

# Comparative assessment of the effects of Soderm<sup>®</sup>-Forte, Cytoflavin<sup>®</sup> and their combination on microcirculation in the gingival mucosa in rats

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## Abstract

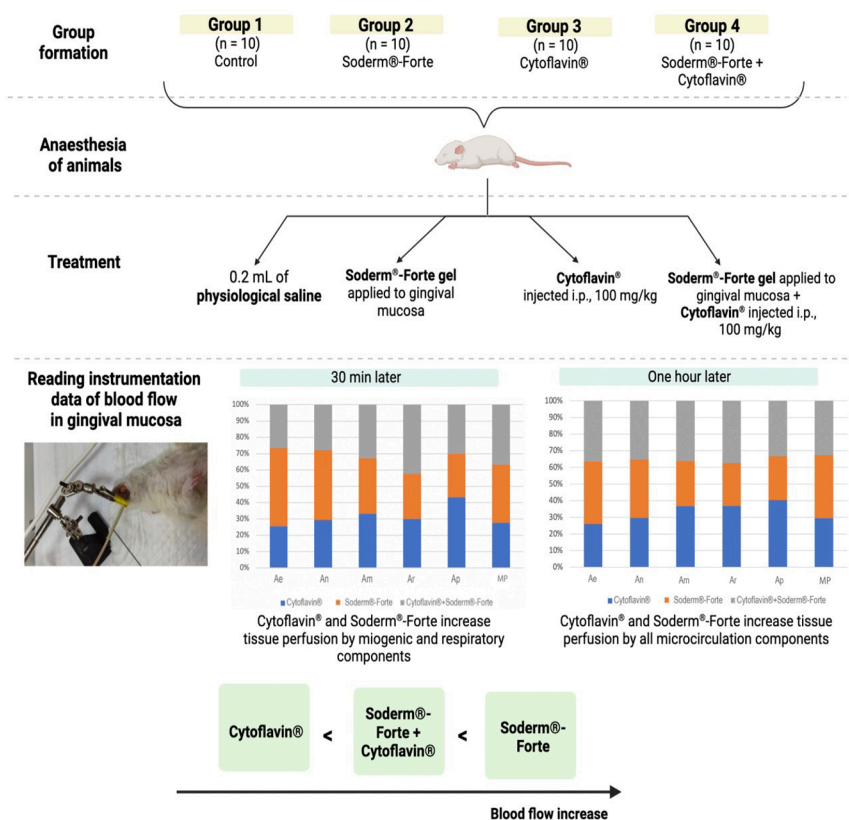
**Introduction:** Changes in the microcirculation (MC) system reflect abnormalities of physiological processes in the body and serve as a diagnostic and prognostic factor in a number of pathological conditions, including inflammatory lesions of periodontal tissues. Since in the pathogenesis of microcirculatory disorders an important role is played by the processes of free-radical oxidation, medications with antioxidant effects are of certain interest in terms of pharmacological correction of blood flow disorders in the periodontal complex. It was of interest to conduct a comparative assessment of the effects of Soderm<sup>®</sup>-Forte, Cytoflavin<sup>®</sup> and their combination on MC in the gingival mucosa in rats. **The aim of the study** was to identify whether Soderm<sup>®</sup>-Forte, Cytoflavin<sup>®</sup> and their combination can improve microcirculation in the gingival mucosa in rats.

**Materials and Methods:** The study of MC in the gingival mucosa in rats was carried out by using the laser Doppler Flowmetry method. Four groups of rats with 10 animals in each were formed: Group 1 – control; Groups 2-4 – experimental groups, in which Soderm<sup>®</sup>-Forte gel was applied to the gingival mucosa of the lower incisors, Cytoflavin<sup>®</sup> (100 mg/kg intraperitoneally – i.p.) was injected, and gel Soderm<sup>®</sup>-Forte was applied to the gingival mucosa against the background of injecting Cytoflavin<sup>®</sup>, respectively. The indicators of blood flow were recorded 30 and 60 minutes later.

**Results and Discussion:** Soderm<sup>®</sup>-Forte improved MC in the gingival mucosa by increasing the basal level of NO, the activity of precapillary sphincters and metarteriolas and decreasing the activity of adrenergic vasomotors. Cytoflavin<sup>®</sup> increased the activity of precapillary sphincters and metarteriolas, the extravascular components of MC, without changing perfusion of the gingival mucosa. The combination of Soderm<sup>®</sup>-Forte and Cytoflavin<sup>®</sup> improved MC to a lesser extent than only Soderm<sup>®</sup>-Forte, but to a bigger extent than Cytoflavin<sup>®</sup>.

**Conclusion:** According to the capacity to increase blood flow in the gingival mucosa in rats, the tested substances and their combination can be arranged in the following way: Soderm<sup>®</sup>-Forte > Soderm<sup>®</sup>-Forte+Cytoflavin<sup>®</sup> > Cytoflavin<sup>®</sup>.

## Graphical abstract:



**Note:** IP - intraperitoneal injection; Ae - amplitude of endothelial oscillations; An - amplitude of neurogenic oscillations; Am - amplitude of myogenic oscillations; Ap - amplitude of pulse oscillations; Ar - amplitude of respiratory oscillations; MP - microcirculation perfusion.

## Keywords

Laser-Doppler flowmetry, microcirculation, Soderm®-Forte, Cytoflavin®

## Introduction

Changes in the microcirculatory bed are a logical response of the body to the damaging factors of various origin. Disturbances of blood flow in small blood vessels are manifested prior to the appearance of clinical symptoms of the disease and are recognized as the most sensitive indicators of various pathologies, since the changes observed in them are associated with impaired systemic microcirculation – MC (Zyulkina et al. 2017; Ravaeva et al. 2018).

The high prevalence of diseases linked to changes in MC makes it imperative to search for pharmacotherapy for blood flow disturbances in the vessels of the microcirculatory bed. Correction of MC in the gingival mucosa is a difficult task, since at the moment there are no effective therapeutic agents with proven effectiveness.

Since the micro-vascular network plays a key role in the trophic support of tissues, the state of the vascular channel is definitive in the development of inflammatory and ischemic lesions of periodontal tissue (Lira-Junior et al. 2014; Tsubokawa and Sato 2014; Lengert et al. 2021). Since the central link in the pathogenesis of microcirculatory disturbances is increased lipid peroxidation caused by reactive oxygen species, medications with antioxidant

effects are of a certain interest (Bains and Bains 2015; Tóthová and Celec 2017).

The most active anti-radical enzyme that protects the cell from oxidative stress by transferring reactive oxygen species into hydrogen peroxide, which is almost 10 times less toxic, is superoxid dismutase (SOD), a natural cytoprotector that acts at the initial stages of free-radical oxidation (Polcar et al. 2022). A decrease in the activity of SOD is an indicator of disruption of protective mechanisms and significantly contributes to cell damage (Kwiecien et al. 2014; Borstahl and Oberley-Deegan 2018).

The use of SOD-containing medications is justified in oncology, dermatology, dentistry, gerontology, gastroenterology, ophthalmology, neurology, gynecology, when treating viral infections, autoimmune diseases, diabetes mellitus, thermal injuries, and other pathological processes (Mansuroglu et al. 2015; Shakhmartanovova et al. 2016; Coudriet et al. 2017).

Soderm®-Forte is micellar gel containing SOD and nanocluster zero-valent metal silver, with pronounced anti-inflammatory and regenerative effects. To date, there are some data about the positive effect of this medication on the antioxidant-prooxidant system of red blood cells and the early regeneration of the gingival tissue in experimental periodontitis in rats (Galenko-Yaroshevsky

et al. 2022a; Galenko-Yaroshevsky et al. 2022b).

Cytoflavin® is a drug that combines amber acid, riboxinum (inosine), riboflavin (B<sub>2</sub>) and nicotinamide (PP) and that has an antioxidant effect due to the capacity to reduce free radical products and restore the activity of antioxidant enzymes. Amber acid, an intermediate of the Krebs cycle, acts as the main antioxidant, whereas the role of riboflavin and nicotinamide in the composition is to enhance its pharmacological activity (Chutko et al. 2017). Cytoflavin® has a polymodal effect due to the impact on the exchange of neurotransmitters, modulation of signaling processes and synaptogenesis (Kamchatnov et al. 2019). The drug showed its effectiveness and safety in the treatment of cognitive and emotional disorders, as well as asthenic and depressive states (Afanasyev et al. 2016; Iskra 2016; Chutko et al. 2019).

Our previous studies have shown that the use of the composition of Soderm®-Forte and Cytoflavin® has a pronounced normalizing effect on pathomorphological changes in the gingival tissues in experimental periodontitis in rats, characterized by the leveling of inflammation signs through the activation of regenerative processes (Popkov et al. 2022).

The aim of the study was to identify whether Soderm®-Forte, Cytoflavin® and their combination can improve microcirculation in the gingival mucosa in rats.

## Materials and Methods

### Experimental animals

The studies were conducted on 40 Wistar male rats, weighing 210-230g. The animals were kept in groups of 5 animals in the standard conditions of the vivarium, at a temperature of 18-20°C, relative humidity of 50-70%, and 12-hour light – 12-hour light cycle. The rats received a standard food diet and had free access to water. The study protocol was approved by the Bioethics Committee of Rostov State Medical University of the Ministry of Health of the Russian Federation (29 Nakhichevansky Lane, Rostov-on-Don, Russia), Minutes No. 16/21 of October 21, 2021. The conditions for keeping and handling the animals complied with the principles of the Declaration of Helsinki on the humane handling to animals, the Directive of the European Parliament and the

Council of the European Union 2010/63/EU of September 22, 2010 on the protection of animals used for scientific purposes, GOST 33044–2014 “Principles of Good Laboratory Practice” approved by order of the Federal Agency for Technical Regulation and Metrology No. 1700-ST of November 20, 2014.

For the experiment, male rats were selected without any signs of diseases after a two-week quarantine in the vivarium (study inclusion). No animals weighing under 210g and over 230g or having any signs of diseases (study exclusion) were used in the experiments. An accidental gum injury was a criterion for excluding animal from the experiment.

### Pharmaceutical substances

The test substances are: Soderm®-Forte gel (LLC “Chemical and Biological Unit “VITA” of the Russian Academy of Sciences”, Russia) and Cytoflavin® in ampoules for injections (Scientific and Technological Pharmaceutical Company “Polysan” LLC, Russia).

For anesthesia of rats, Telazol and Meditin were used: Telazol (Zoetis, Spain); Meditin (Api-San LLC, Russia); and atropine sulfate (Federal State Unitary Enterprise “Moscow Endocrine Plant”, Russia).

### Experiment design

Rats were divided into 4 groups of 10 animals in each: Group 1 – control, to which 0.2 ml of physiological saline was administered intraperitoneally (i.p.); Group 2 – where Soderm®-Forte gel was applied to the gingival mucosa of the lower incisors; Group 3 – where Cytoflavin® was administered i.p. at a dose of 100 mg/kg; Group 4 – where Soderm®-Forte gel was applied to the gingival mucosa against the background of injecting Cytoflavin® i.p. at a dose of 100 mg/kg.

Before conducting the experiments, the animals were anesthetized with Telazol and Meditin to produce a prolonged analgesic effect within 60 minutes according to the following pattern: Telazol 0.3 mg intramuscularly (i.m), Meditin 0.8mg i.m. and 0.1% solution atropine sulfate subcutaneously, calculated as 0.01 mL per 100g of body weight of the animal. The effect of anesthesia was assessed by a weaker or no response to the stimulus in the form of depressing the normal corneal reflex. The layout of the experiment is shown schematically in Figure 1.

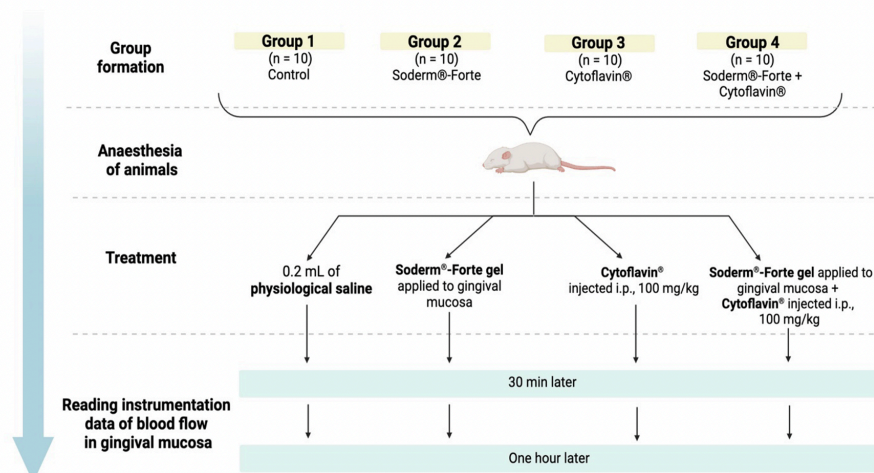


Figure 1. The layout of the research design.

**Research methods**

To study the MC processes in the gingival mucosa in rats, the laser Doppler Flowmetry method (LDF) (Krupatkin and Sidorov 2005) was used. This method is the most effective when studying MC in soft tissues; it is a well-established method, which is often used for non-invasive assessment of MC and is based on the effect of light on the flow of red blood cells in limited tissue (Krupatkin 2018). Among its advantages are simplicity, painlessness, high sensitivity to changes in microhemodynamics, and this method makes it possible to quickly carry out measurements. At the same time, the method is very sensitive to changes in the external research conditions and internal factors of the examined subject (gender, age, time of day and year, psycho-emotional state, etc.), which requires strict adherence to the conditions of conducting the analysis.

The study of changes in the MC parameters in the gingival mucosa of rats was carried out by using the laser analyzer of the blood flow “Lazma MC-1” (R&D Company “Lazma Ltd.”, Russia) and LDF 2.20.0.507WL program with a laser light source operating at the wavelength of 0.8 μm (Fig. 2).

Since the method is highly sensitive, while recording LDF-grams, the rats were in a state of anesthesia. The Lazma-MC probe was fixed perpendicular to the gum under the lower incisors. The signal was recorded after the animal had been preliminarily (for 10-15 minutes) placed on the heated plate of the TC 1000 Temperature Controller device (temperature 28-32°C). To assess the state of MC in rats during the LDF-metry, the following non-oscillometric indicators of the basal blood flow were recorded:

1) Perfusion indicator (Microcirculation perfusion, MP, perfusion unit, PU), formula 1:

$$MP = N_{RBC} \times V_{av} \quad (1),$$

where  $N_{RBC}$  is the number of red blood cells (RBC) in a probe volume,  $V_{av}$  is the average velocity of red blood cells.

2) Indicator  $\sigma$  (“flux”, RMS, PU) is the root-mean-square deviation of the amplitude of blood flow oscillations from the arithmetic mean. This indicator characterizes the temporal variability of MC. The higher  $\sigma$ , the greater the modulation of blood flow is observed at a given time.

3) Coefficient of variation (CV) is the ratio between blood perfusion and its flux, formula 2:

$$CV = \frac{\sigma}{MP} \times 100\% \quad (2),$$

where  $\sigma$  is the root-mean-square deviation of the amplitude of blood flow oscillations from the arithmetic mean, MP is the arithmetic mean value of the MC indicator.

Due to the range of oscillations in the amplitude of rates (A), their normalized characteristics were analyzed according to the formula 3:

$$A_{norm} = \frac{A}{3\sigma} \quad (3),$$

where A is the amplitude of oscillations in any range from 0.02–2 Hz;  $\sigma$  is the root-mean-square deviation of the MC indicator (Krupatkin and Sidorov 2005).

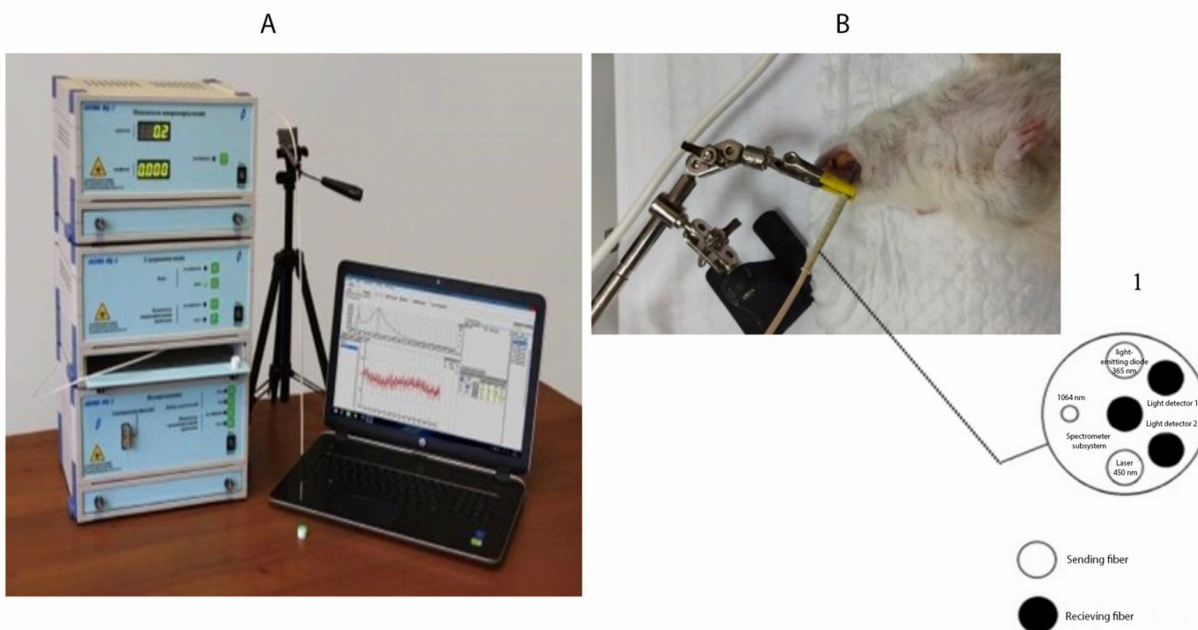
The use of the LDF 2.20.07WL program makes it possible to automatically calculate the normalized amplitudes of blood flow oscillations to RMS (A/RMS) for each frequency range.

The sum ( $\Sigma A_{max}$ ) in endothelial, neurogenic, myogenic and pulse frequency ranges was regarded as the capacity of the mechanisms that provide blood flow into the microcirculatory bloodstream according to the formula 4 (Krupatkin and Sidorov 2005):

$$\Sigma A_{max} = A_E + A_N + A_M + A_P \quad (4),$$

where  $A_E$  is amplitudes of perfusion oscillations in the endothelial range,  $A_N$  is amplitudes of perfusion oscillations in the neurogenic range,  $A_M$  is amplitudes of perfusion oscillations in the myogenic range,  $A_P$  is amplitudes of perfusion oscillations in the pulse range.

$A_R$  amplitudes of perfusion oscillations in the respiratory range ( $A_R$ ). They are present both in the



**Figure 2.** A – Laser analyzer of the blood flow “Lazma MC-1”; B – fiber-optic probe unit. *Note:* 1 – fiber-optic probe head, in section.

afferent link in the microvascular bed and in capillaries; their amplitude reflects perfusion pressure in microcirculation vessels, caused by both cardiac outputs, changes in systolic and diastolic pressure, and by the influence of postcapillary resistance.

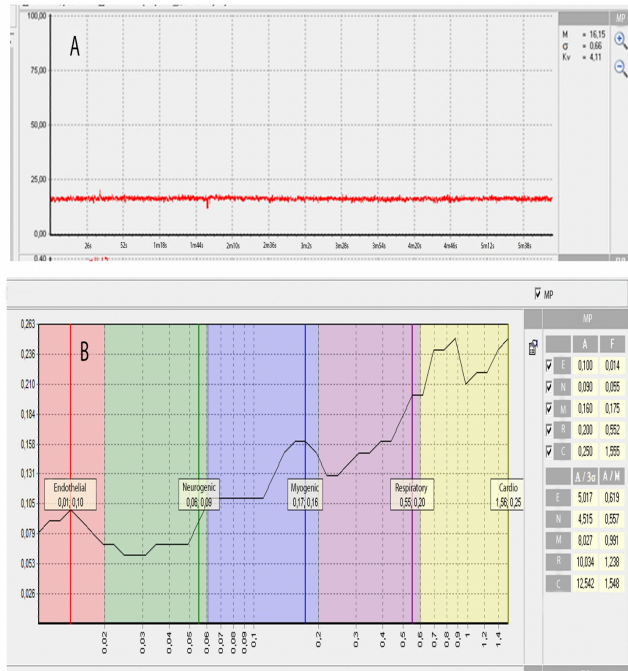
A decrease in the amplitude of oscillations is linked to an increase in the tone and stiffness of the vascular wall itself and, conversely, an increase in amplitudes results from a decrease in the vascular tone (Krupatkin and Sidorov 2005).

### Statistical data processing

The calculations, statistical processing and graphic design of the data obtained in the study were carried out using a Microsoft Excel program, StatSoft/STATISTICA 8 software package. The significance of the differences between the groups was evaluated using non-parametric single-factor analysis. The differences were statistically different at  $p \leq 0.05$ . The values of the indicators were calculated as a percentage of the values of the control group, taken as 100%.

## Results and Discussion

In the animals of the control group, the values of the MC indicators under study are shown in Figure 3. As can be seen from the data, the effect of anesthesia was reflected in minor fluctuations in the oscillatory and non-oscillatory MC indicators throughout the whole study.

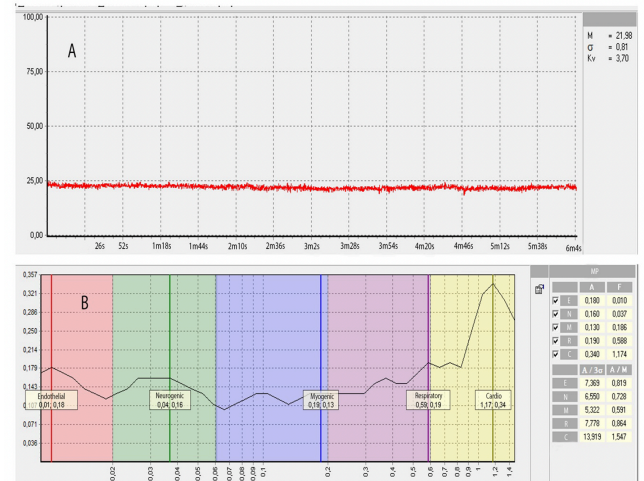


**Figure 3.** Typical LDF-gram of the gingival mucosa of lower incisors of the anesthetized rat in the Control group. **Note:** *A* – reference line (baseline) without assigned frequencies; *B* – LDF-gram against anesthesia.

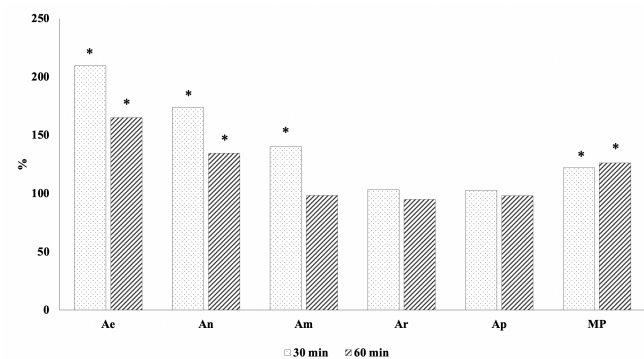
Thirty minutes after the application of Soderm®-Forte gel to the gingival mucosa of the lower incisors, the rates increased when compared with those in the control group of animals: endothelial rate – by 109% ( $p < 0.05$ ), neurogenic rate – by 73.8% ( $p < 0.05$ ), and myogenic rate – by 40% ( $p < 0.05$ ). At the same time, MP increased by

21.9%, while CV decreased by 55.3% ( $p < 0.05$ ) (Figs 4 and 5).

Sixty minutes after the application of the Soderm®-Forte gel to the gingival mucosa of the lower incisors, there was a slight decrease in  $A_E$ ,  $A_N$ , and  $MP$  values compared to those obtained by the 30<sup>th</sup> min of the study, but they were higher by 65.1% ( $p < 0.05$ ), 34.5% ( $p < 0.05$ ) and 26.3% ( $p < 0.05$ ), respectively, than those of the control group, while the values of indices  $A_M$ ,  $A_P$ , and  $A_R$  reached the control values (Figs 4 and 5).



**Figure 4.** LDF-gram when applying Soderm®-Forte gel to the gingival mucosa of the lower cutters of the anesthetized rat. **Note:** *A* – reference line (baseline) without assigned frequencies; *B* – LDF-gram after applying Soderm®-Forte gel.

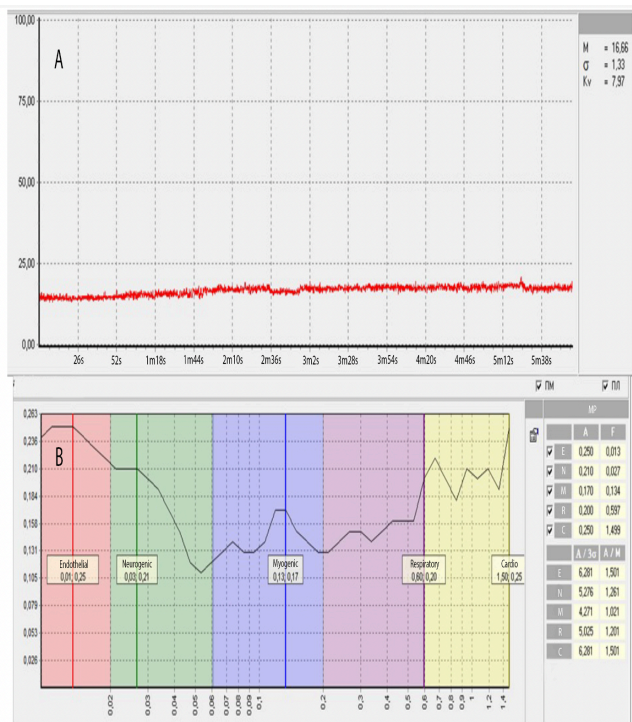


**Figure 5.** MC indicators when applying Soderm®-Forte when compared to those in control. **Note:**  $A_E$  – amplitudes of perfusion oscillations in the endothelial range;  $A_N$  – amplitudes of perfusion oscillations in the neurogenic range;  $A_M$  – amplitudes of perfusion oscillations in the myogenic range;  $A_P$  – amplitudes of perfusion oscillations in the pulse range;  $A_R$  – amplitudes of perfusion oscillations in the respiratory range.  $MP$  is a perfusion indicator. Data labeling is the confidence level of the differences in the experimental group according to the Mann-Whitney criterion, with  $p \leq 0.05$ ; \* – differences are statistically significant compared to the control.

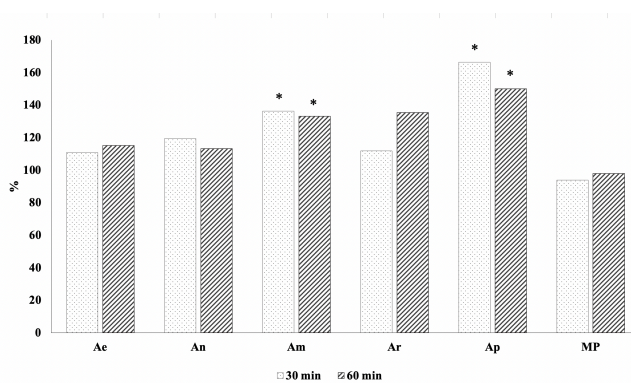
So, the application of Soderm®-Forte to the gingival mucosa of the lower incisors in rats increased the basal level of NO secretion and the activity of precapillary sphincters and precapillary arterioles, reduced the activity of sympathetic adrenergic vasomotors, which, in general, led to an increase in tissue perfusion. At the same time, Soderm®-Forte had the most potent impact within the first 30 minutes after being applied to the gingival mucosa, and 60 minutes later its effect decreased. The application of Soderm®-Forte led to an increase in  $A_E$ ,

which reflects the effect of humoral metabolic factors on MC and characterizes the state of nutritional blood flow.

With i.p. administration of Cytoflavin® to the rats, some changes were recorded in both the oscillatory and non-oscillatory MC indicators, when compared with the similar parameters obtained in the control group of animals. For example, 30 minutes after the administration of Cytoflavin®, changes were observed in the amplitudes of all oscillations, but only two indicators increased statistically significantly:  $A_M$  rate – by 36.2% ( $p < 0.05$ ) and  $A_P$  rate – by 66.4% ( $p < 0.05$ ), compared with those in the control group of animals. At the same time, the rest of the oscillatory indicators increased slightly, and the non-oscillatory indicators reduced slightly (Figs 6 and 7).



**Figure 6.** Typical LDF-gram when administering Cytoflavin®. *Note:* **A** – reference line (baseline) without assigned frequencies; **B** – LDF-gram after administering Cytoflavin®.

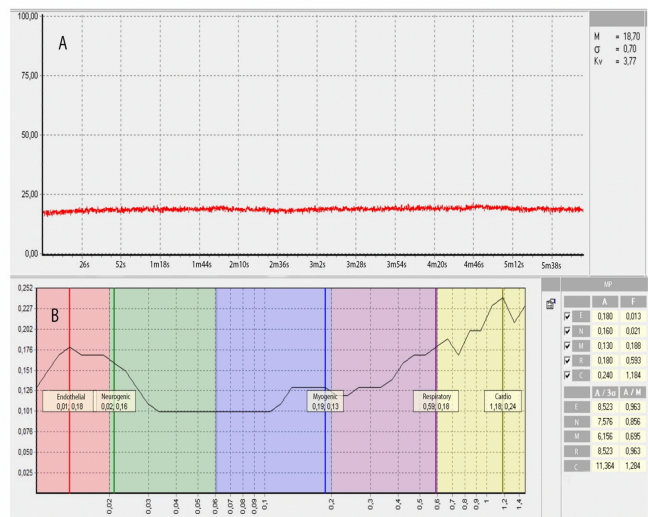


**Figure 7.** Microcirculation indicators with administering Cytoflavin®, % to control. *Note:*  $A_E$  – amplitudes of perfusion oscillations in the endothelial range;  $A_N$  – amplitudes of perfusion oscillations in the neurogenic range;  $A_M$  – amplitudes of perfusion oscillations in the myogenic range;  $A_P$  – amplitudes of perfusion oscillations in the pulse range;  $A_R$  – amplitudes of perfusion oscillations in the respiratory range. MP is a perfusion indicator. Data labeling is the confidence level of the differences in the experimental group according to the Mann-Whitney criterion, with  $p \leq 0.05$ ; \* – differences are statistically significant compared to the control.

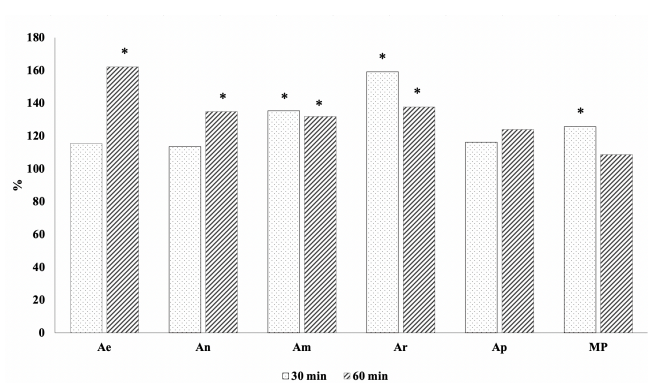
After the injection of Cytoflavin® by the 60<sup>th</sup> minute of the study, a further increase in  $A_M$  indicators was observed by 33.1% ( $p < 0.05$ ),  $A_P$  – by 50% ( $p < 0.05$ ) and a decrease in CV by 53.3% ( $p < 0.05$ ), compared to those in the control group of animals (Figs 6 and 7).

Thus, Cytoflavin® increased the activity of precapillary sphincters and metarteriolas, extravascular MC components, but did not change the perfusion of tissues.

The combined use of Soderm®-Forte gel and Cytoflavin® led to changes in MC, which were less pronounced than when applying Soderm®-Forte alone, but more pronounced than those when applying only Cytoflavin®. For instance, 30 minutes after administering the above combination, there was a statistically significant ( $p < 0.05$ ) increase in  $A_M$  indicators by 35.4%,  $A_R$  – by 59.2% and MP – by 25.7%, whereas RMS and CV decreased by 50.7% and 63.2%, respectively, compared with those in the control (Figs 8 and 9).



**Figure 8.** Typical LDF-gram for combined effects of Soderm®-Forte and Cytoflavin®. *Note:* **A** – reference line (baseline) without assigned frequencies; **B** – LDF-gram after the combined use of Soderm®-Forte and Cytoflavin®.



**Figure 9.** Microcirculation indicators for combined effects of Soderm®-Forte and Cytoflavin®, % to control. *Note:*  $A_E$  – amplitudes of perfusion oscillations in the endothelial range;  $A_N$  – amplitudes of perfusion oscillations in the neurogenic range;  $A_M$  – amplitudes of perfusion oscillations in the myogenic range;  $A_P$  – amplitudes of perfusion oscillations in the pulse range;  $A_R$  – amplitudes of perfusion oscillations in the respiratory range. MP is a perfusion indicator. Data labeling is the confidence level of the differences in the experimental group according to the Mann-Whitney criterion, with  $p \leq 0.05$ ; \* – differences are statistically significant compared to the control.

Sixty minutes after the combined use of Soderm®-Forte gel and Cytoflavin®, there was a statistically significant ( $p < 0.05$ ) increase in  $A_E$  indicators by 62.1%,  $A_N$  – by 34.8%,  $A_M$  – by 31.9%,  $A_R$  – by 37.8%, compared with those in the control group of animals; the non-oscillatory components RMS and CV decreased by 60.1% and 59.6%, respectively, with MP reaching the baseline values (Figs 8 and 9).

Interpretation of the data obtained shows that slow oscillations around a 0.01 Hz rate are synchronized with periodic NO release by vascular endothelium, which plays an important role in regulating blood pressure and distribution of blood flow. It is known that a NO pool is derived in the endothelium, which ensures the basal level of secretion of this vasorelaxant, which helps maintain the normal vascular tone. Besides, NO is involved in a number of other functions of the endothelium and is most sensitive to various negative influences on it. The positive effect of NO on the endothelium is expressed in inhibiting intimal hyperplasia, reducing the proliferation of smooth muscle cells (SMCs), and in active vasodilation.

The observed increase in the amplitude of  $A_E$  rates when applying Soderm®-Forte to the gingival mucosa of the lower incisors of rats indicates an increase in the basal level of NO secretion. The vasodilation of microcirculatory vessels is also evidenced by an increase in the amplitudes of oscillations in the  $A_M$  range, which are due to the periodic activity of SMC arteriolas, leading to a change in their lumens (vasomotion) and closely correlate with the number of functioning capillaries (Krupatkin and Sidorov 2005).

A significant increase in  $A_M$  in animals indicates an increase in the activity of myocytes of precapillary sphincters and precapillary metarteriolas, which is accompanied by dilatation of precapillaries when measuring the basal blood flow, an increase in the number of functioning capillaries, and, as a result, to the immediate flow of blood into the nutritional bloodstream (Krupatkin and Sidorov 2005).

An increase in  $A_N$  reflects the activity of sympathetic adrenergic nerve fibers, and they impact SMCs of microcirculatory vessels. A pronounced increase in the amplitudes of flux motions in the neurogenic frequency range in the LDF-gram of animals of these groups indicates the limited vasoconstrictor control of arteriolar tone by sympathetic nerves (Krupatkin and Sidorov 2005).

The increase observed in the amplitude of oscillations in the myogenic  $A_M$  range when administering Cytoflavin® i.p., which are due to the periodic activity of SMC arteriolas leading to a change in the diameter of their lumens (vasomotion) and closely correlate with the number of functioning capillaries (Krupatkin et al. 2022), indicates an increased activity of myocytes of precapillary sphincters and precapillary metarteriolas, which is accompanied by dilatation of precapillaries when measuring the basal blood flow, an increase in the number of functioning capillaries, and, as a result, to the immediate flow of blood into the nutritional bloodstream (Krupatkin and Sidorov 2013). An increase in the indicator of  $A_P$ , which is directly proportional to the change in the blood flow in the MC system (Krupatkin and Sidorov 2005), indicates an increase in the flow of arterial blood.

The recorded growth in the  $A_R$  indicator, which in the LDF-gram is due to periodic blood pressure oscillations in the venous side of MC, indicates an increase in the venous blood filling, and, possibly, a disturbed venous outflow, which can lead to congestion in this side of MC. A decrease in the amplitude of oscillations goes with an increase in the tone and stiffness of the vascular wall itself and, conversely, an increase in amplitudes results from a decrease in the vascular tone (Krupatkin and Sidorov 2005).

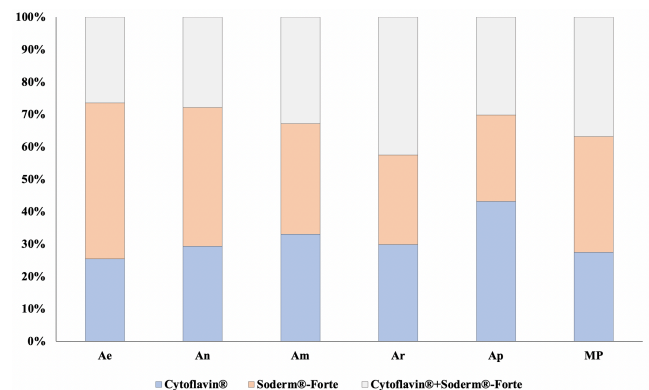
Thirty minutes (Fig. 10) after the combined use of Cytoflavin® and Soderm®-Forte, perfusion in the gum tissues increases due to the growth in the vasomotor component of  $A_M$  and the extravascular component of  $A_R$ . This effect is likely due to the two-way effect: the systemic effect of Cytoflavin® and the topical effect of Soderm®-Forte. Sixty minutes after the combined use of the medications, all the oscillatory parameters of microcirculation in the animals increased.

Thus, the combination of Cytoflavin® and Soderm®-Forte in whole leads to an increase in microcirculation in gum tissues, with an increase in the activity of myogenic and pulse rates 30 minutes later, and an increase in the activity of all oscillatory components 60 minutes later, without a significant increase in the overall tissue perfusion.

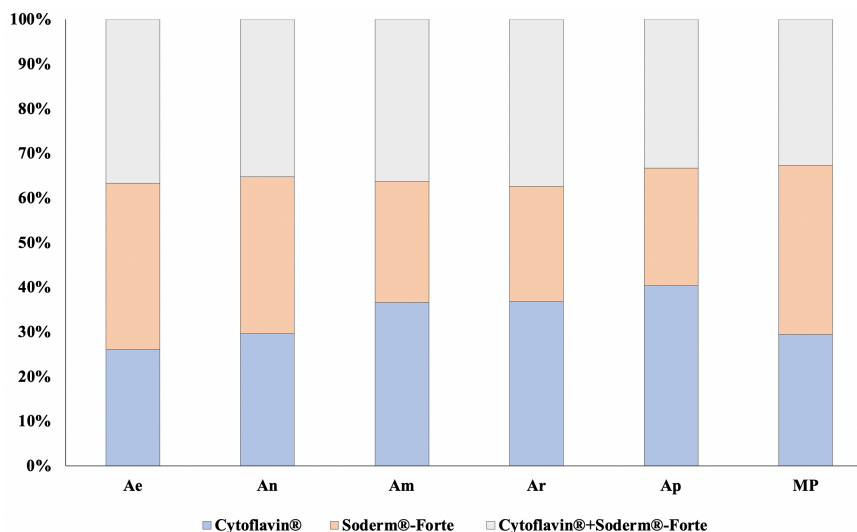
## Conclusion

To carry out a comparative analysis of the effectiveness of different medications and their combination, a normalized histogram was built, which visually assesses the relative contribution of each value into the total (Fig. 10).

The analysis of this histogram showed that 30 minutes after the administration, efficiency of Soderm®-Forte was slightly higher in terms of such parameters as  $A_E$ ,  $A_N$ , and  $A_M$ . According to the effectiveness of 30-minute action (Fig. 10), the medications can be arranged in the following order: Soderm®-Forte – Cytoflavin®+Soderm®-Forte – Cytoflavin®. Cytoflavin® does not seem to contribute to the effectiveness of the combination.



**Figure 10.** Comparative analysis of efficiency of Soderm®-Forte and Cytoflavin® and their combinations 30 minutes after experimental exposure. **Note:**  $A_E$  – amplitudes of perfusion oscillations in the endothelial range;  $A_N$  – amplitudes of perfusion oscillations in the neurogenic range;  $A_M$  – amplitudes of perfusion oscillations in the myogenic range;  $A_P$  – amplitudes of perfusion oscillations in the pulse range;  $A_R$  – amplitudes of perfusion oscillations in the respiratory range. MP is a perfusion indicator.



**Figure 11.** Comparative analysis of efficiency of Soderm®-Forte and Cytoflavin® and their combinations 60 minutes after experimental exposure. *Note:* A<sub>E</sub> – amplitudes of perfusion oscillations in the endothelial range; A<sub>N</sub> – amplitudes of perfusion oscillations in the neurogenic range; A<sub>M</sub> – amplitudes of perfusion oscillations in the myogenic range; A<sub>P</sub> – amplitudes of perfusion oscillations in the pulse range; A<sub>R</sub> – amplitudes of perfusion oscillations in the respiratory range. MP is a perfusion indicator.

A comparative analysis of the effectiveness of the compounds 60 minutes (Fig. 11) after their administration showed that Soderm®-Forte and its combination with Cytoflavin® were equal in efficiency in terms of A<sub>E</sub> and A<sub>N</sub>. However, in terms of the parameters of A<sub>M</sub>, A<sub>R</sub> and A<sub>P</sub>, the efficiency of Soderm®-Forte+Cytoflavin® was comparable to that of Cytoflavin®, and in terms of the MP parameter, Soderm®-Forte+Cytoflavin® fell in between.

Thus, the combined action of Cytoflavin® and Soderm®-Forte 30 minutes after administration increases tissue perfusion due to an increase in the myogenic and

respiratory components, and 60 minutes later – due to an increase in all the components of microcirculation regulation.

By the ability to increase blood flow, the substances under study and their combination can be arranged in the following descending order: Soderm®-Forte > Soderm®-Forte+Cytoflavin® > Cytoflavin®.

## Conflict of interest

The authors do not declare a conflict of interests.

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