

The Impact of Ozone Therapy on Antioxidant Status and Quality of Life in Palliative Care - Exploratory Study

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There is a constant concern about finding new or alternative therapeutical approaches for symptom control and quality of life that are essential in palliative care. Ozone therapy has been studied for over a century, since the development of the first medical ozone-generator able to ensure a correct titration of the ozone-oxygen mixture. When used in precise therapeutic doses O₃ prove many consistent and safe therapeutic benefits, with minimal and preventable side actions. Our prospective exploratory study aimed to analyze the effects of ozone therapy administration on palliative care patients, by dynamically monitoring the antioxidant status (superoxide-dismutase and glutathione-peroxidase serum levels), pain perception, and quality of life. The results confirm ozone therapy as a promising alternative adjuvant therapy for increasing the quality of life in palliative care services.

Keywords: palliative care, ozone therapy, antioxidant status, superoxide-dismutase, glutathione-peroxidase, quality of life

Palliative care is a relatively new discipline introduced in Romania since 1992 [1]. Cancer patients are the main recipients of palliative care services today [2] and due to late presentation for diagnosis two thirds are already in advanced stages of the disease at diagnosis [3] so the goal of care is survival and good quality of life. New modalities are included under the umbrella of palliative care in order to ensure excellent symptom control and alongside drugs [4] non pharmacologic measures have an important contribution. Ozone therapy is not very well researched.

Ozone (O₃) is one of the most important gases in the stratosphere, reaching a maximum concentration of about 1000 μg/m³ at an altitude of 20-30 km. Under normal conditions (temperature 273 K, pressure 101.3 kPa), this ozone layer is only several millimetres in thickness, and has a basic but most important function in protecting humans from harmful effects of UV radiation. Its atmospheric concentration (20 μg/m³) is perfectly compatible with life [5].

Ozone (O₃) molecule was discovered in the mid-nineteenth century. In 1832 Schonbein published a book on this remarkable substance, Ozone Production by Chemical Methods (*Erzeugung des Ozons auf chemischem Wege*).

Despite some dangerous effects, when used in precise therapeutic doses O₃ proved many consistent and safe therapeutic benefits, with minimal and preventable side actions. Since the first technical ozone unit was built in 1857, i.e. *the upper induction tube* developed by Werner von Siemens, ozone therapy has been used and studied for more than a century. Exactly 100 years after the first ozone tube was developed, Joachim Hansler produced the first medical ozone-generator able to ensure a correctly titration of the ozone-oxygen mixture, thus opening up a broad spectrum of therapeutic applications.

The following mechanisms of action and effects of ozone therapy have been identified: optimization of metabolisms and antioxidant systems [6];

immunomodulatory mechanism [7]; improving peripheral microcirculation [8]; restoring the blood oxygen transportation [9]; bactericidal, virucidal and fungicidal effect [10]; blood hypocoagulability [11]; analgesic and detoxifying effect [12].

The concept of *metabolism optimization* refers to the apparent activation of the lipid metabolism (beta-oxidation of fatty acids) and glucose metabolism (glucose-6-phosphate dehydrogenase - G6PDH - activation, and neoglucogenesis through hepatic stimulation). Ozone therapy determines a decrease in serum glucose (by intensifying glycolysis due to activation of G6PDH) and compounds resulting from aerobic-anaerobic glycolysis (lactate-pyruvate). Ozone affects lipoic acid which, through aldehyde reactions, causes a decrease in atherogenic serum lipids (cholesterol, LDL, and VLDL cholesterol) [13]. The *optimization of antioxidant systems* involves the immediate triggering of free radical oxidation by ozone. At the same time, ozone immediately stimulates the antioxidant defense system as well [14-16].

Ozone therapy can induce an increase in the red blood cell glycolysis rate by stimulation of 2,3-diphosphoglycerate, enhancing the amount of oxygen released to the tissues. Krebs cycle is activated by enhancing oxidative carboxylation of pyruvate, and stimulating ATP production. It also causes a significant reduction in NADH and helps to oxidize cytochrome C. Enzymes acting as free radical scavengers and cell-wall protectors: (glutathione peroxidase, catalase and superoxide dismutase) are stimulated. Production of prostacyclin, a vasodilator, is also induced by O₃ [17].

Ozone can increase interferon synthesis, releasing of tumor necrosis factor (TNF) and interleukin-2 when administered in a concentration of 30-55 μg/cm³, launching a cascade of subsequent immunological reactions [18].

By oxidation of the membrane phospholipids, ozone disrupts the integrity of the bacterial cell envelope. O₃ inhibits cell growth at certain stages in fungi. The virucidal effect of O₃ is induced by damaging the viral capsid and

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upsetting the reproductive cycle by disrupting the virus-to-cell contact with peroxidation [5].

The ozone analgesic effect is based on diminishing the pro-inflammatory mediators (prostaglandins and thromboxanes) by inhibiting cyclo-oxygenase [19].

Ozone exposure can significantly decrease the vital capacity, determines a significant reduction of maximal transpulmonary pressure and tidal volume, increasing respiratory rate. It has a toxic effect on the lung epithelium inducing acute inflammation of the respiratory mucosa and altering the pulmonary alveolar surfactant, which can determine increased mean airway resistance, without any change in pulmonary compliance or viscous and elastic pulmonary work [18, 20]. For this reason, when applied therapeutically (internally applied), contact with the respiratory tract should be avoided. Thus, the maximum acceptable air ozone concentration (MAC) per working surface was defined as 0.1 mg/m². Human perception of ozone is 0.02 mg/m³; this means that our olfactory senses are a good indicator of the presence of ozone [21].

Ozone used external (on the skin or on wounds [22]), internal (*per os* or *per rectum*), and parenteral has a concentration within the therapeutic area, with no toxic action on the human body.

Assessment of ozone therapy antioxidant effect by glutathione-peroxidase and superoxide-dismutase monitoring

Glutathione-peroxidase (GPX) catalyses the degradation of organic hydroperoxides resulting from normal metabolic processes using glutathione as an electron donor. It protects proteins, lipids and nucleic acids against the action of oxidizing molecules.

GPX is an intracellular enzyme variable in quantity, while superoxide-dismutase (SOD), is constantly present intracellularly in large quantities.

GPX is selenium-dependent and can be found free in the cytoplasm (70%) and mitochondria (30%), where it is the only mitochondrial antioxidant agent. GPX also provides protection against organic hydroperoxides (involved in changes in vascular wall lipids that promote atherogenesis), and helps in regenerating the reduced form of vitamin C [23].

Quantitative changes in GPX occur during the physiological process of aging and in pathological conditions of cancer, Alzheimer's disease, alcohol-induced oxidative stress, cardiovascular disease, diabetes [5, 24].

Superoxide-dismutase (SOD) is an antioxidant enzyme that transforms superoxide radicals into water and hydrogen peroxide (H₂O₂), which is then catalysed into O₂ and H₂O by GPX. SOD treatment lowers reactive species of oxygen (ROS) generated by oxidative stress and, thus, inhibits the activation of epithelial cells in the colon mucosa and leukocyte-enterocyte interactions. One can therefore assume the major role of these antioxidants in developing new anti-inflammatory therapies targeting enterocolitis [25].

Patients eligible for palliative treatment suffer from chronic progressive oncological or non-oncological diseases and, generally, present with multiple comorbidities. Their afflictions are influenced in terms of evolution by tissue ischemia; compensating for this ischemia should mitigate the progression of their pathogenic evolution, with an improvement of symptomatology, and, subsequently, an increasing quality of life in these patients.

Experimental part

Aim and Objectives

The aim of the study was to explore the impact of ozone therapy on the evolution of patients in palliative care services and to analyse the opportunity of introducing ozone therapy as adjuvant therapy in palliative care.

The objectives of the study were to establish whether systemic and local ozone therapy had a favourable influence on the clinical evolution of patients under palliative care and to determine which forms of ozone therapy were more effectively and better tolerated by palliative care patients.

Methods

Design. Study Population

Ten patients from hospitalized in palliative care, respectively, in different other medical services were enrolled in this prospective experimental study (fig. 1) including a control group (placebo for ozone therapy).

After obtaining the approval of the Ethics Committee of C.F. General Hospital Ploiești, the patients were informed about ozone therapy and signed the informed consent papers [26-33].

The study population was divided in 5 groups, each group consisting of 2 patients who received ozone therapy or placebo over a 3 week time period as follows:

A. Four groups including patients from palliative care services.

Groups 1-3 - received alternative ozone therapy:

a. group 1 - rectal insufflation (RI) - oncologic and neurologic patients;

b. group 2 - subcutaneous injections (ScI) - oncologic and neurologic patients;

c. group 3 - transcutaneous gas baths (GB) - oncologic and neurologic patients;

d. group 4 - control (placebo) - oncologic and neurologic patients;

B. Group 5 - included patients from other medical services than palliative care, who received systemic ozone therapy by rectal insufflation - non-oncologic and non-neurologic patients.

The effects of the therapy was assessed by monitoring the following parameters: Eastern Cooperative Oncology Group (ECOG) performance status (degrees: 0-fully active, 1-slight restriction in activity, 2-active for over 50% of the day, 3-immobilized over for 50% of the time, cannot self-manage); quality of life according to the EORTC-QLQ-PAL Quality of Life Questionnaire; serum GPX and SOD levels; oxygen saturation of arterial blood (pulse oximetry, SaO₂); patients' adherence to different forms of ozone therapy. GPX and SOD levels were assessed in blood drawn once a week (four samples: 0-initial, week 1, week 2, week 3); ECOG and Quality of Life Questionnaire were evaluated once a week (0-initial, week 1, week 2, week 3); pulse oximetry was determined every 2 days.

Experimental ozone therapy administration

Groups 1 and 5 - Rectal insufflation with ozone-oxygen gas mixture: 2 sessions weekly were performed - a total of 6 sessions over the 3 weeks of the study.

Technique: With the patient placed in left lateral decubitus with the thighs flexed, after routine rectal exam, 300 mL of ozone-oxygen mixture 20µg/mL were introduced into the lower rectum *via* the hydro-lubricated Nelaton catheter (15-20cm), followed by anal retention through voluntary contraction of the anal sphincter, for 10-15 min.

Group 2 - Ozone-oxygen gaseous subcutaneous injections: 2 weekly sessions were performed - a total of 6 sessions over the 3 weeks of the study.

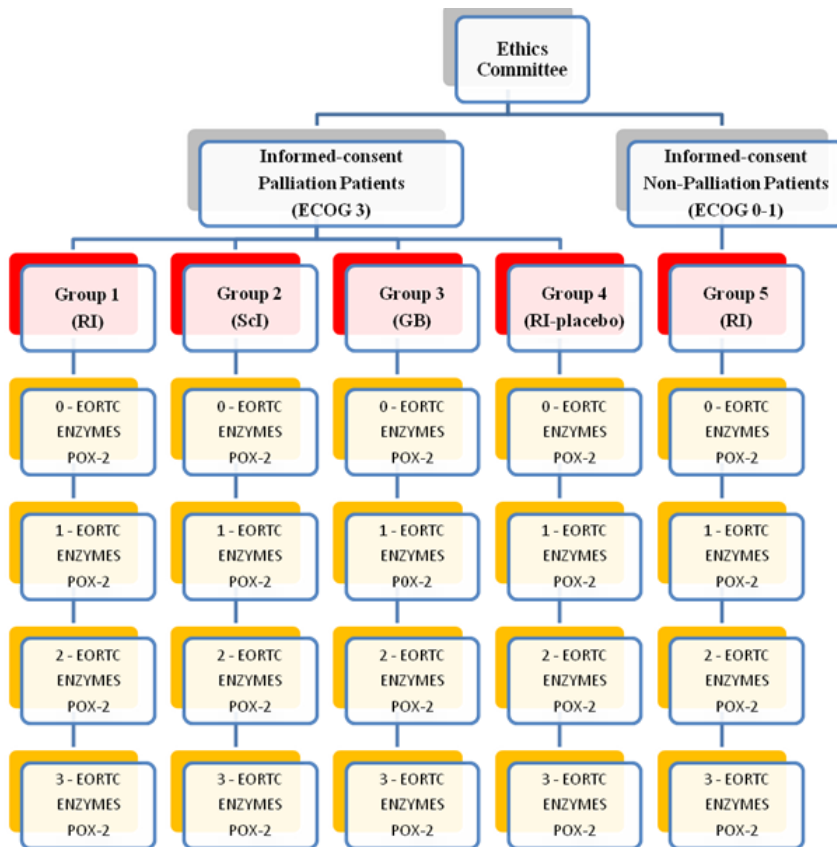


Fig. 1. Study Flowchart:
 ECOG = Eastern Cooperative Oncology Group performance status; EORTC = EORTC-QLQ-PAL Quality of Life Questionnaire; ozone therapy by rectal insufflation (RI), subcutaneous injections (ScI), transcutaneous gas baths (GB); enzymes = superoxide-dismutase (SOD) and glutathione-peroxidase (GPX); POX-2 = pulse oximetry (every 2 days)

Technique: With the patient placed in dorsal decubitus, 10 mL of ozone-oxygen mixture 20µg/mL was administered through a subcutaneous injection performed in the periumbilical region fold.

Group 3 - Transcutaneous oxygen-ozone mixture gas baths: 2 weekly sessions – 6 sessions over the 3 weeks of the study.

Technique: The patient was placed in dorsal decubitus, the selected area of the skin was moistened and the skin segment was inserted into a single-use polypropylene bag sealable with a clamp; the bag was sealed with special tape; 500 mL of ozone-oxygen mixture 20µg/mL was introduced, the bag being maintained for 15 min.

Group 4 - was the control group (placebo), consisting of oncologic and neurologic patients with no ozone therapy: rectal insufflation with atmospheric air was performed in 2 sessions weekly – a total of 6 sessions over the 3 weeks of the study.

Ten patients were enrolled in the study; their demographic characteristics and diagnosis are described in table 1.

Patients 1-8 were hospitalized in the Palliative Care Department – Internal Medicine Department 2 – C.F General Hospital Ploiesti. Patients 9 and 10 were hospitalized in the Internal Medicine Department 1 - C.F. General Hospital Ploiesti.

Efficacy of ozone therapy as assessed by enzymatic (SOD and GPX) monitoring

The antioxidant enzymes superoxide-dismutase (SOD) in oncological (SOD-o) and neurological (SOD-n) patients, and glutathione-peroxidase (GPX) in oncological (GPX-o) and neurological (GPX-n) patients were measured weekly.

Both SOD and GPX serum levels showed a significant increase during week 2 of the study, especially in oncological patients who received ozone-therapy by rectal insufflation (group 1), more pronounced than in the groups

Results and discussions

Study group

No.	Patient	Age	Gender	Diagnosis	ECOG Score
1	M.P.	82	M	Stage IV right colon cancer	3
2	B.A.	76	F	Stage IV lung cancer Chronic respiratory failure	3
3	S.V.	66	M	Stage I prostate cancer	0
4	G.S.	90	F	Stage IV right colon cancer	3
5	P.F.	83	M	Vascular dementia	3
6	M.G.	84	F	Heart failure – NYHA Class II	1
7	S.I.	60	M	Ischemic stroke. Left hemiparesis	3
8	S.C.	69	M	Peripheral artery disease – Fontaine stage III	3
9	D.I.	94	F	Left breast cancer – stage III B	3
10	I.I.	83	M	Alzheimer's Disease	3

Table 1
 CHARACTERISTICS OF THE STUDY GROUP

receiving ozone therapy by subcutaneous injection (group 2) or gaseous baths (group 3) (figs. 2a, b and c).

Group 3 (transcutaneous gaseous baths) showed a sinusoidal variation of antioxidant enzymes serum levels similar to group 2, without expressing a real increase in values. A possible explanation for SOD-o variations in this group could be the existence of a planum eschar that determined, through the cutaneous continuity lesion, the same pattern of ozone transfer to the body comparable to transmucosal rectal transfer, but with absolute values much lower than those corresponding to group 1.

SOD and GPX serum levels measured in group 1 were the highest in the study.

Group 4 (palliative care patients placebo for ozone therapy) that showed the *chaotic* values of the antioxidant enzymes (without any systematisation trend) is shown in figure 2d. The apparently elevated values could be explained by the presence of several oxidative stress factors in this group of patients. In terms of intensity of the enzymatic response, group 4 was similar to groups 2 and 3.

The variation of antioxidant enzymes in group 5 was similarly to group 1, demonstrating etiopathogenic indifference. A peak in week 2 can be observed for all enzymes except for one GPX-2 in case of a young patient (possible with fewer sources of oxidative stress) are shown in figure 2e. One can hypothesise the idea of an *oxidative saturation* 14 days after the onset of treatment (more commonly seen in elderly patients with multiple ischemic comorbidities).

The impact of ozone therapy on the global perception of quality of life

In group 1 (oncological-o and neurological-n palliative care patients receiving ozone therapy by rectal insufflation) a progressive increase in patients' perception of quality of life was noticed (more pronounced for oncological patients) are shown in figure 3a.

Patients from group 2 (oncological-o and neurological-n palliative care patients with ozone therapy through subcutaneous injections) also globally perceived a slight overall increase in quality of life (fig. 3b). However, absolute values were reduced to 50% compared to group 1.

Group 3 described an ascending curve in global perception of improved quality of life of the oncological patient and a stationary curve in the case of the neurological patient (fig. 3c). The evolution curve model is similar to that of group 4.

In group 4 (palliative care patients with placebo rectal insufflation) a progressive increase in quality of life in the perception of patients was noticed, that could most probably be attributed to psychotherapy (fig. 3d).

Patients from group 5 (non-palliative, rectal insufflation ozone therapy) showed the same pattern of the global perception curve of life quality improvement as group 1, with comparable absolute values (fig. 3e).

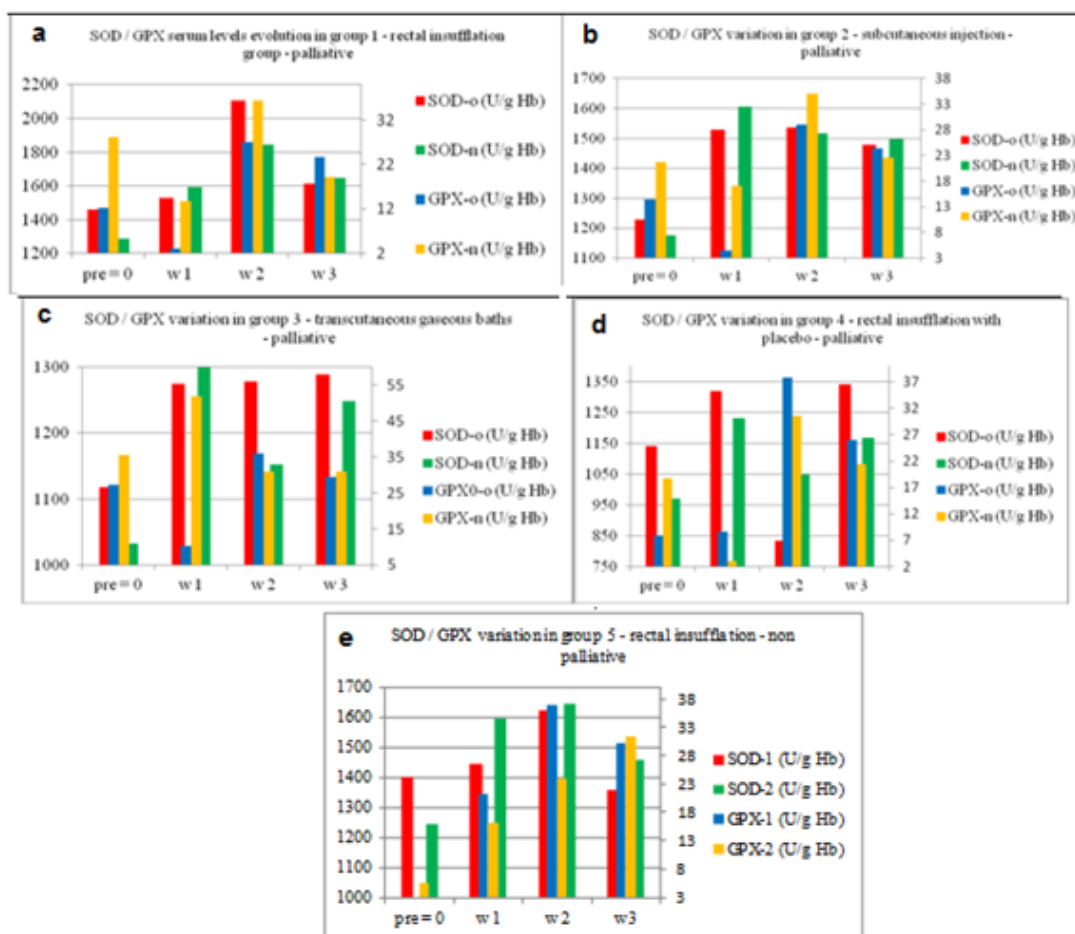


Fig. 2. Evolution of antioxidant enzymes in groups: a. 1 – rectal insufflation (see text); b. 2 – palliative – subcutaneous injections (see text); c. 3 – palliative – transcutaneous gaseous baths (see text); d. 4 – palliative – placebo (see text); e. 5 – non-palliative – rectal insufflations (see text)

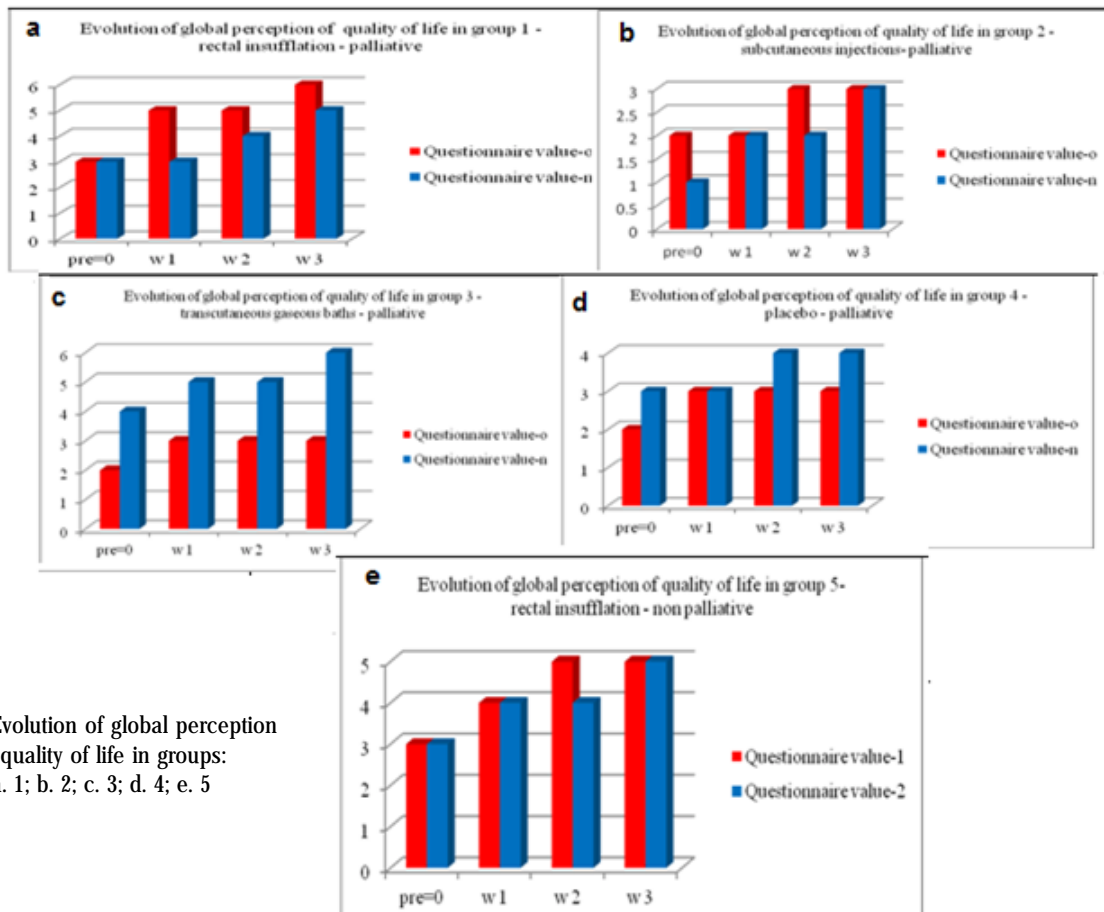


Fig. 3. Evolution of global perception of quality of life in groups: a. 1; b. 2; c. 3; d. 4; e. 5

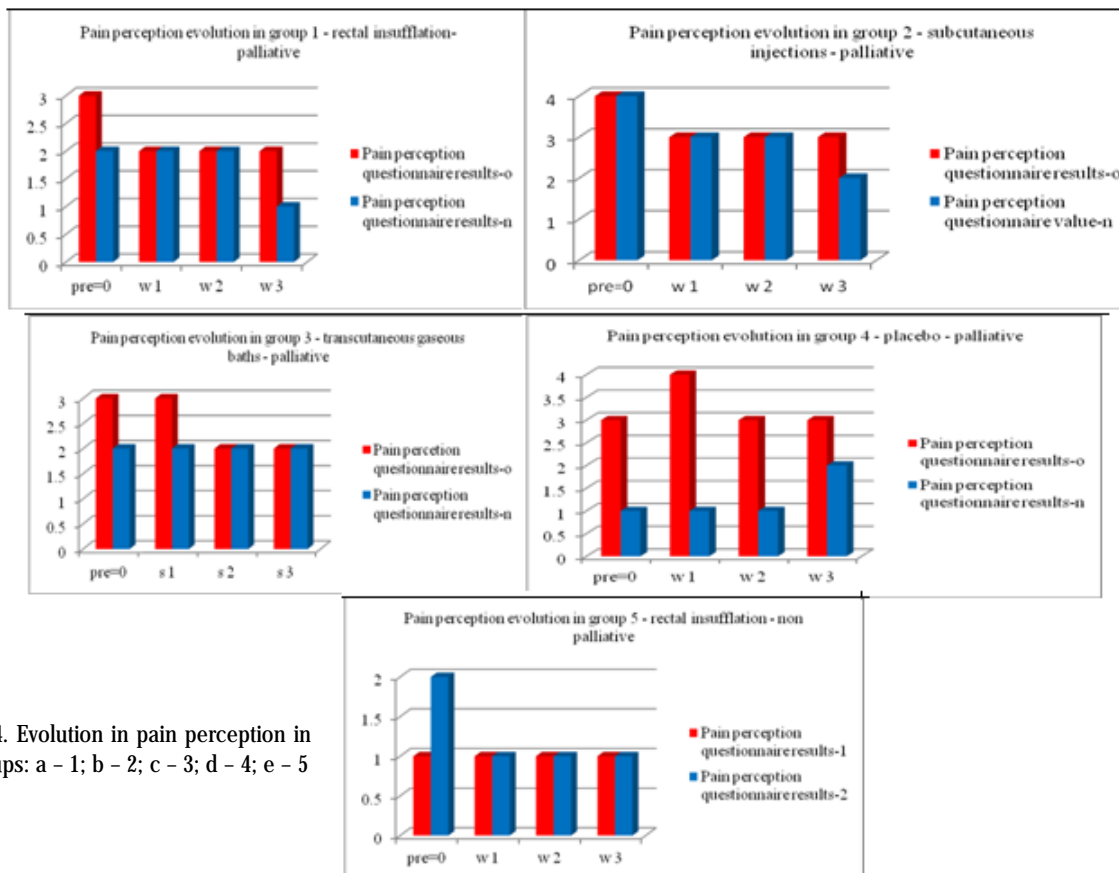


Fig 4. Evolution in pain perception in groups: a - 1; b - 2; c - 3; d - 4; e - 5

Perception of pain

One of the issue evaluated in the quality of life questionnaire was pain perception, graded on a scale from 1 to 4, where 4 represented maximum, 1-minimum pain intensity.

A slight improvement in pain perception in patients of group 1 was observed, especially during week 3, in the neurological patient (fig. 4a).

Patients from group 2 presented similar slight improvement of pain perception, more evident in the neurological patient (fig. 4b).

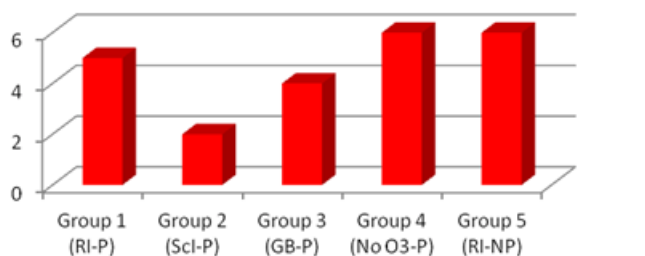


Fig. 5. Ozone therapy administration form acceptance in the study group (see also text)

Perception of pain in group 3 reached a threshold in the neurological patient and was slightly improved in the oncological patient after week 2 (fig. 4c).

In group 4 (placebo) no systematized changes in the perception of pain was noticed, most probably because of the influence of psychotherapy (fig. 4d).

Patients from group 5 showed a pain perception threshold at relatively low values (patients with no serious pathologies, nor in terminal stages) (fig. 4e).

Conclusion: in terms of pain perception, patients from group 1 (palliative - rectal insufflation) and group 2 (palliative - subcutaneous injections) benefited of a significant improvement, most probably due to a fast transfer ozone therapy.

Acceptance of ozone therapy forms of administration

Patients were asked to assess the degree of acceptance of the ozone therapy administration form on a scale from 1 to 6.

Ozone therapy administered by rectal insufflation ozone therapy got the highest score, while the lowest was noticed in case of subcutaneous administration (fig. 5).

Conclusions

Ozone therapy proved a global antioxidant effect within 2 weeks of administration, with further saturation in all our study groups. This improvement of the antioxidant status was best expressed in palliative care group receiving O₃ by rectal insufflation.

The overall increase in quality of life after ozone therapy was evident in all groups, including the placebo group – highlighting the importance of psychotherapy in palliative care compartments (including spiritual therapy).

The favourable effects of ozone therapy appeared regardless of the pathological condition of the patient (etiopathogenic indifference).

Rapid transfer ozone therapy (by rectal insufflation and subcutaneous injections) relieved pain easily in most patients, but with more evident results in neurological patients.

The most effective and accepted form of ozone therapy administration in our study population was rectal insufflation.

The results of our exploratory study point out evidences for considering ozone therapy as a promising alternative adjuvant therapy for increasing the quality of life in palliative care services. However, the reported data of the present study need further confirmation on extended groups of patients.

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