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Effect of Treatment with Silver Sulfate on the Physiological Effects of Natural Mineral Water

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Abstract

The treatment of mineral water with silver allows to significantly extend its shelf life without deteriorating its organoleptic properties, which makes it possible to use mineral water away from the natural deposit and is critical for business and the end consumer. However, possible changes in the physiological properties of mineral waters when treated with silver have not been studied until now. We have carried out a preclinical double-blind randomized placebo-controlled, experimental study, during which the effect of treatment with silver sulfate at a dose of 0.02 mg / liter (according to the EAEU TR 044–2017 regulation) of natural mineral water of sulphate-hydrocarbonate calcium-sodium (Russia, Stavropol Territory, deposit "Slavyanovskaya", well No. 69 bis) for cellular metabolism, microcirculation and micro-lymphocyte when applied externally to the area of the inner surface of the forearm. A comparison of the effect on cell metabolism and microcirculation has been made for applications with native mineral water "Slavyanovskaya", "Slavyanovskaya, enriched with silver sulfate" and placebo (tap water) after 30 minutes and after 24 hours. Number of patients: 15. Number of studies by location: 45. The results were monitored using the LAZMA ST device. The study carried out simultaneous registration of diagnostic parameters of blood microcirculation, lymph microcirculation, as well as fluorescence amplitudes of coenzymes participating in oxidative metabolism - reduced nicotinamide adenine dinucleotide (NADH) and oxidized flavin adenine dinucleotide (FAD). It was revealed that the mineral water "Slavyanovskaya enriched with silver" differs in its physiological effect on cellular metabolism, microcirculation and micro-lymph flow from the physiological effect of the mineral water "Slavyanovskaya", namely that, compared to "Slavyanovskaya", the mineral water "Slavyanovskaya enriched with silver" has a more pronounced positive effect on cellular metabolism, metabolic reserves of the cell, promotes the activation of microcirculation and micro-lymphatic flow. Mineral water "Slavyanovskaya, enriched with silver" has a longer effect on cellular metabolism, microcirculation and micro-lymphatic flow than mineral water "Slavyanovskaya". A statistically significant positive effect of cell metabolism activation was detected both 30 minutes and 24 hours after exposure.

Thus, this method of processing mineral water with silver sulfate not only does not decrease its positive physiological effect, but also improves it, prolonging its action, which makes further use of silver preparations in the processing of mineral water justified.

Keywords: mineral water, spa treatment, prevention, cell metabolism, microcirculation, laser fluorimetry.

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Introduction

The treatment of mineral water with silver allows to significantly extend its shelf life without deteriorating its organoleptic properties, which makes it possible to use mineral water away from the deposit and is critical for business and the end consumer. According to the TR EAEU 044–2017 regulations, treatment of mineral waters is permissible [1], including the treatment of natural mineral waters with silver, which extends the shelf life of the water. For the mineral water bottling industry, it is a most important question whether the medicinal properties of mineral water deteriorate when enriched with silver sulfate to 0.02 mg / dm^3. The therapeutic effect of the Slavyanovskaya mineral water can be associated with the trace elements it contains (magnesium, sulfates, hydrocarbons) affecting blood circulation, cellular metabolism and lymph flow. Magnesium affects blood flow and activated cellular metabolism. Slavyanovskaya mineral water contains 50 mg / l of magnesium, which is sufficient for the activation of cell metabolism at the site of application. [2]. The multifaceted effect of sulfates in natural sulfate mineral waters is known [3]. The antioxidant effect of sulphate thermal waters has been observed in various diseases of the respiratory tract and in *in vitro* experiments [4; 5, 6]. The antioxidant effect of sulphate thermal waters is probably due to the increase in the activity of superoxide mutase and the raised level of glutathione upon the intake of small doses of exogenous hydrogen sulfide [5; 7]. Inhalation of sulfate mineral water may promote IgA synthesis [8; 9]. The activation of mucociliary clearance under the influence of sulfate water inhalations has been noted in most of the works related to this topic [10; 11]. Sulphate thermal waters have a pronounced antibacterial effect [12]. A number of authors have noted a decrease in the contamination of the respiratory tract mucosa when using inhalations of sulfate thermal waters [13; 14].

Silver sulfate is used to treat natural mineral water in accordance with TR EAEU 044–2017, and the process does not affect the level and ratio of cations (calcium, magnesium, sodium and potassium), anions (hydrocarbonates, sulfates, chlorides), as well as biologically active components [1].

In addition to the known ability of silver to suppress a wide range of microorganisms: bacteria, viruses and fungi, silver activates the synthesis of energy in mitochondria. Silver, depending on the dose, can act not only as an inhibitor, but also as a catalyst for enzymes [15]. For instance, in the work of Chappel J.B. et al. [16], experiments on mitochondria obtained from cells of the cerebral cortex of rabbits show a significant (up to 200%) increase in metabolism under the influence of $AgNO_3$. Under the influence of silver, the rate of phosphate release (as a result of exposure to the adenosine triphosphatase enzyme) increases by 2–3 times. According to Lazarenko D.I. [17], silver significantly increases the metabolic reserve of myocytes.

Studies of the metabolic effect of mineral waters at the cellular level have been limited by the lack of non-invasive methods of observing tissue metabolism. Currently, there are non-invasive accurate and reproducible methods for studying basic physiological functions - blood circulation, cell metabolism and lymph flow [18–20], which makes it possible to observe physiological changes caused by slight alterations in the chemical composition of mineral water.

Materials and Methods

Objective: to study the effect of natural mineral water treated with silver sulfate on metabolism and microcirculation in healthy individuals when applied externally.

Subject of research: Volunteers who do not suffer from chronic diseases in the acute stage, or acute diseases. Number of volunteers: 15 people.

Application: External application as a compress.

1) Sulphate-hydrocarbonate calcium-sodium mineral water from well No. 69 bis.
2) Sulphate-hydrocarbonate calcium-sodium mineral water from well No. 69 bis, modified in accordance with TR EAEU 044–2017. Treatment with silver sulfate 0.02 mg / l.
3) Tap water (placebo).

Impact area:

The inner surface of the forearm.

Exposure: 30 minutes.

Control method: Laser fluorimetry using the LAZMA-ST apparatus.

Control points: First control point before the procedure, second – 30 minutes after the end of the exposure, third – 24 hours after the end of the procedure.

Blinding: Mineral water, mineral water enriched with silver and tap water do not differ in color or smell. The patient and the investigator performing the procedure do not know which bottle contains mineral water and which one is tap water (placebo). Vials with liquid for the compress only have serial numbers. Tap water was chosen as a placebo since the patients are maximally adapted to it due to regular and prolonged exposure.

All study participants have been receiving the application of mineral water with silver, without silver, or a placebo, one time per day, at the same time.

Grouping and Randomization

All patients received applications of Slavyanovskaya mineral water (MV), Slavyanovskaya mineral water enriched with silver (MB + Ag) and tap water (placebo). On the inner surface of the forearm, areas for applying a compress were highlighted with a biologically inert marker. The distance between the compresses was no less than 2 cm. The location for the compresses was selected at random.

The location of compress was used as a criteria for distribution into groups. Thus, the study involved 15 patients, each of whom had 3 locations on the forearm (upper, middle and lower) with 3 types of water applied. A total of 45 locations have been allocated. The application of a compress with a specific type of water to a specific location was determined randomly using an MVC random number generator. After creating a database with the results of observations, the locations on which compresses with a certain type of water were applied were divided into 3 groups: the "Mineral water" (MW) group, the "Silver-enriched mineral water MW + Ag" group and the "Placebo" group. Group assignment information was not available to study participants other than the Principal Investigator, Study Coordinator, and Ethics Committee monitors.

Ethics Committee Control

The study was carried out in accordance with the ethical principles of the WMA Declaration of Helsinki, in accordance with applicable Russian laws and regulations. Before the start of this study, the main documents of the study (including Protocol No. 1 dated 06.16.2020 and the informed consent form) were reviewed and approved in accordance with the established procedure by the local ethics committee of the Federal State Budgetary Institution "NMIC RK" of the Ministry of Health of Russia. The ethics committee did not amend the

protocol and approved the promotional information used to enroll patients in the study in accordance with local regulations. The study was supervised by the ethics committee.

Inclusion Criteria

Volunteers, aged 18–60, who did not have acute diseases and/or chronic diseases in the acute stage at the time of the start of the study, who have expressed a desire to participate in the study, signed voluntary informed consent and consent to the processing of personal data.

Non-inclusion Criteria

Acute diseases and chronic diseases in the acute stage.

Intoxication the day before the study.

Rash or skin damage in the study area.

Lactating and pregnant women.

Persons who are not allowed to participate in preclinical and clinical studies, according to 61 Federal Law, Art. 43. p. 6.

Exclusion Criteria

The patient could refuse to participate in the study at any time at will. In addition, the physician could terminate the patient's participation in the study in the patient's interests. Possible reasons for early termination of participation in the study include, but are not limited to:

1) refusal to participate;
2) development of an acute disease or exacerbation of a chronic one;
3) appearance of undesirable effects;
4) intoxication during the study period (including alcohol intoxication);
5) rashes and skin damage the study area.
6) taking medications, physiotherapeutic influences that affect cell metabolism and microcirculation;
7) non-compliance with research procedures;
8) non-attendance by the patient for follow-up;;
9) cancellation of therapy due to the development of an undesirable phenomenon;
10) administrative reasons;
11) other reasons that impede the conduct of the study or distort the results obtained.

Research methods

Preclinical, double-blind, randomized, placebo-controlled, experimental study.

The study was carried out in accordance with GOST R ISO 14155–2014. (National standard of the Russian Federation. Clinical research. Good clinical practice).

The control of the results was carried out using the apparatus "LAZMA ST", consisting of the "LAZMA-D" analyzer and the "LAZMA-TEST" block.

1. The study carried out simultaneous registration of diagnostic indicators of blood microcirculation, lymph microcirculation and fluorescence amplitudes of coenzymes participating in oxidative metabolism - reduced nicotinamide adenine dinucleotide (NADH) and oxidized flavin adenine dinucleotide (FAD) - "LAZMA-D" analyzer.

2. The registration of indicators was carried out in the initial state of the tissue (the skin temperature was also monitored), when cooled to 10 ° C (decreased activity of microcirculation and metabolism) and when heated to 35 ° C (increased activity of microcirculation and metabolism). Temperature control, heating and cooling - "LAZMA-TEST" block.

3. At the level of the microcirculatory blood flow and lymph flow, the dysfunctions of the regulatory (neurogenic and myogenic) mechanisms of vascular tone were analyzed using software algorithms.

4. Temperature test: heating and cooling. The metabolic processes of the body's cellular structures are energy-dependent. Utilization of coenzymes and substrate decreases with cooling and increases with heating. Based on the results of the temperature test, a quantitative assessment is made of the non-utilized constituents of coenzymes and the substrate that are not involved in chemical reactions at rest. The more pronounced the changes in the concentrations of NADH and FAD are during the test with heating, the less utilized are coenzymes and substrate in the initial state of the tissue, and the more significant is the decrease in oxidative metabolism in the patient.

The normalization of oxidative metabolism is associated with reactivation of utilization of coenzymes and substrate. The concentration of coenzymes should be within the control values.

"The new method for studying tissue changes employs simultaneous control of microcirculation compartments: blood and lymph flow and oxidative coenzymes. The metabolic processes of the cellular structures of the tissue are energy dependent. Changes in energy metabolism underlie most functional and energy disorders in tissues.

Diagnostics is performed based on the simultaneous assessment of the tissue coenzymes activity (reduced nicotinamide adenine dinucleotide (NADH) and oxidized flavin adenine dinucleotide (FAD)) by fluorescence spectroscopy and indicators of microcirculation of blood and lymph flow using laser Doppler fluometry in three tissue states: initial state, cooled to 10 ° C (reduced microcirculation and metabolism) and heated to 35 ° C (increased microcirculation and metabolism).

Investigation of the tissue reaction upon cooling to 10 ° C and heating to 35 ° C allows one to assess changes in both microcirculation and the concentration of coenzymes relative to the initial state. With cooling, the utilization of the substrate and coenzymes decreases, with heating, the utilization of the substrate and coenzymes activates. The more pronounced the changes in the concentrations of NADH and FAD during the sample with heating, recorded through changes in the magnitudes of fluorescence amplitudes, the less substrate and coenzymes are utilized in the initial state of the tissue, and the more significant is the decrease in oxidative metabolism in the patient. The normalization of oxidative metabolism is associated with reactivation of the utilization of the substrate and coenzymes. The concentration of coenzymes should be within the control values.

The increase (with cooling) or decrease (with heating) of the fluorescence amplitudes of coenzymes does not include collagen fluorescence as one of the dominant fluorophores in the skin. Heating and cooling at the indicated temperatures does not change the collagen content of the tissue. When calculating the magnitude of changes in the fluorescence amplitudes of NADH and FAD, the additional part from collagen is subtracted as a constant value.

The choice of the heating temperature 35°C is due to several circumstances. First, at 35°C, protein denaturation does not occur, including that of collagen. Second, this temperature is near the 38–40 ° C range, where the highest rate of enzymatic reactions is observed. Also, at 35 ° C, the activity of local regulatory mechanisms of cutaneous blood flow increases, causing more microvasculature capillaries to start functioning.

During cooling, cold vasodilation occurs in the tissue, which does not allow unambiguous registration of metabolic slowdown reactions, as the blood flow increases to pro-

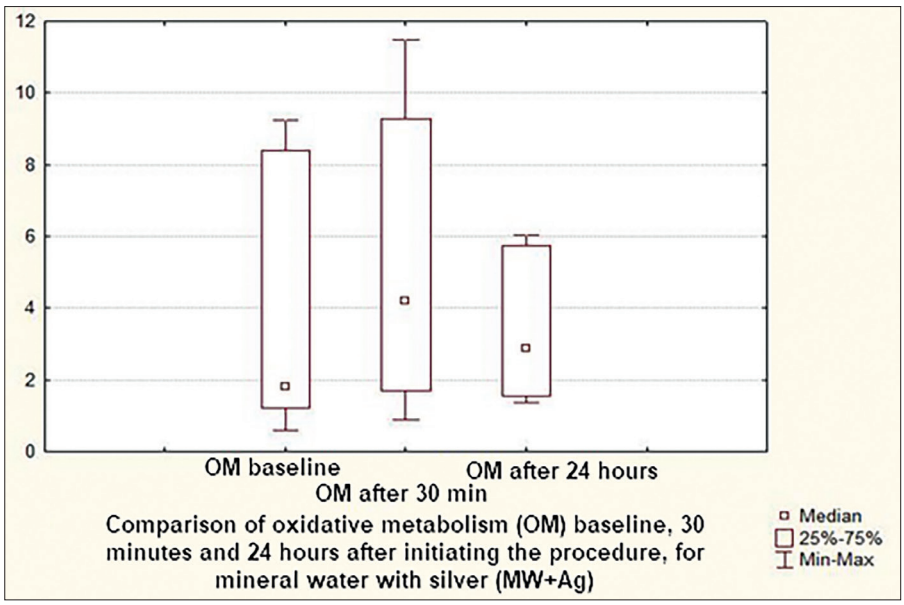


Fig. 1 *Dynamics of the oxidative metabolism (OM) in the group silver-enriched mineral water (MW+Ag)*

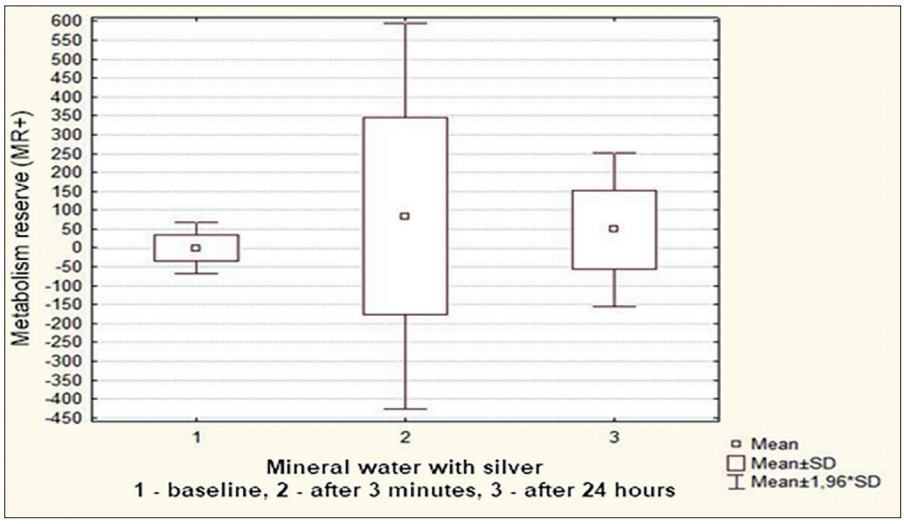


Fig. 2 *Dynamics of the metabolic reserve (MR+) in the group receiving silver-enriched mineral water (MW+Ag)*

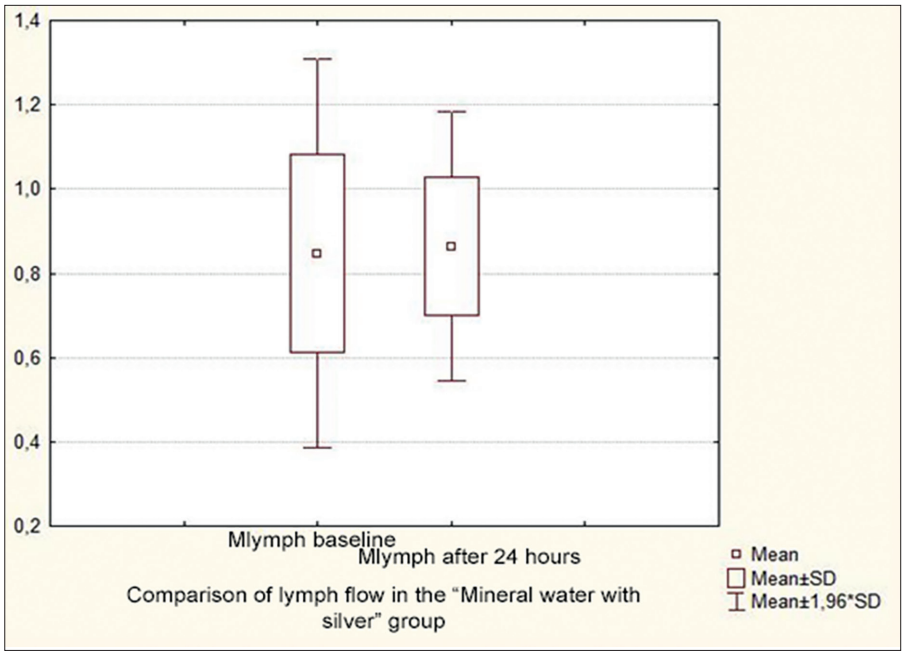


Fig. 3. *Dynamics of the lymph flow index (Mlymph) in the group receiving silver-enriched mineral water (MW+Ag)*

vide heating to the tissue. 10°C is chosen due to the method of assessing the tissue reaction, as at this temperature the time before the onset of cold vasodilation is about 1 minute, during which it is possible to correctly obtain data on the decrease in utilization of the substrate and coenzymes." [19]

Statistical processing: Intra-group comparison used Friedman test, ANOVA, and Wilcoxon paired t-test. Inter-group comparison used the Mann-Whitney U method. The study of patterns of physiological effects was carried out using cluster analysis (hierarchical, K-means).

Results

1. Dynamics compared to baseline

In the group receiving applications of mineral water (MW), one day after the exposure, a statistically significant increase compared to the initial values was found only in microcirculation indicators (T_w – 10,0; p<0.01). Intra-group differentiating in the Friedman test (χ^2 – 111,6; p<0.001) (Friedman ANOVA).

In the (MW + Ag) group, the effect of exposure manifested itself in a statistically significant increase in several indicators of cellular metabolism, microcirculation and lymph flow (χ2 - 120.3; p <0.001) (Friedman ANOVA). There was a statistically significant increase in oxidative metabolism (OM) after 30 minutes (TW - 15.0; p = 0.01) (Fig. 1) and metabolic reserve (MR), (TW - 9.9; p = 0.007) (Fig. 2). In addition, a day later, statistically significant dynamics of the lymph flow was revealed (TW - 78.0; p = 0.004) (Fig. 3).

In the placebo group, there was no statistically significant dynamics in comparison with the baseline in any indicator (OM p = 0.3; MR p = 0.1; Mblood p = 0.2; Mlymph p = 0.1) (Fig. 1, 2,3). Thus, mineral water enriched with silver has a statistically significant effect on tissue metabolism, increases the metabolic reserves of the cell, activates lymph flow, while mineral water that does not contain silver has a statistically significant effect only on microcirculation, and placebo does not have a statistically significant effect on metabolism and microcirculation.

2. Comparison of the physiological effects of mineral waters "Slavyanovskaya" and "Slavyanovskaya enriched with silver"

In the course of the studies, it was found that 30 minutes after the application in the MW+Ag group (mineral water enriched with silver) statistically significant values of the oxidative metabolism index (OM) (U - 242 , 0; p <0.001) (Fig. 4), metabolic reserve (U - 648.0; p <0.01) (Fig. 5), microcirculation (U - 252.0; p <0.001). Statistical differences between placebo and MW+Ag were significant for all parameters (p <0.05). Statistical differences between the placebo and CF groups were significant in terms of OM (p <0.01) and MR (p <0.04) (Fig. 6).

24 hours after application the metabolic reserve (U - 684.0; p <0.01) (Fig. 7) and lymph flow (U - 504.0; p <0.001)

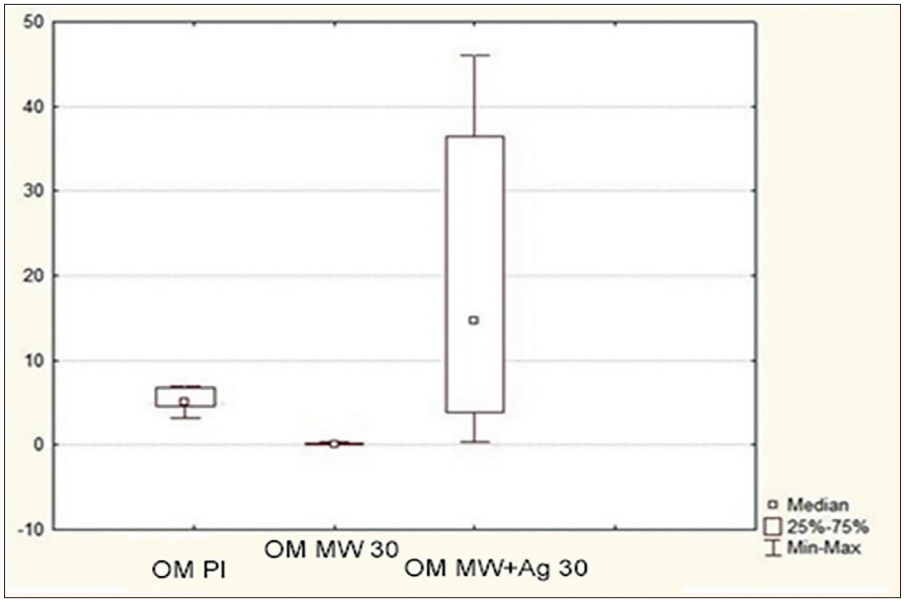


Fig. 4. *Comparison of metabolic activity (OM) in the MW (mineral water), MW+Ag (silver-enriched mineral water) and Placebo groups 30 minutes after exposure*

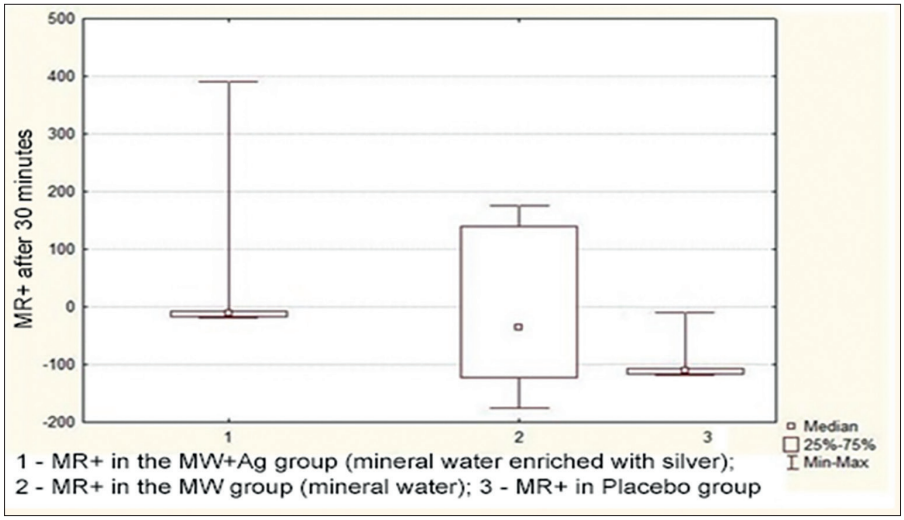


Fig. 5. *Comparison of the metabolic reserve (MR) index in the MW (mineral water), MW+Ag (silver-enriched mineral water) and Placebo groups 30 minutes after exposure*

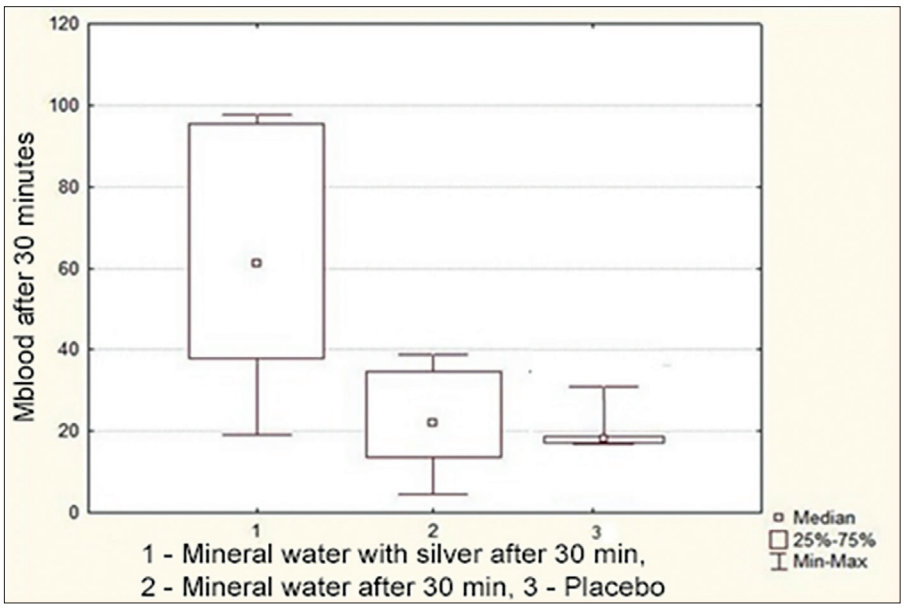


Fig. 6. *Comparison of the blood microcirculation index (Mblood) in the MW (mineral water), MW+Ag (silver-enriched mineral water) and Placebo groups 30 minutes after exposure*

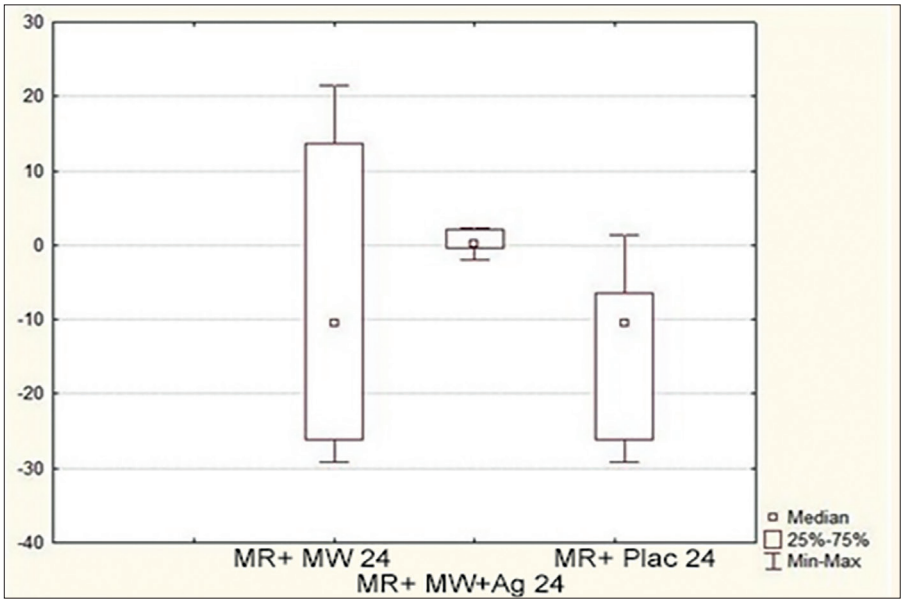


Fig. 7. *Comparison of the metabolic reserve (MR) index in the MW (mineral water), MW+Ag (silver-enriched mineral water) and Placebo groups 24 hours after exposure*

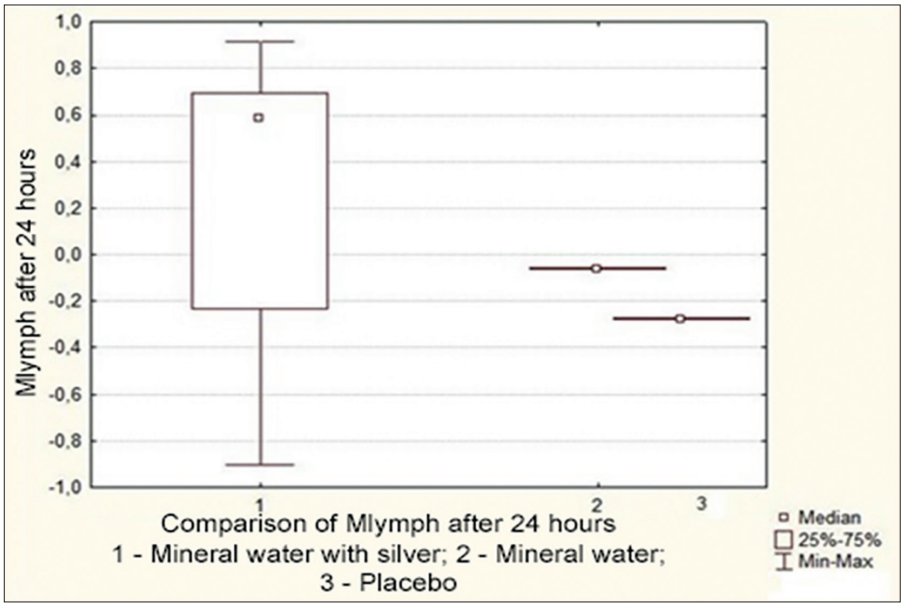
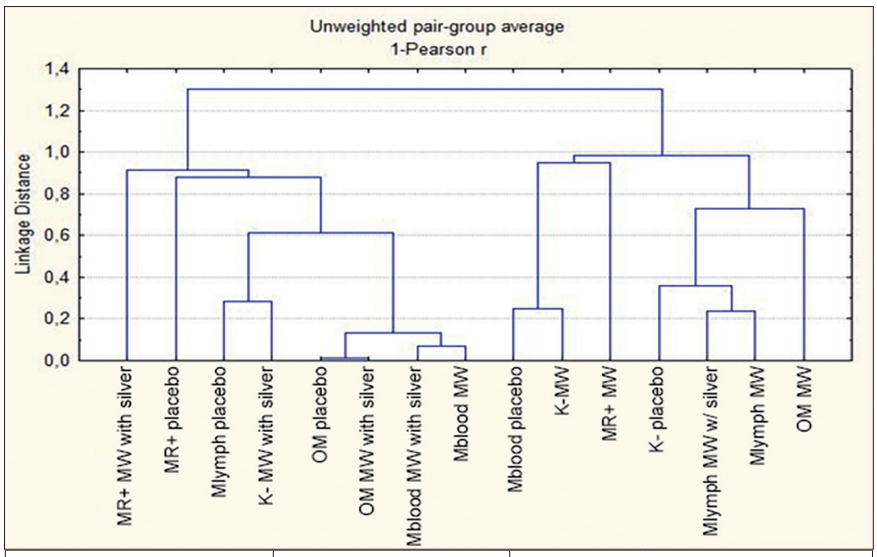


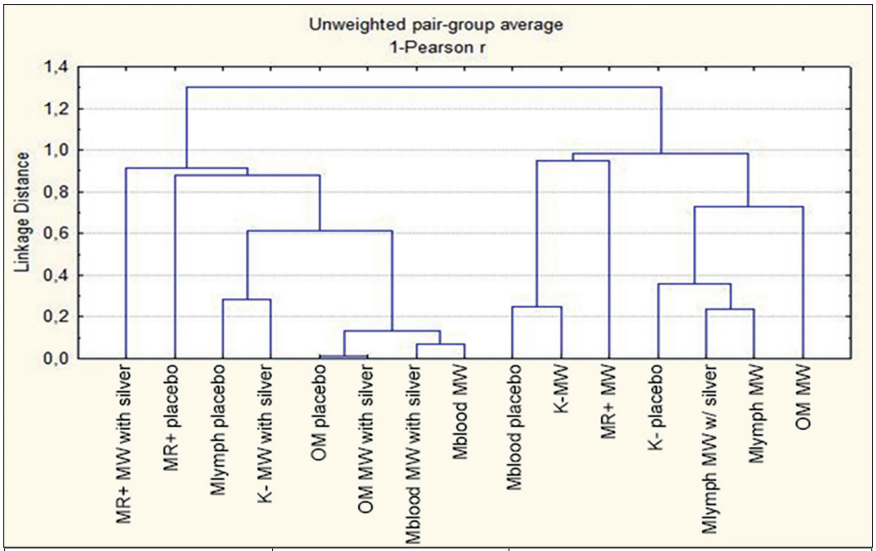
Fig. 8. *Comparison of the micro-lymph flow (Mlymph) in the MW (mineral water), MW+Ag (silver-enriched mineral water) and Placebo groups 24 hours after exposure. Dynamics of the lymph flow index (Mlymph)*

Chart 1. *Pattern of physiological action MW (mineral water), MW+Ag (mineral water enriched with silver). Cluster Analysis (K-Means).*



CLUSTER	DISTANCE	Indicators
1	0,63	OM MW base
1	0,76	Mblood MW base
1	0,61	Mlymph MW base
1	0,57	OM MW 30
1	0,64	Mblood MB 30
1	0,61	Mlymph MB 30
1	0,50	OM MW+Ag base
1	0,51	Mblood MW+Ag base
1	0,84	Mlymph MW+Ag base
1	0,80	MR+ MW+Ag 30
1	0,77	Mlymph MW+Ag 30
1	0,72	Mblood MW+Ag 24
1	0,48	Mlymph placebo base
1	0,45	Mlymph placebo 30
1	0,87	MR+ placebo 24
2	0,90	MR+ MB 30
2	0,57	OM MB 24
2	0,68	Mblood MB 24
2	0,59	Mlymph MB 24
2	0,44	OM MW+Ag 30
2	0,51	Mblood MW+Ag 30
2	0,65	OM MW+Ag 24
2	1,03	MR+ MW+Ag 24
2	0,87	Mlymph MW+Ag 24
2	0,65	OM placebo base
2	0,66	Mblood placebo base
2	0,39	OM placebo 30
2	0,38	Mblood placebo 30
2	0,62	OM placebo 24
2	0,97	Mblood placebo 24
2	0,77	Mlymph placebo 24

Chart 1. *Pattern of physiological action MW (mineral water), MW+Ag (mineral water enriched with silver). Cluster Analysis (K-Means).*



3	0,44	K- MW base
3	0,39	K- MW 24
3	0,56	K- MW+Ag base
3	0,52	K- MW+Ag 24
3	0,74	MR+ placebo base
3	0,40	K- placebo base
3	0,39	K- placebo 24
4	0,40	MR+ MW
4	0,50	K- MW 30
4	1,09	MR+ MW 24
4	0,46	MR+ MW+Ag base
4	0,42	K- MW+Ag 30
4	0,61	MR+ placebo 30
4	0,61	K- placebo 30

Analysis of Variance

Indicator	F	signif. - p
Mlymph MW 24	6,4249	0,015269
OM MW+Ag base	332,26	0,000000
Mblood MW+Ag base	203,168	0,000000
Mlymph MW+Ag base	6,6200	0,013900
OM MW+Ag 30	7,2817	0,010153
MR+ MW+Ag 30	29,0838	0,000003
Mblood MW+Ag 30	16,5249	0,000218
Mlymph MW+Ag 30	10,4126	0,002498
OM MW+Ag 24	16,3639	0,000232
MR+ MW+Ag 24	49,0115	0,000000
Mblood MW+Ag 24	28,7969	0,000004
OM placebo base	34,1429	0,000001
Mlymph placebo base	60,2942	0,000000
Mlymph placebo 30	80,2369	0,000000
MR+ placebo 24	9,2505	0,004143
Mblood placebo 24	7,7725	0,008079

values in the MW+Ag group were significantly higher than in the MW group. Statistical differences between placebo and MW+Ag were significant for all parameters ($p < 0.05$). Statistical differences between placebo and MW were revealed only in terms of OM ($p = 0.04$) (Fig. 8).

Cluster analysis shows that the pattern of physiological effects of MW+Ag on cellular metabolism, microcirculation, and blood flow significantly differs from the pattern of physiological effects of MW and is characterized by a closer association of cellular metabolism 30 minutes and 24 hours after exposure (Chart 1).

Conclusions

1. Mineral water "Slavyanovskaya enriched with silver" differs from mineral water "Slavyanovskaya" in its physiological effect on cellular metabolism, microcirculation and micro-lymphatic flow.

2. Compared to mineral water "Slavyanovskaya", mineral water "Slavyanovskaya enriched with silver" has a more pronounced positive effect on cellular metabolism, metabolic reserves of the cell, promotes the activation of microcirculation and micro-lymphatic flow.

3. Mineral water "Slavyanovskaya, enriched with silver" has a longer effect on cell metabolism, microcirculation and micro-lymphatic flow than mineral water "Slavyanovskaya". A statistically significant positive effect of activation of cell metabolism was revealed both 30 minutes and 24 hours after exposure, while when using the mineral water "Slavyanovskaya", a statistically significant effect was revealed only 30 minutes after exposure. Although there was a positive trend in comparison with the baseline, 24 hours after exposure the differences did not reach the level of statistical significance for any of the indicators.

Treating mineral water with silver sulfate does not decrease its positive physiological effect, and improves its physiological effect, which makes further use of silver preparations in the processing of mineral water justified.

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