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Clinical applications of ozone: a review of 94 cases from Iraq

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Objectives Ozone (O_3) has been used for medical purposes more than a century ago. Although, its precise mechanism of action is still unclear, many disease conditions are currently treated by ozone. In Iraq, the use of medical ozone is recent. Herein, we present our first experience.
Methods This is a retrospective study of 94 patients (67 females and 27 males) with different painful disorders treated by ozone in a private clinic in Kirkuk, Iraq over 1 year period (July 1, 2016–June 30, 2017). Longevity resources EXT50 Ozone Generator with oxygen tank and CGA870 Oxygen Regulator were used. Ozone was prepared as, O_2–O_3, ozonized olive oil (OOO) or ozonized platelet rich plasma (OPRP) and given via subcutaneous (S), intra-muscular (IM) or intra-articular (IA) injections. A sample of patient's own blood was used to prepare PRP by a process of two repeated centrifugation and then activated by passing ozone in a concentration of 68.7 gammas. A questionnaire was used to grade the patients' responses as excellent, good, fair and poor. *Z*-test was used for statistical analysis.
Results The mean age was 53 ± 15 years. The two major treated groups were osteoarthritis (OA) of the knee (n = 40) and lower back pain (LBP) (n = 22). Overall, ozone yielded excellent to good results in 68 patients (72.3%) and a poor outcome in 9 (9.5%) patients.
Conclusion Ozone therapy is an inexpensive therapy, which seems to be safe and effective in palliating pain of OA and intervertebral disc herniation as well as other pain disorders.
Keywords knee osteoarthritis, low back pain, disc herniation, ozone, ozonated olive oil, platelets rich plasma, Iraq

Introduction

Ozone (O_3) is a form of oxygen in which three atoms bind together instead of the two atoms of O_2. It was discovered in 1834 by Schoenbein who considered it an oxidant and a disinfectant. Ozone was initially used to treat gangrene during the First World War (WWI).[1] Beside its use to sterilize water,[1] currently high-dose ozone is recognized as an antiviral and bactericidal agent.[2,3] Ozone therapy has been used for more than a century to treat many disease conditions, such as coronary artery disease,[4] chronic severe hepatitis,[5] sudden sensorineural hearing loss,[6] hypersensitive teeth,[7] periodontitis,[8] chronic low back pain (LBP),[9] diabetic wounds as well as trophic and ischemic ulcers.[3,10–12]

The mechanism of ozone action is by inactivation of infective agents, such as bacteria, viruses, fungi, yeast and protozoa, stimulation of oxygen metabolism and activation of the immune system. It gives proven consistent results and has minimal side effects.[1] Ozone therapy can be delivered to patients in different forms like, O_2–O_3 mixture, ozonized olive oil (OOO) and ozonized platelet rich plasma (OPRP) and used via different routes like subcutaneous, intra-muscular (IM) and intra-articular (IA) injections of O_2–O_3 and OPRP as well as rectal insufflations of O_3 and topical application of OOO.[13]

In Iraq, the use of ozone therapy is recent. So far, there are no published studies of its use in our country. In this paper, the author's experience of using ozone in the treatment of a variety of painful clinical conditions is presented.

Patients and Methods

This is a retrospective study of a group of patients with different medical problems treated with ozone in the author's private clinic. Over 1 year period (July 1, 2016–June 30, 2017), 120 patients received ozone therapy. Unfortunately, 26 of them were lost for follow-up. The remaining 94 patients (67 females and 27 males) were enrolled in the study.

The clinical notes were reviewed to ascertain the clinical presentations and response of patients to different modes of ozone therapy. Longevity resources EXT50 Ozone Generator (Fig. 1) with oxygen tank and CGA870 Oxygen Regulator (Fig. 2) were used. The generated ozone was delivered to the patients in different forms, such as OPRP, OOO or O_2–O_3 gas mixture (in a concentration of 12.7 gammas). The OOO was produced by using the highest ozone gas concentration necessary to charge olive oil with ozone and was locally applied to areas of pain. On the other hand, O_2–O_3 gas mixture was injected to trigger painful points subcutaneously or given via a well-lubricated catheter into the rectum. Moreover, it was also injected to muscles and joint spaces when necessary.

In order to prepare OPRP, autologous blood from the patient's own vein was drawn by a 50-ml syringe; the amount of blood determined by the size of the area to be treated. The withdrawn blood was then placed in aseptic tubes, each one filled with 9 ml blood and 1 ml 3.8% sodium citrate as an anticoagulant. The tubes were then placed in a centrifuge at 1500 rpm for 10 min separating the sample into three parts; the upper part made of plasma, the middle part (buffy coat) made of white blood cells (WBCs) while the lower part made of red blood corpuscles (RBCs). The upper two thirds of plasma were then discarded while the lower third was transferred to another tube and placed in a centrifuge again. After 15 min of centrifugation at 3000 rpm, the upper half of the sample was discarded while the lower half would form the PRP. Platelet rich plasma was then activated by passing ozone in a concentration of 68.7 gammas and injected into the joint spaces, trigger points or muscles when needed.

In this study, the author used a symptom-based patient-directed questionnaire to assess the outcome after ozone therapy. The questionnaire was similar to that described by Bhattacharya et al. in their study of thoracic outlet compression but slightly modified. The questionnaire asked patients to

Fig. 1 **Longevity resources EXT50 ozone generator.**

Fig. 2 **CGA870 oxygen regulator.**

grade their perception of symptomatic relief using the terms "Excellent" for complete relief of symptoms, "Good" for relief of most major symptoms, "Fair" for relief of some symptoms, but persistence of others and "Poor" for no improvement.[14] Statistical analysis was performed using Z-test for comparing two population groups.

Results

There were 94 patients (67 females and 27 males) with a female:male ratio of 2.5:1. The mean age was 53 ± 15 years. The youngest patient was a 22 years man and the oldest was a 83 years woman. Table 1 displays the age and sex distribution of the studied patients.

Table 1. **Age and sex distribution**

Age (year)	Females, *n* (%)	Males, *n* (%)	Total, *n* (%)
20–30	3	5	8
31–40	10	6	16
41–50	16	2	18
51–60	21	6	27
61–70	9	5	14
71–80	7	3	10
81–90	1	0	1
Total	67 (71.3)	27 (28.7)	94 (100)

The peak was in the 6th decade of life (n = 27, 28.7%).
Table 2 reveals the jobs of patients.

Table 2. **Job distribution**

Job	Gender		Total
	Females	Males	
House wife	55	0	55
Government employee	11	9	20
Free worker	0	12	12
Retired	0	5	5
Teacher	1	0	1
Student	0	1	1
Total	67	27	94

Most of the female patients were housewives (n = 55, 82.1%) while most males were either free workers (n = 12, 44.4%) or government employees (n = 9, 33.3%).
Table 3 shows the co-morbid conditions.

Table 3. **The co-morbid conditions**

Co-morbidity	Gender		Total
	Females	Males	
DM	1	1	2
HT	10	2	12
DM & HT	8	4	12
DM & CAD	1	0	1
DM & HF	1	0	1
DM, HT & CAD	1	0	1
Bronchial Asthma	0	1	1
Migraine	1	0	1
Nil	44	19	63
Total	67	27	94

DM, diabetes mellitus; HT, hypertension; CAD, coronary artery disease; HF, heart failure.

Thirty one patients (33%) had one or more co-morbid condition. The commonest one was hypertension (n = 25, 26.6%) followed by DM (n = 17, 18.1%).

In Table 4, the different clinical conditions treated by ozone are displayed.

Table 4. **The clinical conditions treated by ozone**

Indication of ozone therapy	Gender		Total
	Females	Males	
Neck pain	4	1	5
Shoulder pain	1	2	3
Lower back pain	15	7	22
Neck & lower back pain	1	1	2
Knee OA	27	13	40
Neck pain & knee OA	1	0	1
Lower back pain & knee OA	5	0	5
Shoulder pain & knee OA	0	1	1
Neck, lower back pain & knee OA	3	0	3
CTS	5	0	5
Peripheral neuropathy	2	0	2
Lower back pain & knee OA + neuropathy	1	0	1
Neck, shoulder, lower back pain & knee OA + trigger finger	1	0	1
Shoulder & lower back pain, trigger finger & neuropathy	1	0	1
Diabetic foot + neuropathy	0	2	2
Total	67	27	94

Pain in different parts of the body was the main indication. Osteoarthritis (OA) of one or both knees was on the top (n = 52, 55.3%). It was of different severities and occasionally associated with joint effusion. Lower back pain mainly due to inter-vertebral lumbar disc prolapse was seen in 35 patients (37.2%). Neck pain due to cervical inter-vertebral disc prolapse occurred in 12 patients (12.8%). Less frequent conditions included shoulder pain (n = 6, 6.4%), carpal tunnel syndrome (CTS) (n = 5, 5.3%), peripheral neuropathy (n = 2, 2.1%) and trigger finger (n = 2, 2.1%). Seventeen patients (18.1%) had multiple painful conditions.[2–5] Females far exceeded males in the occurrence of the above conditions.

Table 5 shows the forms and routes of administration of ozone to the patients with isolated painful conditions.

The OPRP was used in 70/88 occasions while O_3 gas used in 18 occasions. Patients with painful knee(s) were managed mainly by IA-OPRP injection while the group of LBP received mainly paravertebral IM-OPRP. All cases of painful shoulder were managed by IA-OPRP. All painful neck cases received IM-OPRP injections. Trigger finger patients and CTS received subcutaneous O_3 or OPRP. The total number of treatment sessions was 483 with an approximate mean of 5.[1–28]

Table 6 shows the forms and routes of administration of ozone to the patients with multiple painful conditions. Ozone gas and OPRP were almost equally used in the treatment of these patients.

Table 5. **Isolated painful conditions vs. forms & routes of ozone therapy**

Clinical condition	Modes and routes of O_3						
	S-O_3	S-OPRP	IM-O_3	IM-OPRP	IA-O_3	IA-OPRP	R-O_2/O_3
Neck pain	0	0	0	5	0	0	0
Shoulder pain	0	0	0	0	0	3	0
Lower back pain	3	2	7	15	0	0	0
Knee OA	1	5	0	0	1	36	0
CTS	4	4	0	0	0	0	0
Peripheral neuropathy	2	0	0	0	0	0	0
Total	10	11	7	20	1	39	0

S, subcutaneous; R, rectal. Some patients received more than one form and/or route of ozone; hence, some figures in this table exceeded the numbers of patients.

Table 6. **Multiple painful conditions vs. forms and routes of ozone therapy**

Clinical condition	Modes and routes of O_3						
	S-O_3	S-OPRP	IM-O_3	IM-OPRP	IA-O_3	IA-OPRP	R-O_2/O_3
Neck and lower back pain	1	0	1	2	0	0	0
Neck and knee OA pain	0	0	0	1	0	1	0
Lower back and knee OA pain	0	0	2	1	1	2	0
Shoulder and knee OA pain	0	0	0	0	0	1	0
Neck, lower back & knee OA pain	0	0	0	2	0	3	0
Lower back & knee OA + neuropathy	1	0	1	0	1	0	1
Neck, shoulder, lower back & knee OA + trigger finger pain	0	0	0	0	0	0	0
Shoulder & lower back, trigger finger & neuropathy pain	1	1	1	0	0	0	0
Diabetic foot + neuropathy	1	0	0	0	0	0	0
Total	4	1	5	6	2	7	1

Table 7. **The clinical conditions vs. results of ozone therapy**

Clinical condition	Results of ozone therapy				
	Excellent, *n* (%)	Good, *n* (%)	Fair, *n* (%)	Poor, *n* (%)	Total, *n* (%)
Neck pain	2	2	1	0	5
Shoulder pain	2	0	0	0	2
Lower back pain	10	6	4	2	22
Knee OA	15	12	7	6	40
CTS	5	0	0	0	5
Peripheral neuropathy	0	0	2	0	2
Multiple painful conditions	8	6	3	1	18
Total	42 (44.7)	26 (27.7)	17 (18.1)	9 (9.5)	94 (100)

Table 8. **Forms vs. results of ozone therapy**

Form	Results of ozone therapy				
	Excellent, *n* (%)	Good, *n* (%)	Fair, *n* (%)	Poor, *n* (%)	Total, *n* (%)
O_2–O_3	2	1	4	0	7
OPRP	29	19	9	8	65
Total	31	20	13	8	72 (100)

Some of the patients responded very well to a single treatment session while others required many sessions and forms of ozone therapy. Some patients failed to respond despite repeated sessions. Table 7 shows the clinical conditions vs. results of ozone therapy.

Overall, the results of ozone therapy in this study were excellent to good (n = 68, 72.3%) particularly in painful knee (n = 27, 67.5%) and LBP (n = 16, 72.7%). Minority of patients experienced a poor outcome (n = 9, 9.5%). There was no significant difference in the outcome of ozone therapy between the subgroup of painful knee (27/40 good-excellent result, 67.5%) and the subgroup of multiple painful conditions (14/18 good-excellent result, 77.8%) ($P < 0.05$).

Table 8 displays the therapeutic results of the two major forms of ozone used in this study, namely gaseous O^2–O^3 and OPRP Fair, good and excellent results were 7/7 (100%) in the O_2–O_3 sub-group vs. 57/65 (87.7%) in the OPRP sub-group. This difference, however, was not significant ($P < 0.05$).

Discussion

In this study, OA of the knee was the most frequent painful condition treated by ozone (n = 52, 55.3%). Osteoarthritis is a chronic degenerative musculoskeletal disease affecting approximately 10% of people older than 55 year old.[15] The most commonly affected joint by OA is the knee.[16] Although the specific etiology of OA is poorly understood, its pathological changes are well known namely the gradual loss of articular cartilage, formation of osteophytes, sub-chondral bone remodeling and joint inflammation. Currently, there are many pharmacological and non-pharmacological treatment options.[15] Intra-articular injection of ozone or blood products such as PRP is an example of newly used therapeutic options.

Oxygen–ozone is a mixture of O_2 and O_3 that can be used in the treatment of several painful conditions. At present, the exact mode of action of O_2–O_3 has not been fully clarified. However, there is an evidence to suggest that the pharmacological effect of this substance is achieved through immune modulation, anti-inflammatory activity and analgesia. In the past few years, O_2–O_3 has been implemented in the treatment of different pathological conditions including lumbar disc herniation.[15]

Platelet-rich plasma is a promising treatment option for cartilage damage associated with OA. It has been widely used in clinical studies. Platelets are present in PRP at a higher concentration than in full blood. The active platelets have biologically active proteins that bind to trans-membrane receptors in the target cells. This binding leads to gene expression resulting in cellular recruitment, growth and morphogenesis and at the same time reduction in inflammation.[16] Sundman et al.[16] studied the mechanism of action of PRP and found that it stimulated hyaluronic acid (HA) production and reduced cartilage catabolism.

In a randomized clinical study, Duymus et al. evaluated 102 patients with knee OA divided into three groups receiving IA-PRP, IA-HA and IA-ozone, respectively. The PRP was more successful than HA and ozone injection as the application alone was sufficient to provide at least 12 months of pain-free daily living activities.[16] Invernizzi et al. from Italy very recently presented a series of 42 patients with OA of the knee divided into two groups, the first received IA-O_2O_3 while the second received IA-HA showing that both options were safe and yielded similar improvement in quality of life.[15] Of note, data about IA-O_2O_3 treatment in humans currently are scarce. So far, these were the only two randomized studies performed with IA-O_2O_3 in knee OA patients.[15]

In the present study, ozone was added to PRP creating the OPRP. One patient only received IA-ozone while the vast majority of patients with knee OA (36/40) received IA-OPRP. The outcome was excellent to good in 27 patients (67.5%).

The second largest group of patients treated by ozone in this study had LBP (n = 35, 37.2%). About two thirds of these patients (n = 22) had isolated LBP while the remaining 13 patients had other associated conditions. The main mode of therapy was paravertebral IM-OPRP, but other modes (S-O_3 and S-OPRP) were used less frequently. The outcome of ozone therapy was good to excellent in 16 patients (72.7%) of this group.

Low back pain is one of the most common and important health problems affecting the population worldwide and remains mostly unsolved.[17] The underlying pathological lesion is usually disc herniation. Surgery used to be the traditional treatment for lumbar disc herniation. However, nowadays, it is only indicated for intolerable pain, progressive neurological deficit or impending cauda equina syndrome.[18] The other approach for therapy is conservative. Paravertebral IM-O_2–O_3 injection seems to be safe and effective in relieving pain, as well as reducing both disability and the intake of analgesic drugs.[19] It has the advantages of being minimally invasive outpatient procedure, performed without radiological armamentarium and is relatively inexpensive.[19]

In the study of Paoloni et al. from Italy, 60 patients with lower back pain due to disc herniation were randomized to an IM-O_2–O_3 or control group. Pain intensity, LBP-related disability and drug intake were significantly lower in the former group throughout 6 months of observation.[19] Similarly, Zhang et al. from China found that O_2–O_3 nucleolysis provided an excellent pain relief in most herniated disc patients who failed

to respond to conservative therapy. They suggest its use as a first-choice treatment before recourse to surgery or when surgery is not possible. Moreover, they think that epidural steroid infiltration is not required.[20]

Beside relief of pain, ozone helped our patients to markedly reduce the intake of pain killers. This result is particularly important in patients with co-morbid conditions that require additional medications. Worthy to note, a significant number of our patients were hypertensive (n = 25) or diabetics (n = 17).

In this study, beside OA of the knee and lumbar disc prolapse, ozone was also effective in the treatment of other disorders, such as CTS, neck and shoulder pain, trigger finger and peripheral neuropathy. Even patients with multiple painful disorders (n = 18) responded very well to ozone application achieving good to excellent results in 14/18 cases (77.8%).

Conclusion

Ozone therapy is an inexpensive therapy which seems to be safe and effective in palliating the pain of OA and inter-vertebral disc herniation as well as other pain disorders. Although our study lacked a control group, both patients and physicians were happy to achieve such good results which match the published international studies.

Conflict of Interest

None declared.

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