drug minoxidil.

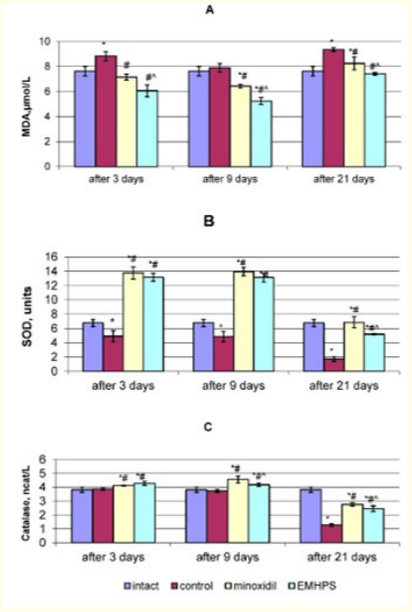

Figure 1: *The influence of topical application of the EMHPS gel on oxidative stress biomarkers in the blood after chemical depilation. A - MDA concentration, B - SOD activity, C - Catalase activity. Results are expressed as mean ± standard error of the mean (n = 5). * - p < 0.05 as compared to intact animals, # - p < 0.05 as compared to control, ^ - p < 0.05 as compared to minoxidil, a reference preparation.*

The activity of SOD in the blood of rats with chemical depilation probably decreased ($p < 0.005$), which reached a maximum after 21 days when the activity of the enzyme decreased by 3.9 times ($p < 0.001$) compared to the intact group (Figure 1B). The use of topical minoxidil increased the activity of the enzyme after 3 days by 2.8 times ($p < 0.001$), after 9 days - by 2.9 times ($p < 0.001$), and after 21 days - by 4 times ($p < 0.001$) compared to control. EMHPS gel also contributed to the growth of SOD activity in all periods of observation ($p < 0.001$). This effect was not significantly different from the effect of minoxidil after 3 and 9 days and was slightly weaker than it after 21 days ($p < 0.005$).

Blood catalase activity in the control group did not change after 3 and 9 days of the experiment and decreased after 21 days ($p < 0.001$) (Figure 1C). Under the influence of minoxidil, it increased by 1.1 times ($p < 0.02$), 1.2 times ($p < 0.001$) and 2.2 times ($p < 0.001$) against control in the corresponding periods of observation. Under the topical EMHPS action, this indicator increased by 1.1 times after 3 days ($p < 0.001$) and after 9 days ($p < 0.005$), by 1.9 times -- after 21 days ($p < 0.001$) in comparison with the control. In terms of the expressiveness of the effect after 9 days and 21 days, these changes were somewhat inferior to the effect of the reference drug ($p < 0.05$).

Oxidative stress biomarkers in the therapy of UV skin damage

Changes in biomarkers of oxidative stress were also observed in the blood of animals exposed to UV irradiation (Figure 2). In the control, the content of MDA was increased by 2.3 times 1 day after irradiation ($p < 0.001$) and remained elevated after 2 ($p < 0.001$) and 3 days ($p < 0.001$) compared to the values of intact animals (Figure 2A). The panthenol ointment did not reduce the accumulation of MDA in the blood at any time of observation. In contrast to the reference preparation, the EMHPS gel did not affect the concentration of this LPO intermediate after 1 day, but reduced it by 1.3 times ($p < 0.001$) after 2 days and by1.4 times ($p < 0.001$) after 3 days of treatment ($p < 0.005$) compared to control.

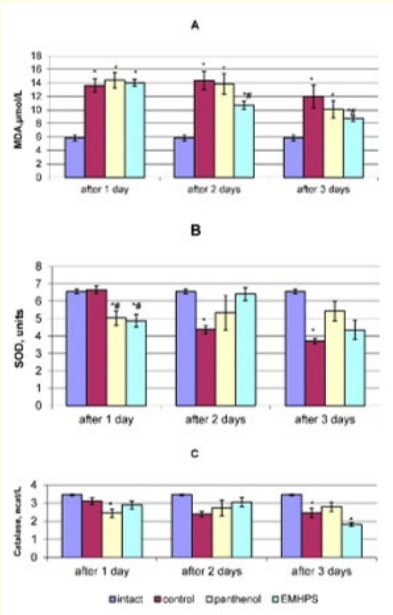

Figure 2: *The influence of topical application of the EMHPS gel on oxidative stress biomarkers in the blood after UV irradiation. A - MDA concentration, B - SOD activity, C - Catalase activity. Results are expressed as mean ± standard error of the mean (n = 5). * - p < 0.05 as compared to intact animals, # - p < 0.05 as compared to control, ^ - p < 0.05 as compared to panthenol, a reference preparation.*

Ultraviolet irradiation did not cause any changes in the activity of SOD and catalase in the blood of animals of the control group 1 day after the exposure (Figure 2B). After 2 and 3 days, there was a significant decrease in SOD activity ($p < 0.05$ and $p < 0.01$, respectively) compared to intact rats. Catalase activity underwent changes only 3 days after UV irradiation, when the activity of this enzyme was reduced by 1.4 times ($p < 0.01$) compared to the values of intact animals (Figure 2C). The EMHPSe gel reduced blood SOD activity after 1 day of treatment ($p < 0.01$), showed a tendency to its increase after 2 days ($p < 0.1$) and did not change it after 3 days of the gel application compared to control. Panthenol had a similar effect on the SOD activity in the blood. The catalase activity did not change with the application of EMHPS gel 1 and 2 days after UV irradiation and had a tendency to decrease by 1.3 times ($p < 0.1$) after 3 days compared to control. Under the influence of panthenol, blood catalase activity did not change during the entire observation period.

As shown by the above results, UV irradiation of the skin area of rats caused an increase of LPO and decreased the activity of antioxidant enzymes in the blood. The studied gel counteracted the accumulation of LPO products in the blood and reduced the activity of SOD in the early term of observation.

Oxidative stress biomarkers in the therapy of psoriatic-like dermatitis

The development of imiquimod-induced dermatitis over 6 days caused a 2.3-fold increase in the MDA concentration in the blood ($p < 0.001$) compared to intact animals (Figure 3A). At the same time, SOD activity decreased 2-fold ($p < 0.001$) (Figure 3B), and catalase activity decreased 1.9-fold ($p < 0.001$) (Figure 3C) compared to the values of intact rats.

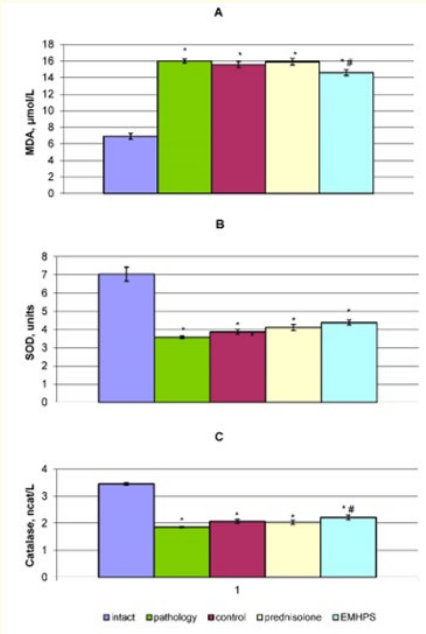

Figure 3: *The influence of topical application of the EMHPS gel on oxidative stress biomarkers in the blood in imiquimod dermatitis. A - MDA concentration, B - SOD activity, C - Catalase activity. Results are expressed as mean ± standard error of the mean (n=5). * - $p < 0.05$ as compared to intact animals, # - $p < 0.05$ as compared to developed pathology.*

The treatment started against this background lasted 6 days, after which the oxidative stress biomarkers in the blood were examined again. The MDA content and the activity of SOD and catalase in the control with the use of the gel base and in the reference group with the use of prednisolone were at the level of pathology at the start of therapy and significantly differed from the values of intact rats. They also did not differ from each other.

The use of EMHPS gel reduced the concentration of MDA in the blood by 1.1 times ($p < 0.05$) compared to the initial pathology, which was somewhat stronger than the effect of prednisolone ointment ($p < 0.1$). When treating psoriasis-like dermatitis with EMHPS gel, there was a tendency ($p < 0.1$) to increase SOD activity compared to that in the group with experimental pathology before treatment. Under the influence of the gel, the catalase activity of the blood increased by 1.2 times to the end of treatment ($p < 0.01$). During this period, there were no reliable differences in the activity of the studied antioxidant enzymes between the control, reference and experimental groups.

Thus, against the background of developed imiquimod-induced dermatitis, topical EMHPS application reduced the accumulation of LPO products in the blood and increased catalase activity compared to the initial pathology,

Discussion

Oxidative stress is a non-specific response of the body to changes in homeostasis caused by internal or external factors. Such factors include skin diseases, which has been described by many researchers [1,17,18]. Our results confirmed that modeling of dermal pathology in laboratory animals is accompanied by oxidative stress, the manifestations of which in the form of accumulation of LPO products and decreased activity of antioxidant enzymes are recorded not only locally, but also in the blood [19]. Such changes appeared in animals with the model pathology in the first 1 - 3 days after a single exposure to a damaging agent in the form of a chemical depilatory or UV radiation and persisted until the end of the observation period, being maintained due to inflammation and regeneration of damaged tissues [20]. With daily serial use of imiquimod, noticeable changes in oxidative stress biomarkers developed after 6 days and persisted for at least the next 6 days after cessation of the inducing agent. The intensity of changes in the MDA concentration and antioxidant enzyme activity in the blood at the time of the first observation were different for different experimental dermal pathologies, which can possibly be explained by both the nature of the active factor and the period before testing the studied parameters.

In all series of experiments, topical application of EMHPS was accompanied by a decrease in the concentration of LPO products in the blood, which corresponds to the main property of this compound as an antioxidant and membrane protector [8]. The systemic effect of EMHPS with local use of this agent in the form of a gel can apparently be explained by several reasons: firstly, by inhibition of the local pathological process and a decrease in the entry of LPO products into the blood; secondly, by changing the cytokine profile by influencing the signaling pathways associated with ROS [21]; thirdly, by the absorption of EMHPS through the damaged skin into the blood where its antioxidant effect is realized.

When creating topical dosage forms, they usually strive to reduce their resorptive effect, but in the case of an antioxidant and its use against the background of dermal pathology with generalized oxidative stress, the EMHPS systemic effect should obviously be regarded as positive, especially given its sedative and nootropic activity, numerous organoprotective properties, and low toxicity [8], since skin diseases can increase the risk of damage to internal organs [22,23] or be manifestations of systemic diseases [24,25].

Analyzing the effect of EMHPS gel on the activity of SOD and catalase in the blood, it was possible to notice that it was most pronounced in the treatment of the consequences of chemical depilation, while against the background of UV irradiation, only blood SOD reacted to EMHPS topical application 1 day after the start of treatment, and with the imiquimod-induced dermatitis - only catalase after 6 days of

treatment. These facts can be explained by the multicomponent nature of antioxidant protection, when the role of its individual components depends on the source of ROS and their amount [26]. Apparently, the degree of EMHPS absorption from the site of its application plays a certain role in some pathologies, since it is known that the depilatory agent thioglycolate increases the permeability of the skin [27], and psoriasis-like dermatitis with epidermal thickness and hyperkeratosis worsens the permeability of the skin barrier for drugs [28].

In the study, the effect of EMPHS gel was compared with the effect of minoxidil solution, panthenol or prednisolone ointments on oxidative stress biomarkers in the blood in different series of experiments. Topical use of panthenol during UV irradiation was limited only by a decrease in the SOD activity at one observation period, although panthenol has antioxidant properties [29]. Apparently, such a minimal effect on LPO and antioxidant protection parameters is explained by the route of drug administration and the pharmacokinetic features of the used dosage form. When prednisolone ointment was used as a reference preparation for psoriasis-like dermatitis in rats, the absence of antioxidant effect was natural and did not contradict the properties of prednisolone and other corticosteroids described in the literature with chronic administration [30,31]. At the same time, 6-day treatment with prednisolone ointment did not cause a pro-oxidant effect, apparently due to topical application, features of the dosage form and its dosage regimen.

Among the reference drugs, topical minoxidil demonstrated an unexpectedly significant antioxidant effect in the blood against the background of chemical depilation. The antioxidant component of the reference drug effect concerned both the inducible antioxidant enzymes SOD and catalase, and the accumulation of LPO products, the main part of which is MDA. This property of minoxidil is practically not covered in the literature, but it can inhibit LPO in a conjugation with polyamines [32]. However, there is evidence that minoxidil disrupts glutathione and ascorbate metabolism and is also capable of ROS generating in cell culture [33,34], so it is possible that the drug's antioxidant effect *in vivo* is not as clear-cut as it seems at first glance and in our case it can be maintained by increasing the permeability of the skin during chemical depilation, as well as by the vasodilation inherent in the drug with increased absorption from the site of application, or mediated by an anti-inflammatory effect [35].

Conclusion

The studies have confirmed that local pathological processes of an inflammatory nature in the skin of laboratory animals, modeled as chemical depilation, UV irradiation and psoriatic-like dermatitis, are accompanied by oxidative stress at the level of the whole organism with an increase in the concentration of MDA in the blood and changes in the activity of SOD and catalase. Under these conditions, 5% EMHPS gel, a known synthetic antioxidant used as a topical treatment, produced an antioxidant effect at the systemic level, which, given its neuro- and organoprotective properties and low toxicity, is a positive aspect of the experimental therapy for dermal pathology. Of course, both the local and resorptive effects of the proposed antioxidant gel require further study, but the established facts can potentially be useful in the clinic for dermatological patients with co-morbidity or skin manifestations of systemic diseases.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

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Author's Contribution

All authors contributed to the study conception and design. Investigation, data collection, and analysis were performed by Olena Baliuk. Dr. Antonina Sydorenko prepared the first draft. Professor Elena Vazhnichaya supervised the experiments and prepared the final draft of the manuscript.

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Volume 12 Issue 12 December 2024