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Ozone + Arthroscopy: Improved Redox Status, Function and Surgical Outcome in Knee Osteoarthritis Patients

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Abstract

Introduction: Ozone preconditioning shows similarities to ischemic preconditioning mechanism which protects against ischemic reperfusion injury that is associated to surgical procedures as well as osteoarthritis clinical condition so the Objective of this study was to compare beneficial effects of medical ozone before and 30 days after of arthroscopy with regard to who were not ozone pretreated.

Methods: Osteoarthritis patients (n = 40) were random distributed in two groups (n = 20 each): Group I Arthroscopy (AT), patients who were not pretreated with ozone and Group II (Ozone + AT), patients who received 20 ozone treatments previous to AT. Before received the surgical procedure and 30 days after (outcome) the systemic redox balance, pain, knee function and Quality of Life were assessed.

Results: Ozone preconditioning increased protective systemic biomarkers and decreased injury indicators. Improvement of knee functions displayed positive changes before and the outcome of surgery in comparison with patient who didn´t received medical ozone. In line with above results Quality of Life showed similar picture. Both displayed higher positive changes after 30 days of arthroscopy (outcome).

Conclusions: Ozone preconditioning + arthroscopy combination improved the redox balance, pain and GGT activity in knee osteoarthritis patients therefore they received arthroscopy in better conditions.30 days after joint function and Quality of Life were greater than before surgical procedure and outcome improvement was higher in comparison with patients who were not treated previously with medical ozone.

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Introduction

Osteoarthritis (OA) is a common joint disease and the major cause of disability among the aging population. Progressive articular cartilage degradation is central to OA, and is driven by well-understood mechanisms of cartilage matrix catabolic effects and anti- anabolic effects of chondrocytes [1-5]. However, OA is a disease that affects the synovial joint as well as the entire joint system [4]. Changes in periarticular musculature, and in articular and periarticular tendons and ligaments, can induce substantial biomechanical stress, associated with the loss of other joint homeostatic functions including lubricant production [6]. With the high prevalence of knee OA globally, OA is not only a primary cause of disability among older adults in the United States but it is among the top 10 causes of disability worldwide [7,8]. Current therapies focus on alleviating pain but pain control remains poor in 50% of patients [9]. Furthermore, despite the large disease burden, there are currently no approved disease-modifying OA drugs (DMOADs) that can prevent or stop the joint damage caused by the disease [10].

Arthroscopy is one of the most common surgical procedures used worldwide in knee OA [11]. Annually, there are about one million such surgeries performed in the United States and in Sweden (population 9.5 million), the corresponding number being about 35,000 [12,13]. Nevertheless, recent studies have questioned its usefulness [14]. From a systematic review and meta-analysis of arthroscopic surgery with debridement, and/or partial meniscectomy comparing these with conservative management strategies, it is concluded that, on a long-term basis, patients undergoing knee arthroscopy versus those receiving conservative management strategies have no important benefits regarding pain or function. Although knee arthroscopy has traditionally been a common tool in the treatment of knee OA, a published study [15] combined with a Cochrane review of the literature up to 2006 [16], has resulted in NICE guidance recommending that arthroscopy should not be used in knee osteoarthritis [17].

As the above mentioned reports reveal contradictory criteria, this suggests that there is a major need to develop new and effective complementary therapies. The physiopathological status of knee OA patients needing to undergo arthroscopy should play an important role in the surgery outcome. Such patients display both systemic and local oxidative stress inside the joint [18,19], synovitis [20], pain [21] and ischemia/reperfusion (I/R) injury associated with OA clinical condition [22]. Besides, arthroscopy itself promotes minor I/R injury through short and repetitive pressure periods (ischemia) in order to achieve a bloodless field followed by decompression periods (reperfusion). Therefore, if knee OA patients are pre-treated/receive preconditioning before arthroscopy with an agent either avoiding or decreasing such undesirable events, a better surgical outcome may then be hoped for. Medical ozone is an ozone/oxygen mixture administered at low concentrations. It is able to improve the antioxidant protective endogenous system and decrease biomolecules oxidative damage by means of an ozone-oxidative pre-/post conditioning mechanism [23]. The efficacy of medical ozone has been demonstrated in rheumatoid arthritis patients [24] which is similar to OA thus reducing synovitis progression [25], pain intensity in patients with painful disorders [24,26] and protecting against I/R damage [27] .On the other hand, ischemic preconditioning is the most acceptable protective procedure against dangerous effects in I/R [28] and medical ozone has demonstrated a similar protective mechanism in a comparative study using I/R injury in the liver [29] as a model. Taking into account the protective effects of medical ozone against side effects and adverse events which may contribute to the unsatisfactory outcome of knee OA surgery, the aim of this project was to investigate whether medical ozone preconditioning improves knee arthroscopy in two phases: Prior to surgery (how the patients receive arthroscopy after ozone preconditioning) and 30 days later (arthroscopy outcome) analyzed and displayed by systemic antioxidant-pro-oxidant status, Lysholm Knee Scoring Scale and Quality of Life (Medical Outcome Study, MOS) of the patients.

Materials and methods

Study design

This prospective, longitudinal and randomized study was approved by the joint institutional review board (Scientific and Ethics Committees of the National Institute of Rheumatology, Ministry of Public Health, Cuba, and Pharmacy and Food Institute, University of Havana, Cuba) in accordance with the principles of the Declaration of Helsinki [30]. All patients gave their informed consent to enrolment after receiving adequate information concerning the study (characteristics of the study, benefits and possible adverse effects). Before enrolment, all participants attended a training program to familiarize them with the study objectives and treatment plans. Eligible patients were randomized using a computer-generated list of random numbers (Research Randomizer Form v 4.0). The random sequence was created using freely accessible tools which uses the pseudo-random number generator [31], modified by [32]. The demographic characteristics and the medical history of the participants were recorded, and laboratory tests performed. Radiographs of both knees were obtained using anteroposterior projection with support, lateral with 30° flexion, and Merchant (45°) views. Arthroscopies were all carried out by a single orthopedic/arthroscopic surgeon. All patients received three doses of antibiotic (cephazolin 1 g) as a prophylactic measure.

Postsurgical pain treatment comprised oral metamizole/dipyrone 1 g/8 h and cephazolin 500 mg/12 hrs for 7 days.

Inclusion criteria

Men and women, aged 40–75, with body mass index (BMI) < 35 kg/m^2, OA grades III-IV as an indication for knee arthroscopic surgery resulting from radiographic and arthroscopic classification.

Exclusion criteria

Infectious conditions, use of anticoagulants, history of trauma (dislocation or fracture), inflammatory arthritis, microcrystalline arthropathies, history of septic arthritis, ligament injury, non-specific synovitis, angular deformity >10°, chondral lesions G-IV Outerbridge (>1 cm^2), neoplasms, or allergy to any of the components of the products under study. Patients taking antioxidant agents within less than three months before arthroscopy were also excluded.

All patients were premedicated with endovenous midazolam 1 mg, 30 min prior to surgery. Heart rate, non-invasive arterial blood pressure, and peripheral oxygen saturation were monitored in the operating room. Anesthesia was induced using hyperbaric lidocaine 150 mg for spinal anesthesia

The patients were randomized into two different groups of treatment: Group I (n=20), arthroscopy (AT, as control) and Group II (n=20), Medical ozone + arthroscopy (ozone + AT).

Ozone was generated using an OZOMED unit, Cuba. Before surgery, patients received 20 treatments via rectal insufflation as described in our previous papers [24,25] (five applications per week from Monday through Friday).

Concentrations of ozone: 25 mg/L to 35 mg/L were in stepped application as follows: 1st week: 20 mg/L, 100 ml;

2nd week: 25 mg/L, 150 ml;

3rd week: 30 mg/L, 200 ml; and

4th week: 35 mg/L, 200 ml.

Two days after the last ozone treatment, patients underwent arthroscopic surgery.

Evaluation of medical ozone preconditioning effects

In order to compare the status of the patients (pain, knee function, redox balance and Quality of Life (QoL) before arthroscopy and the outcome after 30 days, different phases of total surgical procedure were evaluated (Figure 1).

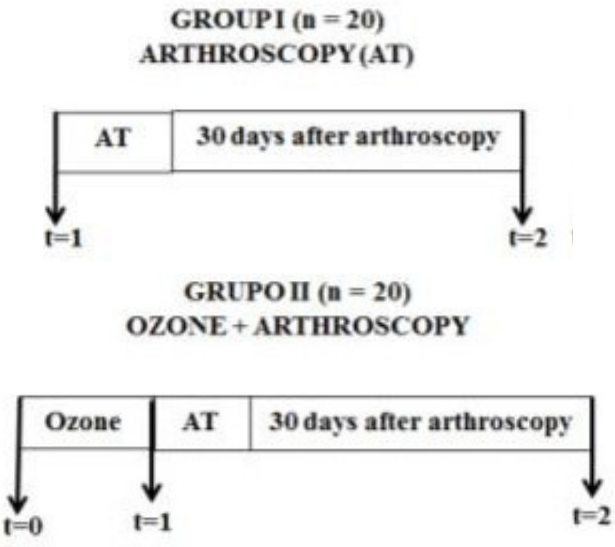

Figure 1: Assessed phases of the arthroscopic surgery in knee osteoarthritis patients Group I, t=1, before arthroscopy and t=2, thirty days after surgery procedure.
Group. II, t=0, before ozone treatments; t=1, at the end of 20 ozone treatments and before arthroscopy, t=2, thirty days after surgery procedure.

Indicators assessed during surgery

Group I, t=1, before arthroscopy: Gamma Glutamyl Transferase (GGT) activity, pain, Lysholm Knee Scoring Scale (Virginia Therapy and Fitness Center), QoL and the patients' redox status. Thirty days after surgery t=2: Pain, Lysholm Scale and QoL.

The follow-up period in most studies has typically been up to some 30 days [33]. In this study, a recovery period of 30 days was chosen as the most common complications, such as infections and other disorders attributable to surgery are likely to be diagnosed within this time frame.

Group II, t=0, before ozone treatment: GGT, Pain, Lysholm Scale, QoL and patients`redox status were determined; t=1, at the end of 20 ozone treatment sessions and before arthroscopy: (same as t = 0) and t=2, thirty days after surgery: Pain, Lysholm Scale and QoL were evaluated.

Pain was assessed using the Visual Analog Scale (VAS) from '10' to '100'. This was classified between '10' (minimum pain intensity) and '100' (maximum pain intensity). The absence of pain was considered as "0". The Lysholm Scale was used to evaluate knee function. Antioxidants (superoxide dismutase, SOD; reduced glutathione, GSH and catalase CAT as well as injury redox markers (total hydroperoxides, TH and lipid peroxidation, MDA) were determined for patients' redox characterization and QoL using the Medical Outcomes Study (MOS)[34]. This questionnaire allows definition of 11 health domains: General health perceptions, physical functioning, role functioning, pain, social functioning, mental health, energy/fatigue, health distress, cognitive function, QoL, and health transition.

The main variables considered were

Reduction in GGT activity, increase in the Lysholm Scale, pain decrease (VAS) ≥ 30%, improvement of redox biomarkers (downregulation or upregulation coming back to the reference interval) and of QoL, with statistically significant differences ($p < 0.05$) between patients receiving ozone preconditioning compared to patients receiving arthroscopy alone (i.e. without ozone preconditioning), recorded before arthroscopy and 30 days after (outcome).

Ozone preconditioning treatment was considered successful if ≥ 70% of the patients treated had a positive outcome, considering the above mentioned variables compared to patients receiving arthroscopy only.

The same protocol of rehabilitation to be followed at the patient's convenience was prescribed to all patients. The rehabilitation protocol started progressively, starting with isometric exercises and muscle stretching from Week 1 post-arthroscopy, adding weight exercises from Week 3, cardiovascular training from Week 7, and high-impact exercises from 3 months onward.

Biochemical determinations

Blood samples for biochemical analysis were obtained after a 12 h overnight fast, at t = 1 for arthroscopy and t= 0, t = 1 for ozone + arthroscopy groups (Figure 1).

Serum Gamma Glutamyl Transferase (GGT) was measured using standard kinetic methods following recommendations of the European Committee for Clinical Laboratory Standards (EC-CLS) [35] and using an Abbott Architect clinical chemistry analyzer (Abbott Laboratories, Abbott Park, IL, USA).

Redox parameters were determined by spectrophotometric methods using a reader plate (SUMA, Cuba) and BOECO Spectrophotometer, Model S 220 Germany. Superoxide Dismutase (SOD) activity was measured using kits supplied by Randox Laboratories Ltd., Ireland (Cat. No. SD125 and No. RS505). Catalase (CAT) activity was measured by following the decomposition of hydrogen peroxide at 240 nm at 10s intervals for 1 min [36]. After precipitation of thiol proteins using trichloroacetic acid 10%, reduced glutathione (GSH) was measured according to the method described by Sedlak et al. [37] with Ellman's reagent [5' 5 dithiobis (2-nitrobenzoic acid) 10−2 M (Sigma St. Louis, MO, USA)]; the absorption was measured at 412 nm. Quantification of Total Hydroperoxides (TH) was measured using a Bioxytech H2O2-560 kit (Oxis International Inc., Portland, OR, USA). The concentrations of Malondialdehyde (MDA) were analyzed using the LPO-586 kit obtained from Calbiochem (La Jolla, CA).

Statistical analysis

To calculate the size of the sample, the Medstat Systems, Inc. (version 2.1, 1989; Fridley, MN, USA) method was used. The statistical difference between the beginning (t = 0) and the end of ozone therapy (before arthroscopy) was 0.2 with a type 1 error of 0.05 [38]. The target level of enrolment was determined to 20 patients.

Comparisons of GGT and each redox variable (before the beginning and at the end of ozone preconditioning treatment and before arthroscopy) were assessed using the Wilcoxon signed rank test and Student t-test for correlated samples, and in order to contrast GGT activity and each redox variable with regard to the treatment (arthroscopy vs ozone + arthroscopy) the Mann-Whitney U and Student t-tests for independent samples were used. Lysholm Scale and QoL variables were evaluated through non- parametric Median Test.

Data were analyzed using IBM SPSS Statistics, version 24, and the statistical significance was set at ≤ 0.05.

Results

Characteristics of the patients involved in the study

In relation to the clinical pictures of the patients (Table 1), both groups were similar in randomization ($p < 0.05$). Group II (ozone + AT) showed a tendency to include more patients with higher OA grading (III-IV, 54% vs 63%) (IV, 0% vs 10%). These results were in line with the complexity of surgery in the ozone + AT group (Table 2).

90% of total surgeries in group II such as partial meniscectomy and cruciate ligament reconstruction were achieved.

Table 1: Clinical picture of knee osteoarthritis patients in each studied groups.

Arthroscopy Demographic data/patient histories	Group I Arthroscopy (n = 20)	Group II Ozone + Arthroscopy (n = 20)
Women (n/%)	15/75	17/88
Men (n/%)	5/25	3/12
Age (years)	60 ± 8[a]	57 ± 9[a]
Osteoarthritis grading		
III	46%	27%
III-IV	54%	63%
IV	0%	10%
Evolution time of the disease (years)	4 ± 2[a]	4 ± 9[a]
Race		
Caucasian (n/%)	15/75	14/70
Non-Caucasian (n/%)	5/25	6/30

The data reflecting age and progress through time of the disease are represented as mean ± SD of each group. Mean values with different letters indicate significant differences ($p < 0.05$) between both groups.

Table 2: Knee arthroscopy procedures in each group.

Procedures	Group I Arthroscopy	Group II Ozone + Arthroscopy
Partial Menisectomy (n/%)	6/30	10/50
Synovial plica repairing (n/%)	8/40	1/5
Cruciate ligament reconstruction (n/%)	2/10	8/40
Repairing of hypertrophic fat (n/%)	4/20	1/5

Glutamyl transferase (GGT) and redox biomarkers

Antioxidant GSH depletion is mediated by an increase in GGT. Reestablishment of GGT activity (27 ± 5 U/L) at reference interval (0-36 U/L) was accomplished after ozone pretreatment ($p < 0.05$) while patients not receiving ozone displayed higher levels (38 ± 2 U/L) of the enzyme (Figure 2A).

In the patients of the ozone + AT group with arthroscopic surgery, 71% showed GGT levels inside the reference interval, compared to patients in the AT group only with 30% (Figure 2B).

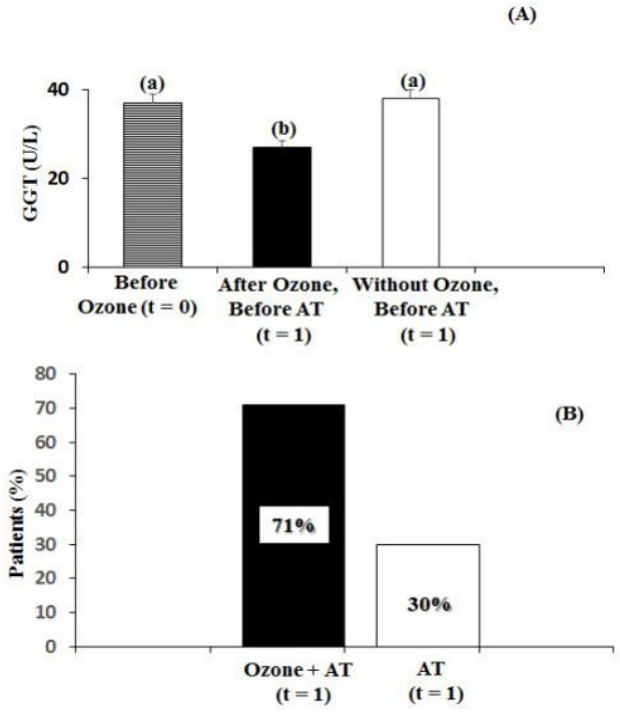

Figure 2: Glutamyl Transferase (GGT) levels in knee OA patients: (A) "Before Ozone", patients´ GGT activity before to receive 20 ozone treatments by rectal insufflation as in Material and Methods; "After Ozone, before AT", patients´ GGT activity before to undergo arthroscopic surgery and "Without ozone, before AT", patients´ GGT activity who didn´t receive ozone pretreatment and were underwent only arthroscopy. (B) Patients per cent who go through to arthroscopy with GGT levels inside to reference interval. Data is represented as mean ± SD. Mean values with different letters indicate significant differences ($p < 0.05$) among groups.

Antioxidant/prooxidant balance of the patients in both groups is shown in Figure 3. Ozone preconditioning was able to improve the systemic redox status of ozone + AT group by reestablishing/increasing the protective biomarkers and by reducing the injury indicators: superoxide dismutase activity (11.7 ± 3 vs 20 ± 5 U/L) reentered reference interval (4.3-12.5 U/L), GSH concentrations increased (380 ± 40 vs 210 ± 15 µg/L) com-

pared with the patients of AT group ($p < 0.05$), whereas there was no change in catalase activity. As a result of the antioxidant improvement in the ozone + AT group, reductions in lipid peroxidation (2.3 ± 0.2 vs 3.8 ± 0.5 µM) and total hydroperoxides (30 ± 2 vs 54 ± 9 µM) were found. This means a decrease in oxidative stress, ie a decrease in Reactive Oxygen Species (ROS) and resultantly a reduction of cellular damage; The opposite was found in the AT group.

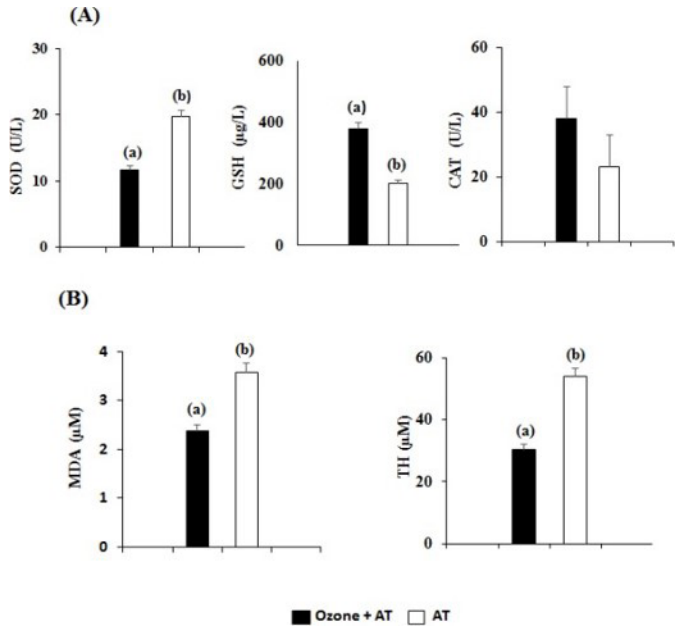

Figure 3: Systemic antioxidant/pro-oxidant balance of knee OA patients preconditioned (n=20) and without previous ozone preconditioning (n=20) before to arthroscopy. (A) Protective redox biomarkers: SOD, superoxide dismutase activity; GSH, reduced glutathione and CAT, catalase activity. (B) Injury redox indicators: MDA, malondialdehyde; TH, total hydroperoxides. Data are represented as mean ± SD. Mean values with different letters indicate significant differences ($p < 0.05$) among groups.

Pain intensity in knee osteoarthritis patients

Both groups (AT and ozone + AT) started without statistical differences in pain intensity (before AT vs before ozone). A pain decrease (34%) after ozone preconditioning and before arthroscopy was observed. 30 days later, an additional pain improvement was achieved in the ozone + AT group (reduction of 50%) compared with their status prior to ozone pretreatment. The patients of the AT group experienced no change in pain perception, and statistically significant differences between both groups were found 30 days after AT (AT vs ozone + AT) (Table 3).

Table 3: Pain intensity before arthroscopy and 30 days after of surgical procedure in the studied groups.

AT Group			Ozone + AT Group	
Before AT	30 days, after AT	Before ozone	After ozone, before AT	30 days, after AT
60.5 ± 1.5[(a)]	60.6 ± 1.2[(a)]	60.8 ± 2[(a)]	40 ± 1.7[(b)]	30 ± 1.5[(b)]

Pain was assessed through Visual Analog Scale (VAS) from '10' to '100' .

Data are are represented as mean ± SD of each group. Mean values with different letters indicate significant differences ($p < 0.05$).

Compared to the AT group (Figure 4), more patients in the ozone + AT group showed a better antioxidant/pro-oxidant balance prior to surgery. Not only was the antioxidant endogenous defense system (SOD, GSH and CAT) better in patients receiving ozone preconditioning than in patients without previous ozone treatment, but also none of the patients receiving AT by itself showed an improvement in their injury biomarkers (MDA and TH), even though the patients in both groups received arthroscopic surgery involving negative effects on lipids and other biomolecules.

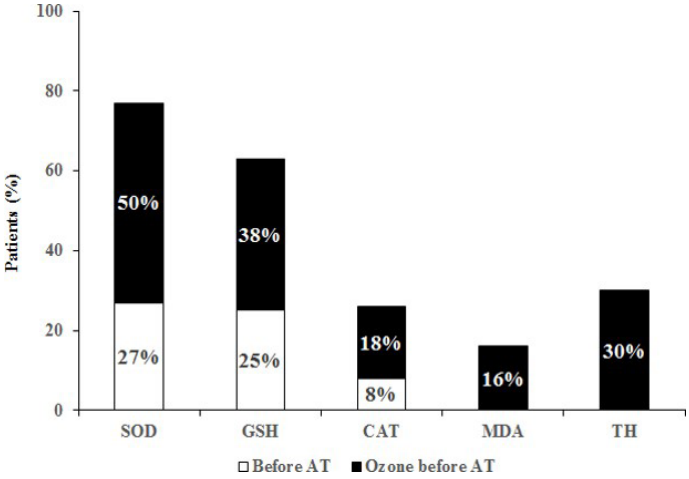

Figure 4: Protective and injury redox biomarkers in knee OA patients before undergo arthroscopic surgery. % mean, patients per cent with positive responsive (redox biomarkers moving toward or returned to reference interval (healthy subjects) in preconditioned patients with medical ozone (Ozone before AT) and patients who were not pretreated with ozone (Before AT).
Protective biomarkers (SOD: Superoxide Dismutase; GSH: Reduced Glutathione and CAT: Catalase Activity. Injury Biomarkers (MDA: Malondialdehyde and TH, Total Hydroperoxides.

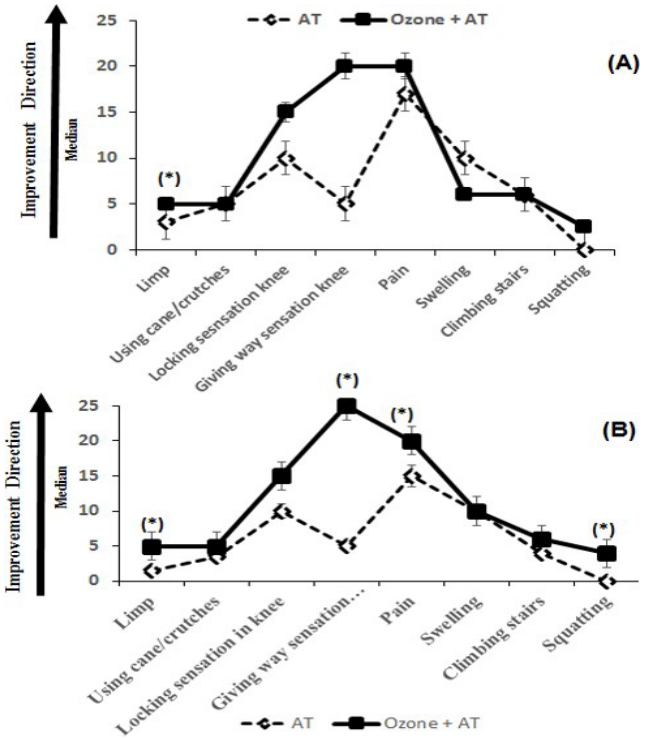

Figure 5: Lysholm scores in knee OA patients with previous ozone preconditioning (Ozone + AT) and without ozone pretreatment (AT). (A) Before Arthrosopy and (B) 30 days after to arthroscopic surgery. Data are represented as Median ± SD. Arrows on y axes indicate direction of improvement. (*) $p < 0.05$ Ozone + AT vs AT.

Lysholm knee scale and medical outcome scores before surgery and 30 days after

Knee function prior to arthroscopy and 30 days after surgery is given in Figure 5. Ozone preconditioning (ozone + AT) achieved an improvement in knee function not only before but mainly as the outcome of surgery in comparison with patients not pretreated with ozone (AT). A further improvement in the outcome could be observed after 30 days. All 8 parameters in the Lysholm knee scoring scale increased, and 50% (4 parameters) displayed statistically significant differences compared with the status prior to arthsocopy (1 parameter, 12.5%).

Medical Outcome Score results agreed with Lysholm Knee Scoring Scale. The beneficial effects of ozone preconditioning were observed in patients prior to arthroscopic surgery. Nevertheless, improvement was greater in the outcome (30 days after surgery), whereby 9 out of 11 parameters (82%) displayed positive changes with statistical significance ($p < 0.05$) compared with patients who had not been pretreated with ozone.

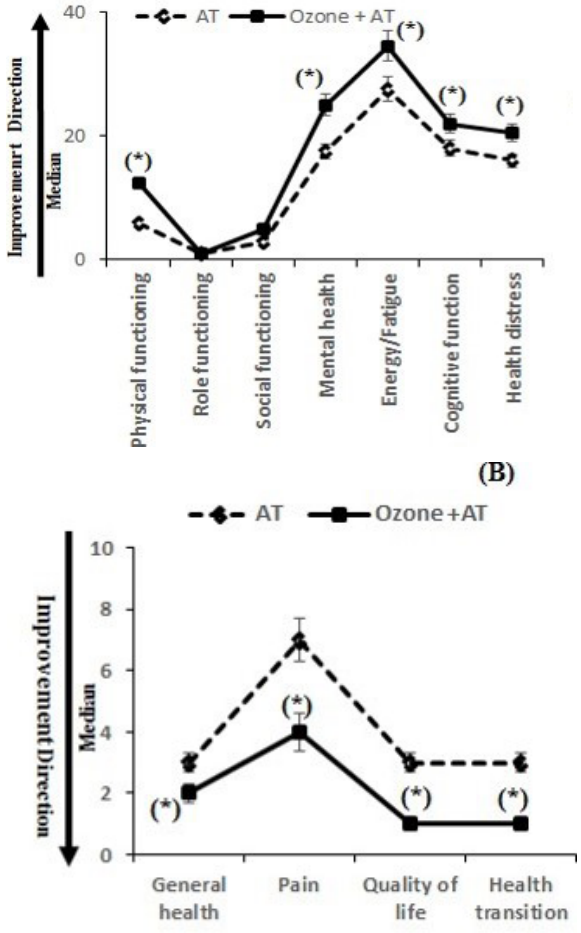

Figure 6: Health attributes (Quality of Life) assessed through Medical Outcome Quetionnarie (MOS) in knee osteoarthritis patients (n = 20) without previous ozone treatment and patients (n = 20) who received ozone preconditioning. (A) Before receive arthroscopy, "AT", patients who underwent only arthroscopy and "Ozone + AT", patients who were previously treated with ozone as in Material and Methods. (B) Outcome, "AT" and "Ozone + AT", same patients 30 days after arthroscopy. Data are represented as Median ± SD. Arrows on y axes indicate direction of improvement (*) $p < 0.05$ "Ozone + AT" vs "AT".

Discussion

Ozone pretreatment in knee osteoarthritis patients prior to arthroscopic surgery improved not only the systemic antioxidant/pro-oxidant balance, knee function and QoL of the patients but also the outcome of surgery (30 days after surgery) compared with patients who had not been pretreated with medical ozone.

The pleiotropic characteristics of medical ozone and its different therapeutic targets explain the efficacy of ozone preconditioning in surgery. Ozone preconditioning induces a reduction in harmful ROS generation (lipid peroxidation and total hydroperoxides) and has a direct impact on adverse events associated with surgery. I/R injury is linked with those forms of surgery which involves a temporary interruption of blood circulation before restoring it at the end of the operation. In addition, I/R is a pathological condition associated with OA. Oxidative stress promoting damage after the reperfusion phase is a well-known process, severity of which depends on I/R time duration. On the other hand, during the ischemic phase, an ATP degradation takes place whereby adenosine is lost. This is one of the mediators associated with the protective effects of ischemic preconditioning [39]. Besides, adenosine maintains cartilage homeostasis and inhibits osteoarthritic progression [40]. Medical ozone preserved endogenous adenosine during ischemic conditions [41] and the beneficial effects of ozone are mediated by adenosine and A1 adenosine receptors (A1R) [25,42]. A1R is closely linked not only with protection against I/R injury and oxidative stress but also with pain relief. Pain pathways involving the A1R, which dominates in mediating the antinociceptive effects of adenosine, have received the most attention [43]. A clinical trial entitled "Dose Response of Adenosine for Perioperative Pain" (www.clinicaltrials.gov identifier NCT00298636) has been carried out in this context [44].

The etiology of pain in osteoarthritis is recognized to be multifactorial, with both endoarticular and extraarticular risk factors. As visualized on MRI, bone marrow lesions, synovitis (prevented by medical ozone) [25] and effusions appear in OA, which have had the greatest impact and relation to pain to date [21,45].

Pain relief in knee OA patients pretreated with medical ozone before and 30 days after arthroscopy suggests that ozone avoids adenosine depletion during ischemia which leads to adenosine local accumulation and activation of A1 adenosine receptors that induces analgesic effects through signal transduction pathways as demonstrated previously [24,26].

In accordance with similar results reported by other authors, there was no change in pain intensity in patients who had not been pretreated with medical ozone [14,17].

Another process that influenced the improvement of the surgical outcome were the medical ozone effects on the reduction of GGT activity. GGT hydrolyzes reduced GSH and decreases the antioxidant defense system thus resulting in oxidative injury to cartilage and bone. In addition, GGT is an activator of osteoclastogenic activity and is recognized by Toll-like receptor 4 (TLR4) to activate inflammation-associated osteoclastogenesis, meaning that high GGT levels are involved in abnormal bone remodeling processes, with decreased bone mass as a result[46, 47]. In 71% of the ozone preconditioned patients receiving arthroscopy, the GGT concentrations were within the reference interval. Such results suggest that GGT contributes to surgery outcome through the reduction of oxidative stress and through protective effects on structural joint components.

Redox status and GGT activity agreed with the subjective perception of the patients in knee function and QoL.

The increase in the improvement of knee function in patients preconditioned with medical ozone, identified 30 days after arthroscopy, indicate that a combined procedure (ozone + arthroscopy) plays a beneficial role. Before arthroscopy in the ozone + AT group, a tendency to improvement could be observed, but only limping as physical parameter displayed statistical significance, while after ozone + arthroscopic surgery (30 days), the factors limping, giving way sensation in the knee, pain and squatting showed an significant improvement ($p < 0.05$) when compared with patients without previous ozone treatment who had no change in knee functions 30 days after arthroscopy.

In this context, it is necessary to emphasize that treatments applying arthroscopic surgery in combined form have been widely used [48]. Adjunctive therapies such as arthroscopy + hyaluronic acid, platelet-rich plasma, nonsteroidal anti-inflammatory drugs and other medications, physiotherapy, and intra-articular steroid injections have been included to improve the outcome [49,50]. The results of this study indicate the advantages of combined ozone pretreatment + arthroscopy.

The primary goal in the treatment of knee osteoarthritis is the alleviation of pain, leading to an improvement in joint function and quality of life (QoL). As ozone preconditioning has turned out to improve knee function it became necessary to investigate how patients perceived their QoL.

At present, QoL questionnaires have received special attention due to the increase in chronic diseases as a consequence of aging population. Therefore it is necessary to know a prospective patient's opinion about his or her health status in an incurable disease where the main goal could be QoL improvement. These studies therefore provide a physical, mental and social health status estimation as perceived by the patient. QoL questionnaires have many advantages as they permit an assessment of treatment outcome, including new drugs, exercise programs or prevention strategies [51].

As a result, the comparison between patients preconditioned with ozone and patients receiving arthroscopy alone showed an improvement 30 days after arthroscopy in the ozone + AT group, which has corroborated the combined role of ozone + arthroscopy in the outcome. In addition, two important parameters achieved maximum values in the Medical Outcome Score: (1) Quality of Life, perceived by patients 30 days after arthroscopy evaluated by them as "Very Well" and (2) Health Transition as "Much Better".

In summary, ozone preconditioning improved the redox balance, pain and GGT activity in knee OA patients; So they could receive arthroscopy under better conditions. 30 days after arthroscopy joint function and QoL had improved to a greater extent than prior to surgery and, as outcome, their improvement was greater when compared with patients not previously treated with medical ozone so ozone preconditioning + arthroscopy combination should be considered as a new strategy in knee OA patients.

Disclosure

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