# Photochemical Closed-Loop Ozone-Generating System for Medicine Application

**Dmitry V. Schitz*, Stanislav A. Sukhikh, Valeria V. Shupletsova, Yuri V. Voyteshonok, Mikhail A. Agapov, Olga O. Babich, and Olga G. Khaziakhmatova**
Immanuel Kant Baltic Federal University, 14 Nevsky str., Kaliningrad 236041, Russian Federation
*e-mail: DSchitz@kantiana.ru

**Abstract.** This article introduces a cutting-edge device that could potentially be used to therapy of septic wounds in prospect. The circulation of ozonized air with concentrations of up to 60 ppm provided under a hermetic ozonation application chamber. Subsequently, this air stream is directed to an ozone reactor for re-ozonation. To ensure both the secure fixation of the ozonation chamber to a surface and to prevent ozone leakage it is pressurized below atmospheric pressure, thereby in addition creating a vacuum therapy effect which contributes to the effectiveness of the treatment. Ozone is generated by irradiation of atmospheric air at a wavelength of 172 nm, which eliminates of toxic nitrogen oxides production, as it happens in gas-discharge ozonators. The device has undergone *in vitro* testing for the ozonation of various strains of bacteria and fungi. Leveraging its potential oxidizing capacity, pathogenic culture colonies were entirely killed within a 3-min treatment process. It has also been shown, that under *in vitro* conditions, short-term medium-mediated ozonation inducing reversible oxidative stress has a positive effect on proliferative activity and adhesion ability in eukaryotic mesenchymal cells. Depending on ozone concentration, duration and exposure conditions, the diverse effects of ozone, establish a foundation for potential therapeutic applications in the treatment of various diseases.

**Keywords:** ozone; photochemical ozonator; VUV radiation; antibacterial effect; eukaryotic cells.

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## 1 Introduction

The advancement of non-medicinal treatment methods and the reduction of antibiotic usage are pivotal components of contemporary medicine. Overreliance on antibiotics has led to the emergence of antibiotic-resistant bacteria, posing a significant threat to human health. Non-medicinal approaches provide compelling alternatives to antibiotics. Ozone, in particular, acts as a potent oxidizing agent, showcasing a notable capacity to readily react with organic substances. This distinctive property positions ozone as a highly effective disinfectant. Unlike antibiotics and ultraviolet radiation, ozone functions through a non-specific mechanism, circumventing the development of habituation (resistance) in microorganisms. The process of ozonation leads to the oxidation and destruction of bacterial or fungal cell membranes without inflicting damage to their DNA – a notable departure from the effects commonly associated with antibiotics or UV radiation.

Scientific evidence [1] supports various properties of ozone, including its effectiveness as a disinfectant, oxygen donor, immunomodulator, inducer of antioxidant enzymes, metabolic enhancer, and inducer of endothelial nitric oxide synthase. However, it is crucial to acknowledge that ozone, despite its beneficial properties, has inherent toxicity and poses respiratory hazardous risks. When employed invasively, it is imperative to exercise caution and adhere to recommended concentrations and doses.

Ozonation therapy, involving the direct application of ozone to a wound, has been utilized for several decades

to treat septic wounds in both humans [1] and animals [2]. This method has shown particular effectiveness in addressing challenging wounds with diverse pathologies. To administer ozone therapy, a special plastic bag is usually placed over the patient's extremity (arm or leg), and ozonized air is injected into the enclosed space [3]. Following wound ozonation, excess pressure is released through a separate tube, ensuring utilization of ozone.

A local ozone therapy (ozone treatment over a wound) resolves the problem of the regional hypoxia in a purulent wound by activating succinate-dehydrogenase and cytochrome c oxidase. The metabolic recovery of tissue is accompanied by elimination of acidosis, improvement of the microcirculation and nourishment of the inflammatory tissues, acceleration of wound healing processes and epithelialization. [4]. The therapy also increases the susceptibility of microbes to antibiotics, which allows for the reduction of the dose and duration of their administration. The wound surface undergoes rapid bacterial decontamination, necrolysis, granulation, and epithelialization along the edges of the wound. In the conditions of ozone therapy, the pain syndrome also disappears after 3−4 days [5].

When pumping ozonized air or oxygen through the bag under pressure, leaks of ozone that are dangerous for breathing are almost inevitable, so surgeons are reluctant to use this method in hospital settings [1]. To apply this method, it is necessary to recycle the used ozone in an $O_3$ reactivator or install a powerful ventilation system.

Beyond ozone therapy, a vacuum-assisted closure, also known as negative pressure wound therapy, is used for non-healing or at risk of non-healing wounds. It involves the application of a vacuum dressing over the wound, creating negative pressure [6, 7], which causes microscopic deformation of the wound surface, inducing a gentle stretching effect that encourages division and proliferation of cells. Furthermore, it stimulates tissue growth and angiogenesis [8], while removing enema fluid and exudate from the extracellular space. Additionally, vacuum therapy aids in the elimination of inflammatory mediators and cytokines [6].

Despite the fact that the treatment of septic wounds by ozonation has been carried out for several decades [1] using commercially available medical ozonizers, such as those produced by LEPSE (Russia) or Hänsler Medical GmbH (Germany), they nevertheless have some disadvantages. The ozonation system described in the paper, on the contrary, allows eliminating these shortcomings and using ozone therapy in medical institutions more effectively and safely.

## 2 Methods and Materials

### *2.1 Photochemical Ozone Generation*

Industrial ozonators based on gas discharge into the air were developed in the mid-19th century. To achieve high concentrations of ozone, oxygen is passed through an ozonator. The introduction of photochemical ozonators is linked to the advancement of potent sources of ultraviolet radiation with a wavelength of less than 200 nm (Vacuum Ultra Violet (VUV) range) [9]. Radiation in this range is characterized by the strong absorption of oxygen, and the energy of quantum is sufficient for the decomposition of $O_2$ and the formation of $O_3$ (Fig. 1). Consequently, VUV radiation and three oxygen molecules make two ozone molecules. Similar processes occur in the upper layers of the Earth's atmosphere during the formation of the ozone layer.

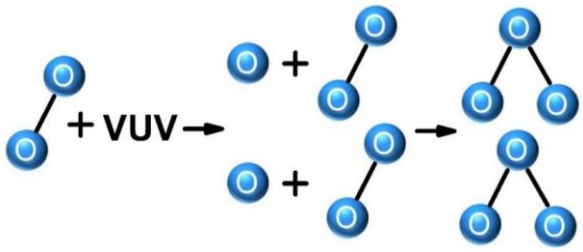



Fig. 1 Photochemical reaction of ozone formation.

The main advantage of photochemical ozonators is as follows: since inert gases (including nitrogen) are transparent in the VUV range, at irradiating the air the radiation directly affects oxygen, which absorbs all VUV radiation in a layer of no more than 5 mm. This means that all the VUV light energy produced by the emitter is utilized for ozone formation. Thus, within the air flow, using a relatively compact device, it is possible to achieve an ozone concentration up to 60 ppm without the need for pure oxygen.

As it is known nitrogen oxides are formed under conditions of high temperature (more than 1000 °C) or as a result of plasma-chemical reaction. There is a necessity to use pure oxygen in gas-discharge ozonators for medical applications, because of $NO_x$ or $N_yO_x$ producing in the interelectrode space in atmospheric air [10], which is toxic to living systems, especially to fresh epithelium during wound healing. Production of nitrogen oxides is excluded in photochemical ozonators by reason of ozone formation driven by VUV (not as a result of plasma-chemical reaction in air).

In the beginning a compact photochemical ozone reactor in the shape of a cylindrical metal tube measuring ø40×200 mm was developed. In this tube, a xenon excimer Dielectric Barrier Discharge (DBD) lamp is coaxially positioned. There is an axial-flow fan at the tube's terminus. The ozone reactor has hermetically fixed fittings at both ends for connection of flexible hoses to pump the air.

The xenon DBD excimer lamp, measuring ø21×170 mm, is equipped with an inner electrode made of aluminium foil, applied a high pulse voltage, while the outer grid electrode is grounded (Fig. 2). The radiation power of the excimer lamp in the VUV range was 1 W at a power consumption of 32 W and plus frequency of 60 kHz. The efficiency of the power supply & lamp system was therefore 3.1%. A VUV power density was measured by UV power meter Hamamatsu C9536

(Shizuoka, Japan) with head H9535-172 on the lamp surface. With the value of the emitting area of the lamp, the total VUV power was calculated. The design and power supply of excimer DBD lamps are comprehensively described in Refs. [11, 12]. Fig. 3 illustrates the emission spectrum of the xenon lamp, as measured by the Ocean Optics Maya 2000Pro spectrometer (Orlando, USA).

Fig. 2 A xenon DBD excimer lamp.

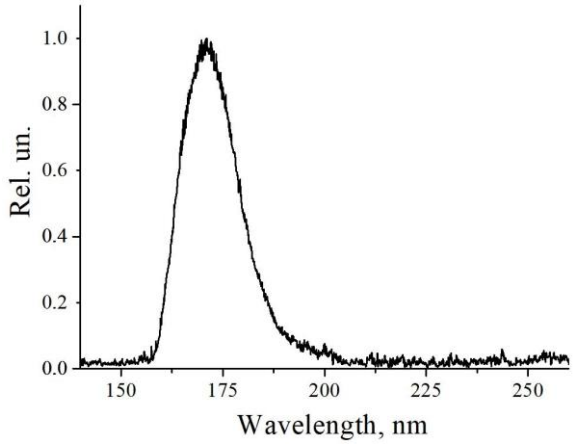



Fig. 3 Emission spectrum of $Xe_2$* molecules.

The designed photochemical ozonator has the capability to generate an ozone flow with a concentration reaching up to 60 ppm at an air pumping rate of 8 l/min and VUV radiation power of 1 W. The value of $O_3$ concentration in the closed system was mainly determined by the radiation power of the DBD excimer lamp and a lesser degree by the flow rate of ozonised air, therefore, in order to ensure better cooling of the lamp, the air pumping rate was 8 l/min. Measurements of ozone concentration were carried out using the ENVEA UV Ozone Analyzer O342e (Poissy, France).

A notable advantage of the developed photochemical ozonator is ability to precisely adjust ozone concentration by linearly adjusting the VUV radiation intensity of the excimer lamp. It was achieved by a special mode of lamp excitation in which pulses of ~2 μs duration with relatively long pauses between them are applied to the electrodes [13]. If the excitation energy of a pulse does not change, the excitation power and the VUV power can be linearly adjusted by the pulse frequency. In this way, a linear adjustment of ozone concentration from 5 to 60 ppm was realised. In addition, a relatively low supply voltage of the ozonator enhances compatibility with other electronic medical equipment.

## *2.2 Closed-Loop Ozone-Generating System*

As was already mentioned, to ozonate a wound on a patient's limb (arm or leg), a plastic bag is used, and ozone is pumped into it. However, it is quite challenging to achieve a leak-proofness when the wound is on plane parts of the body (for instance, the abdomen, thigh, back, etc.). To address this issue, an ozonation vacuum chamber **1** has been developed (Fig. 4); it has flexible hoses (**2** and **3**) connected to it for the supply and withdrawal of ozonized air to the ozone reactor **4**.

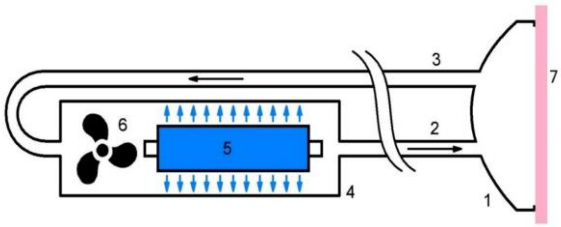



Fig. 4 The photochemical ozonation system: 1 – application chamber, 2 – ozone supply channel, 3 – ozone withdrawal channel, 4 – ozone reactor, 5 – VUV lamp, 6 – fan, 7 – treated surface.

By securely fixing application chamber **1** onto treated area **7**, a leak-proofness is achieved due to the close-loop of ozonation system via channels **2** and **3**. Activation of the fan **6** and lamp **5** initiates a cyclical airflow along the close-loop. In each cycle through the reactor **4**, the air undergoes ozone enrichment, and then it traverses through the chamber **1**, contributing to the treatment of the patient's wound. To securely affix the chamber **1** to the wound, a controlled sub-atmospheric negative pressure ranging from 675 to 710 mm Hg (−75 to −40 mm Hg relative to atmospheric pressure) is maintained in the ozone pumping close-loop. This is achieved by integrating a hermetic outlet into an ozone reactor **4** (not depicted in Fig. 4), and connecting it to a vacuum pump. A microprocessor control unit, along with a pressure sensor integrated into the reactor, monitored the pressure within the closed-loop ozone-generating system. This control unit facilitates the adjustment of ozone concentration levels and monitors the duration of the ozone therapy procedure.

The close-loop of ozonation system, coupled with the negative pressure maintained, effectively eliminates any potential ozone leaks, ensuring the safety of ozone therapy for both the medical personnel and the patient. Additionally, the versatility of the system allows for adaptability in the type of the application chamber **1**. For instance, it can be substituted with a plastic bag for treating limbs or replaced with an overlay chamber of varying dimensions suitable for different wound contours and the relief of different body areas. This flexibility may enhance the applicability of the ozonation system in perspective, catering to a range of therapeutic requirements with precision and convenience. Through the creation of a low-level vacuum within the chamber **1**,

the system also may contribute to the expeditious healing of septic wounds.

Notably, the system's control unit features a vacuum therapy function without wound ozonation. In this mode, both the fan **6** and excimer lamp **5** remain inactive, and the control unit establishes negative pressure within the application chamber based on the parameters set by the medical professional.

## 3 Results and Tests

### *3.1 General Design of the Closed-Loop Ozone-Generating System*

The system is a prototype of medical device designed to administer ozone treatment to surfaces beneath the application chamber or within a plastic bag. The functional diagram of the system is given in Fig. 5. The main part of the control unit is an operation panel **1** featuring a built-in microprocessor and a touch screen. The operation panel **1** connected with a 4-channel relay module **2** and a pressure sensor **7**. This configuration makes it possible to independently activate four components of the system as needed: power supply **3** of VUV excimer lamp, fan **4**, fill-up valve **5** and vacuum pump **6**. The outlet of the vacuum pump was connected to a carbon-based ozone destructor (not shown on the Fig. 5). The operation panel **1** can manage and regulate the pressure within the ozone reactor through the integrated pressure sensor **7** and vacuum pump **6**. VUV lamp excitation timing pulses were generated from the control panel **1** and applied to the power supply **3** at a frequency corresponding to the set ozone concentration level.

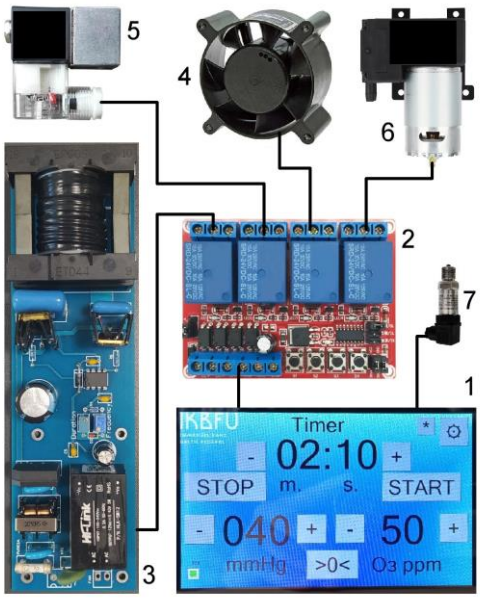



Fig. 5 Functional diagram of the system: 1 – operation panel, 2 – relay module, 3 – power supply, 4 – fan, 5 – fill-up valve, 6 – vacuum pump, 7 – pressure sensor.


Fig. 6 Closed-loop ozone-generating system.

All parts of the system are arranged within in a case measuring 325×220×120 mm (Fig. 6). Two fittings, located on the back panel of the case, are used to attach flexible hoses for the cyclical pumping of ozonized air through the chamber or bag, each hose measuring a length of 70 cm.

Prior to commencing ozonation, it is essential to set the required ozone concentration, procedure duration, and the negative pressure level on the operation panel screen. Once the treated area is appropriately covered with the chamber, pressing the "START" button sets off the vacuum pump, evacuating air from the ozone reactor up to the set pressure level. Following this, the VUV lamp automatically switches on, the fan **4** (Fig. 5) starts to operate, and the countdown for the procedure time commences.

If the application chamber is not properly contacted with treated surface thus preventing the air from being pumped out of the ozone reactor, a related message appears on the operation panel screen. If, for any reason, the pressure in the chamber exceeds the set value, the vacuum pump is activated to achieve the required pressure parameters. Pressing the "STOP" button pauses the procedure, and pressing the "START" button resumes it. Upon the expiration of the set time or by pressing "STOP" twice during the procedure, the system operation is ceased, and valve 5 (Fig. 5) opens to allow air into the ozone reactor. At the moment the vacuum pump **6** was switched on for 90 s to remove the residual ozone from the entire system volume.

### *3.2 Evaluation of the Antibacterial Effect of Ozone*

The pathogenic strains selected for the study included *Escherichia coli* ATCC 25922 (Gram-negative conditionally pathogenic bacterium), *Bacillus subtilis* (a gram-positive, spore-forming, facultative aerobic bacterium), *Candida albicans* EMTC 34 (the causative agent of opportunistic infections), and *Aspergillus niger*

(a mold fungus capable of inducing mucormycosis in humans).

The mechanisms of action and metabolic processes of the selected bacteria are identical to other Gram-negative and Gram-positive bacteria, and some of them are antibiotic resistant, making them a standard bacterium present in wounds [14, 15] so they were taken as a case study to investigate wound infections.

*C. albicans* – yeast-like microscopic fungi, which can also be used to assess the effectiveness of antifungal therapy for wounds. *A. niger* is capable of causing disseminated invasive aspergillosis, an infection that spreads widely throughout the body, including on the wound surface [16]. These fungi also have similar metabolism to other microscopic fungi, and can be used as example microorganisms to investigate the efficacy of wound infection treatment [16].

All test strains were inoculated into Petri dishes with agarized medium and cultured following the protocol described in Ref. [17]. Subsequently, the Petri dishes were placed on a rubber mat and securely sealed with the application chamber of the ozonator. The ozone exposure duration at a concentration of 60 ppm was 3 min. Following ozonation, the test strains were incubated on agarized growth medium at 37 °C (*A. niger* at 28 °C) for 24−48 h. Petri dishes in which the same microorganisms were cultured were used as a negative control; however, their suspensions were not treated with ozone. The test strains in the control Petri dishes were co-incubated with the ozone-treated Petri dishes.

The experiment was conducted in two repetitions. The presence of an antibacterial effect of ozone (sensitivity of microorganisms to the action of ozone) was evaluated by counting colony-forming units (CFU/ml) on inoculated media *in vitro*. In cases of no bacterial growth, a value of <10 CFU/ml (detection limit) was used [18–20]. Some of the results are shown in Table 1 and Fig. 7. Notably, gaseous ozone showed a strong antimicrobial effect, leading to the complete eradication of all microorganisms examined. This included both Gram-negative and Gram-positive bacteria, as well as yeast-like and mold fungi. It demonstrates the effectiveness of gaseous ozone in eliminating a wide range of pathogens. Analysis of the data presented in Fig. 7 also indicates that ozone treatment resulted in complete prevention of the growth of opportunistic microorganisms.

Table 1 Ozone treatment of *E. coli*, *B. subtilis*, *C. albicans* and *A. niger*.

| Microorganism | Without ozone treatment, CFU/ml | After ozone treatment, CFU/ml |
|---|---|---|
| *E. coli* | $6.3 \cdot 10^6$–$10^7$ | <10 |
| *B. subtilis* | $3.2 \cdot 10^7$–$10^8$ | <10 |
| *C. albicans* | 748.2 | <10 |
| *A. niger* | 976.6 | <10 |

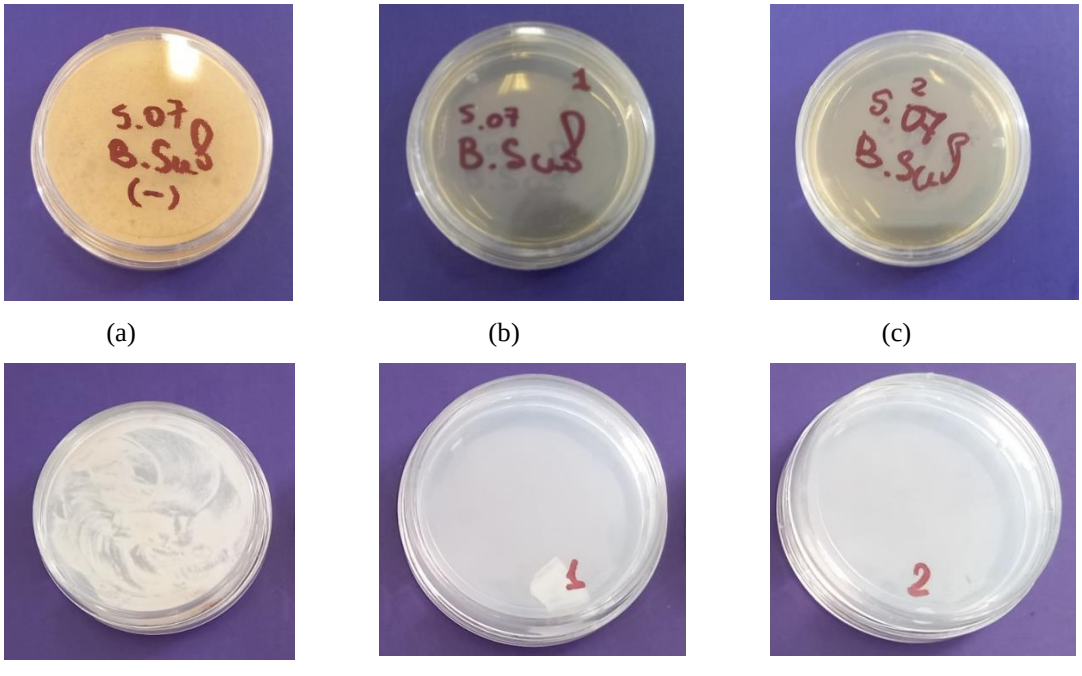



Fig. 7 (a−c) *B. subtilis* and (d−f) *A. niger* after incubation: (a, d) control (no ozone exposure), (b, e) after ozone treatment (repetition 1), (c, f) after ozone treatment (repetition 2).

The bactericidal effect observed in the studies corroborates the previously established data on the non-specific antibacterial efficacy of ozone against prokaryotic organisms [15−16]. High doses of ozone cause bacterial cell death by disrupting the lipids and lipoproteins of cell membranes and triggering cell death pathways (apoptosis). Additionally, ozonation disrupts bacterial populations by affecting adhesion proteins and mechanisms involved in the formation of intercellular matrix and intercellular bonds within bacterial biofilms, supporting the notion that high-dose ozonation is an effective non-specific disinfection strategy.

Other studies have also demonstrated that short-term exposure to high ozone concentrations leads to the activation of a series of anti-inflammatory and regenerative mechanisms in the cells and tissues of humans or animals, activating signalling pathways and subsequent synthesis of a complex of anti-inflammatory, regulatory, and growth factors [20−21].

### *3.3 The Effect of Ozonation on Eukaryotic Cells*

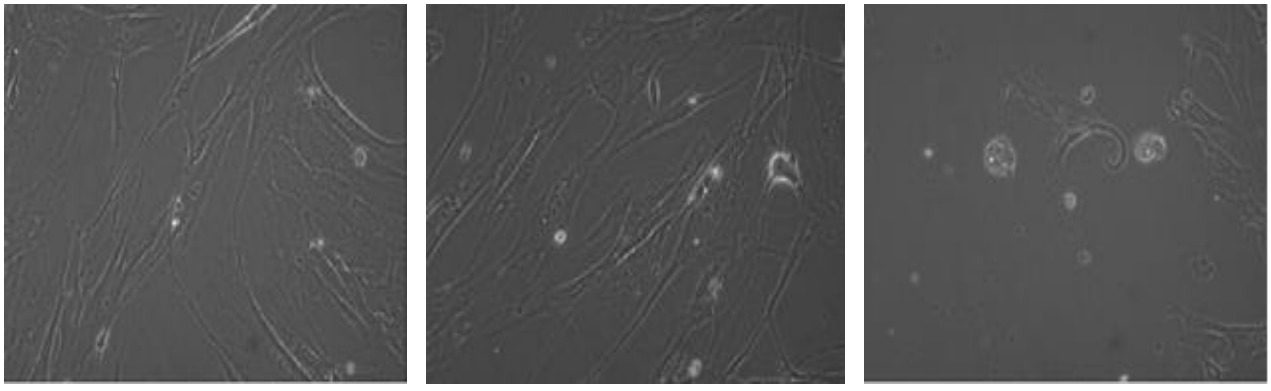
Human multipotent mesenchymal stromal cells (MMSCs) of adipose tissue have been isolated by enzymatic method from the lipoaspirates of healthy donors obtained during the esthetic liposuction. The lipoaspirates were provided for research purposes by partners of the plastic surgery clinic. The receipt and transfer of the material was carried out in accordance with the ethical and legal norms in force on the territory of the Russian Federation, with the signing of informed consent, in accordance with the procedure approved by the Local Ethical Committee of the Innovation Park of the Immanuel Kant Baltic Federal University (permission No. 7 on 9 December 2015). Multipotent stem cells have been obtained from the lipoaspirates and cryopreserved using liquid nitrogen in the cryobank of the Center for Immunology and Cellular Biotechnology of the Immanuel Kant Baltic Federal University. For our study, MMSCs from the cryopreservation have been morphologically stabilized on plastic, cleaned up of debris by a cascade of washing procedures and removed from plastic by trypsinization and introduced into model cultures on a 6-well plate after achieving confluency of 80%.

Experiments were conducted on healthy stem cells primary cultures, since these cells are among the first cells recruited in the remodeling of the tissues of a wound. The fifth passage of human MMSCs derived from subcutaneous adipose tissue were used for an *in vitro* experiments. Cells were expanded on plastic under standard conditions [22]. Cells ozonation contact was under both during direct and indirect (mediated a liquid medium) conditions, the exposure time was 3 min.

The experimental cultures were analysed using an inverted microscope with an integrated OLYMPUS Video Zavr Standard camera (Tokyo, Japan) for the morphological characteristics, INVITROGEN CountessTM Automated Cell Counter (Waltham, USA) with Trypan blue 0.4% was used to determine the viability parameters. The relative number of apoptotic cells was assessed by flow laser cytometry using a MILTENYI BIOTEC MACS Quant Analyzer flow cytometer (Bergisch Gladbach, Germany) following the manufacturer's protocols.

The experiments showed that the morphology of eukaryotic cells of vertebrates did not change during medium-mediated contact with ozone (Fig. 8). However, direct ozonation led to various changes in cell morphology. The degree of such morphological changes associated with severity of the exposure conditions.

The number of live cells was increased by 22% after 24 h while exposed to ozone for 3 min (model 2E − ozonation of a medium, followed by the 3-min ozonation of cells in a monolayer on plastic, after which the medium was removed) (Fig. 9). In the control cultures (1K − 3K are control cultures undergoing the same experimental cycle, but without ozonation) this indicator was 31%, under the same conditions.



(a) (b) (c)

Fig. 8 Morphological changes of MMSCs in different ozonation models (magnification ×200). (a) Control cells (without ozonation), (b) after medium-mediated ozonation (3-min exposure), (c) cells after short-term direct ozonation (3-min exposure).

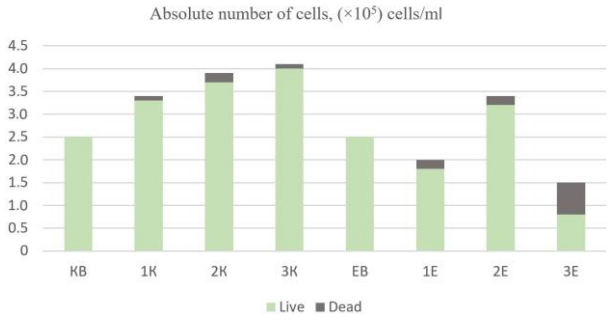



Fig. 9 Absolute indicators of culture viability in the control and experimental models of MMSCs: KB in the control models before the experiment; 1K − 3K in the control models after 24 h; EB in experimental models before the experiment; 1E − 3E in experimental models after 24 h.

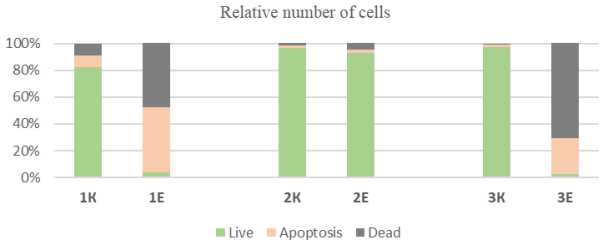



Fig. 10. Relative number of live, dead, and apoptotic MMSCs obtained by flow cytometry: 1K − 3K in the control models after 24 h; 1E − 3E in the experimental models after 24 h.

Using these models, the highest survival ratios of the culture could also be demonstrated. Both direct exposure to ozone (model 1E cells were ozonated without the presence of nutrient medium only in a humid atmosphere), and indirect exposure with prolonged cultivation in ozonated medium (model 3E − the ozonated medium surrounding the cells at the time of exposure was not changed, and the cells were for left for 24 h in a state of hyperoxygenation) led to a decrease in the absolute number of live cells in the culture (1.5−2 times) (Fig. 10).

## 4 Conclusion

The prototype closed-loop ozone-generating system, unlike the $O_3$ generators used for ozone therapy, has a special mode of operation in which ozone is supplied to the application chamber and then returned for re-ozonisation. To avoid $O_3$ leakage, ozonised air with a concentration of up to 60 ppm is cyclically pumped through a sealed, closed-loop ozone-generating system under negative pressure. The ozone-generating closed-loop system is primarily designed for the safe and effective treatment of septic wounds with high concentration ozone without the need for an oxygen supply, and has the ability to perform vacuum therapy.

The ozone flow emanating from the system exhibits potent antibacterial and fungicidal properties. Leveraging its potential oxidizing capacity, pathogenic culture colonies were entirely killed within a 3-min treatment process. This suggests that the suggested ozone treatment method holds considerable potential for diverse applications in both the medicine and food industries.

Our study also showed that *in vitro* conditions, short-term medium-mediated ozonation inducing reversible oxidative stress has a positive effect on proliferative activity and adhesion ability in eukaryotic mesenchymal cells.

Depending on ozone concentration, duration and exposure conditions, the diverse effects of ozone, establish a foundation for potential therapeutic applications in the treatment of various diseases. This includes leveraging cytotoxic/cytostatic effects in oncology and aiming to stimulate reparative regeneration processes in cases of chronic inflammatory conditions and non-healing wounds, even those complicated by antibiotic-resistant bacterial microflora.

## Disclosures

The authors have no relevant financial interests in this article and no potential conflicts of interest to disclose.

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