Retrospective Study

Feasibility of Ultrasound-Guided Peritoneal Perfusion with Ozone in the Treatment of Chronic Pelvic Pain: A Bicenter Retrospective Analysis

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Background: Numerous therapies have been developed for the treatment of chronic pelvic pain (CPP). Oxygen-ozone therapy is a new method for the treatment of CPP.

Objectives: This article evaluated the feasibility of ultrasound-guided peritoneal perfusion with ozone in patients with CPP.

Study Design: This is a bicenter retrospective study.

Setting: The study was conducted at 2 pain centers of a university hospital.

Methods: The medical records of patients with CPP (n = 60) from March 2016 until October 2018 were collected and reviewed. Group A contained 19 patients who were treated with a 1500 mcg dose of ozonated water (10 mcg/mL concentration and 150 mL volume), group B contained 23 patients using the same dose of ozonated water but a 15 mcg/mL concentration and 100 mL volume. Group C included 18 patients using a similar ozone dose but delivered in an oxygen-ozone mixture (15 mcg/mL concentration and 100 mL volume oxygen-ozone mixture). Visual Analog Scale (VAS) scores for pain of the 3 groups were compared at pretreatment, posttreatment, 1, 3, and 6 months posttreatment. The injection pain was evaluated using a 4-point verbal rating scale. Quality of life (QoL), anxiety, and depression were assessed at pretreatment and at 6 months posttreatment.

Results: The VAS scores of the 3 groups decreased over time following treatment. Group A showed much higher pain scores compared with groups B and C at 1, 3, and 6 months posttreatment. However, the injection pain for groups B and C was higher than group A, but there was no difference seen between group B and C. At 6 months posttreatment, the QoL for all patients improved compared with pretreatment, whereas the anxiety and depression did not demonstrate differences.

Limitations: The main limitations of this study are the retrospective study design, limited case number, and short follow-up period.

Conclusions: Ultrasound-guided peritoneal perfusion with ozone is a feasible therapy for patients with CPP.

Key words: Chronic pelvic pain, ozone, peritoneal perfusion

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The American College of Obstetricians and Gynecologists and the ReVITALize data definitions initiative define chronic pelvic pain (CPP) as "pain symptoms perceived to originate from pelvic organs/structures typically lasting more than 6 months" (1). Studies have found that the prevalence

of women with CPP worldwide ranges from 6% to 27% (2). CPP in women is rarely caused by a single factor, and possible pathological causes include endometriosis, chronic pelvic inflammatory infection, adhesions, irritable bowel syndrome, interstitial cystitis, and pelvic congestion syndrome (3).

At present, analgesics, antibiotics, hormone modulating agents, antidepressants, and anticonvulsants are extensively used in the treatment of CPP; nonpharmacologic therapies such as pelvic physiotherapy, psychotherapy, acupuncture, and neuromodulation are also broadly used, but these methods are nonspecific, and their effect is limited (4,5). Moreover, deleterious side-effects of opioids can affect the gastrointestinal tract, and there are many adverse reactions related to psychiatric drugs that can affect the quality of life (QoL) of patients. According to several studies that focused on surgical interventions, such as laparoscopic uterosacral nerve ablation (6), hysterectomy (7), and laparoscopic adhesiolysis (8), as accepted as treatments for CPP, there is, however, no firm evidence that any of these procedures (7,9-11) are beneficial. Furthermore, surgery is a traumatic procedure that may bring additional postoperative complications that only complicate diagnosis and treatment. Several studies have found that patients with CPP are more likely to have mood disorders such as anxiety (10%–20%) and depression (25%–50%) because of the long-term history of pain and reduced QoL associated with ill health (12,13). Therefore a safe, effective, and easily accessible therapy for patients with CPP is required.

Ozone for medical use consists of a gas mixture of O3 and O2, obtained from medical-grade oxygen using an ozone generator device that has to be administered in situ because of its short half-life. Ozone is used in a broad spectrum of diseases such as infection (14), neuropathic pain (15-17), and posttreatment adhesion formation (18). Oxidative stress, inflammation, and ischemia/hypoxia are the principal mechanisms involved in pain (17). The previous studies demonstrated that ozone can favorably modify those processes for the resolution of zoster-associated pain, complex regional pain syndrome, and refractory pelvic pain syndromes secondary to cancer treatment (15-17). It has been in continuous medical use for over 100 years, having been used by German soldiers in the trenches to disinfect wounds in World War I (14-20). However, no current study has evaluated the clinical effectiveness of ozone therapy for patients with CPP. In this report, we examine our retrospective bicenter analysis of ultrasound-guided intraperitoneal ozone injection for patients with CPP, aiming to determine the feasibility and efficacy of this therapy.

Methods

This research is a retrospective bicenter analysis, which was performed by the Aviation General Hospital of China Medical University and Maternity and Child Care Hospital in Lanzhou. This research followed the tenets of the Declaration of Helsinki, and the approval from the Institutional Review Board of the Aviation General Hospital of China Medical University was obtained (approval number HK2019-12-31). The approval included a waiver of informed consent because the analysis did not include direct contact with the study population. Basic data from study patients were collected and analyzed utilizing existing medical records and standardized questionnaires.

We retrospectively reviewed 79 patients with CPP from 2 institutions who were treated with intraperitoneal ozone under ultrasound guidance from March 2016 to October 2018. Nineteen patients were excluded because of the following exclusion criteria: absence of posttreatment follow-up data (Fig. 1). All patients received a 1500 mcg dose of ozone but in 3 different dosage formulations. Patients in group A (19 patients) received ozone in a 10 mcg/mL concentration in 150 mL volume of ozonated water, patients in group B (23 patients) received their dosage in a 15 mcg/mL concentration in a 100 mL volume of ozonated water, and patients in group C (18 patients) received their dosage in a 15 mcg/mL concentration and 100 mL volume of an oxygen-ozone mixture.

Preoperative Management

We conducted further diagnostic evaluations on patients to delineate the causes of CPP preoperatively. The diagnostic evaluations included obtaining a complete clinical history, performing a physical examination, and a pelvic magnetic resonance imaging scan. Patients were excluded from the study if they met at least one of the following exclusion criteria: age less than 18 years; puncture site infection; coagulopathy and bleeding disorders; severe cardiopulmonary disease; ozone contraindications (patients with a significant deficit of glucose-6 phosphate dehydrogenase); pregnancy or the intention to become pregnant during the process; patients being treated with angiotensin converting enzyme inhibitors; patients with hyperthyroidism, thrombocytopenia, and serious cardiovascular instability; allergy to ozone; or

a history of mental disorders. All patients with CPP were treated with ozone administered on Mondays, Wednesdays, and Fridays, 3 times a week, 10 sessions constituting one course.

Treatments

Ozone procedures at each center were performed by an attending physician and his assistants. All patients received ozone therapy in the treatment room of our pain clinic. The heart rate, blood pressure, and pulse oxygenation of patients were recorded every 5 minutes.

During the treatment process, the patients lay in a supine position, with the head and the lower limbs raised approximately 30°, meanwhile intravenous access was obtained. First, the physician located the puncture site and disinfected the site. Typically, the puncture site was located within an area of abdominal skin covering a region defined by the xiphoid process of the sternum at the superior and the pubic symphysis at the inferior and bilaterally by the midaxillary line. The puncture site was identified taking the lateral and middle third of a line between either the left or right anterior superior iliac spine and the umbilicus (Fig. 2A).

Second, the puncture site of skin was anesthetized with 1% lidocaine, and the puncture was guided using an ultrasound device (Navi series; Wisonic Medical Technology Co., Ltd, Shenzhen, China). An abdominal ultrasound probe was covered with a sterile sheath and positioned transversely to the puncture site to obtain a transverse longitudinal view (Fig. 3A). From superficial to deep the following structures are recognized: skin and subcutaneous fat, external oblique, internal oblique, transversus abdominis

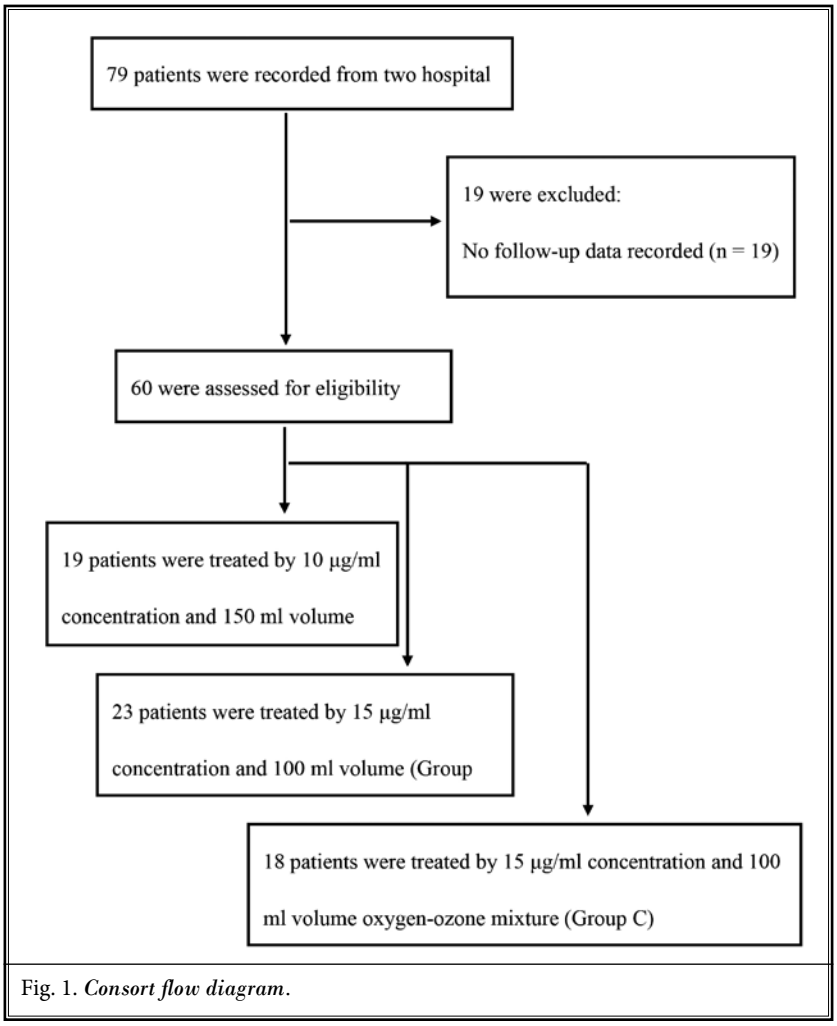

Fig. 1. *Consort flow diagram.*

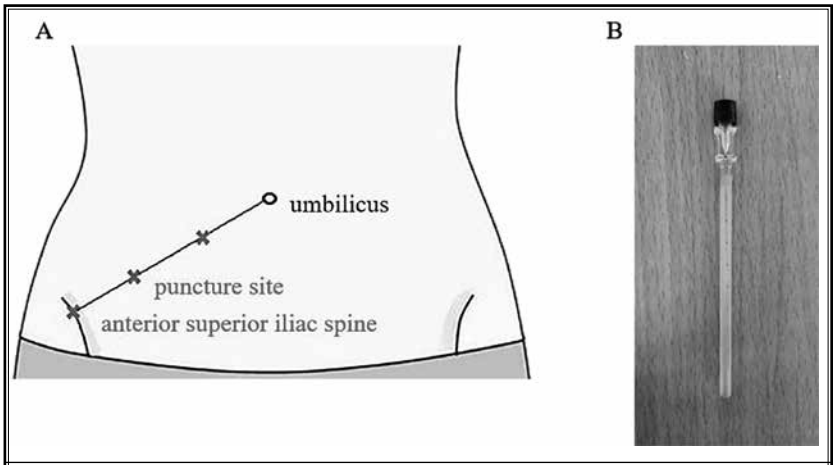

Fig. 2. *(A) Puncture site: the lateral and middle third of a line between the right anterior superior iliac spine and the umbilicus. (B) A 90-mm 22-gauge needle was used for patients with CPP.*

muscles, peritoneum, and abdominal cavity (Fig. 3A). A 90-mm 22-gauge needle (Fig. 2B) was advanced slowly under in-plane ultrasound guidance from skin through the peritoneum (Fig. 3B, 3C).

Once the needle penetrated the peritoneum (Fig. 3D), a syringe was connected to the needle by an extension tube. The assistant withdrew the plunger of the syringe to make sure that no blood or intestinal contents were withdrawn. Then, approximately 20 mL local anesthetic (0.2% lidocaine hydrochloride solution and 0.1% ropivacaine hydrochloride solution) was injected into the abdominal cavity. Following this, abdominal cavity perfusion of the oxygen-ozone mixture or ozonated water was performed with a syringe attached to a medical infusion apparatus. The whole procedure took approximately 1 hour. If a patient complained of injection pain during the ozone procedure, the assistant would provide an additional local anesthetic injection of 5 mL. All patients were observed for 20 minutes after the procedure. We recorded all complications including injection pain during the ozone procedure.

Data Collection

The following clinical characteristics of the patients were collected and analyzed from the medical records: age, duration of pain, severity of pelvic pain, severity of injection pain during the therapeutic period, history of abdominal surgery, and history of pelvic inflammatory disease (PID) records.

The severity of pelvic pain was evaluated with a Visual Analog Scale (VAS) for pain intensity before treatment and immediately posttreatment, as well as at 1, 3, and 6 months posttreatment. The VAS consisted of a 10-cm horizontal line with the words "no pain" on the left side and "most intense imaginable pain" on the right side. The clinical effectiveness of ozone therapy was recorded in a dichotomous fashion as either "successful remission" or "unsuccessful remission." Successful remission was defined by a decrease in pain of 50% or greater as measured by the VAS at 6 months posttreatment (21). The severity of injection pain was recorded by a physician according to a 4-point verbal rating scale of none, mild, moderate, and severe pain (22).

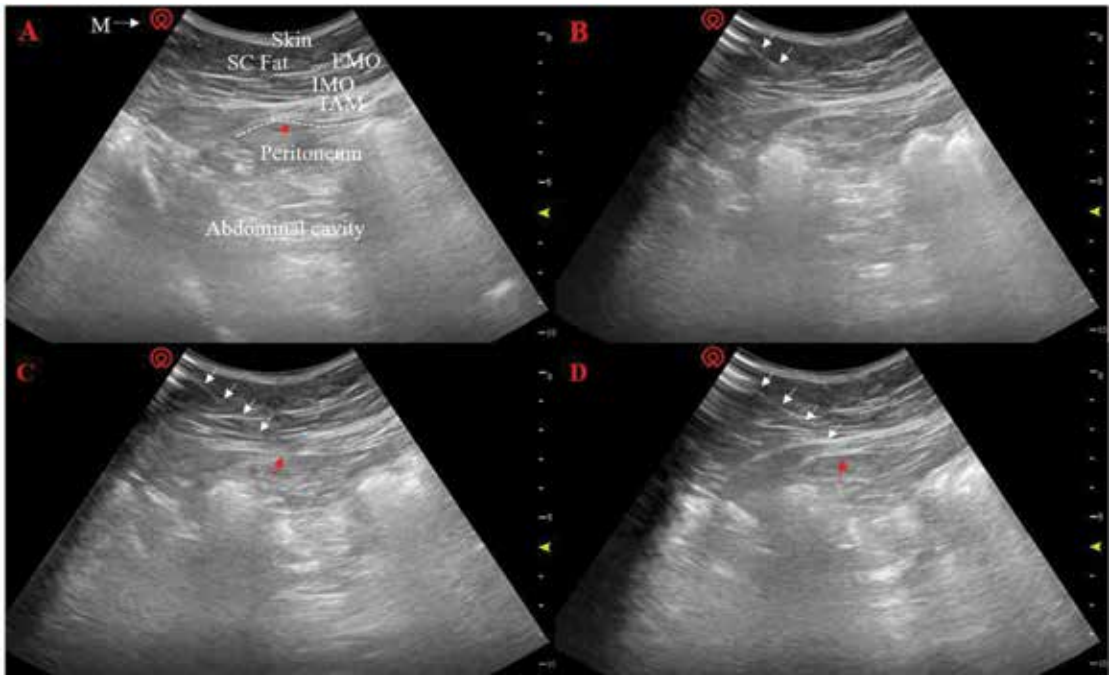

Fig. 3. *(A) Preinjection short axis sonogram showing the abdominal wall anatomic layer. The dotted line shows the peritoneum. The arrow indicates the position of the peritoneum. (B) The arrow indicates the position of the puncture needle. (C) The white arrow displays the position of the puncture needle, and the red arrow indicates the area where the needle tip reaches the peritoneum. (D) The white arrow reveals the position of the puncture needle, and the red arrow indicates the possible area where the needle tip is located (needle tip is not shown in the ultrasound images). M = transducer probe marking; SC Fat = subcutaneous fat; EMO = external oblique muscle; IOM = internal oblique muscle; TAM = transversus abdominis muscle.*

QoL, anxiety, and depression were assessed at pretreatment and at 6 months posttreatment using the following questionnaires: the Chinese version of the 36-Item Short-Form Health Survey (SF-36), the 14-Item Hamilton Anxiety Scale (HAMA), and the 17-Item Hamilton Depression Rating Scale (HAMD). The SF-36 was a brief self-administered questionnaire, constructed to evaluate functioning and well-being in adults across 8 basic health scales: physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. The maximal score within each domain was 100. A higher score relates to a better QoL (23). Patients with a HAMA score of ≥ 8 were considered to have symptomatic anxiety (a higher level of anxiety resulting in a higher score). Anxiety severity was classified by the following severity range for the HAMA score: normal (0–7), mild or probable anxiety (8–14), moderate or definite anxiety (15–21), and severe anxiety (≥22). Patients with a HAMD score of ≥8 were considered to have existing depressive symptoms (a higher score related to a higher level of depression). Depressive symptom severity was classified using the following severity range for the HAMD score: normal (0–7), mild depression (8–16), moderate depression (17–23), and severe depression (≥24) (24).

Statistical Analysis

The Shapiro-Wilk test was used to assess whether the continuous data met the criteria for a normal distribution. Categorical variables are shown as frequency rates and percentages, and continuous variables as mean (standard deviation) and median (interquartile range [IQR]). One-way analysis of variance was used to compare continuous variables among groups (VAS for pain intensity). Age and duration of pain of the 3 groups were compared by the nonparametric Kruskal-Wallis test. Repeated measures analysis of variance was used to assess changes in pain intensity over time, with the Student-Newman-Keuls q test used for pairwise comparison. The Wilcoxon signed-rank test was used to related-samples (SF-36, HAMA, and HAMD scores variable). The Fisher exact test was used for categorical variables (severity of injection pain). The Statistical Package for the Social Sciences, Version 25.0 (IBM Corporation, Armonk, NY) was used, and a $P < 0.05$ was used to describe statistically significant changes in all measures.

Results

There were 2 patients with a medicine use history of ibuprofen after ozone therapy for 1 month. These 2 patients achieved unsuccessful remission at the 6 months follow-up. One patient received the compound lidocaine cream due to the severe post-puncture pain of the skin around the puncture site (Table 1).

The median age and duration of illness in the remaining 60 cases were respectively 45 years (IQR, 33–54) and 24 months (IQR, 12–48). Thirty-two of 60 patients were noted to have had prior abdominal surgery, and 34 of 60 patients presented with a history of PID. Fifteen of 60 patients experienced both abdominal surgery and a history of PID, and 9 of 60 patients had no prior surgical or infectious etiology (Table 2). Forty-seven of 60 patients (78%) achieved successful remission at the 6-month follow-up (Table 2). The injection pain during the procedure occurred in 54 of 60 patients (90%) (Table 2).

Overall, the median patient age was 45 years (IQR, 29–61), 44 years (IQR, 38–47), 45 years (IQR, 33–54), and the duration of pain was 24 months (IQR, 12–36), 12 months (IQR, 10–36), and 30 months (IQR, 12–63) in groups A, B, and C, respectively. There were no significant differences between the groups with respect to duration of pain.

The VAS scores for pain intensity of the 3 groups decreased significantly over time following treatment ($P < 0.05$) (Fig. 4). The pretreatment VAS scores for pain intensity were 6.00 ± 1.76, 5.91 ± 1.00, and 6.17 ± 1.20 in groups A, B, and C, respectively, which were not significantly different ($P > 0.05$) (Fig. 4). The posttreatment

Table 1. *Medication use history after the study intervention.*

Patients No.	Pretreatment (VAS)	Posttreatment (VAS)	First Month (VAS)	Third Month (VAS)	Sixth Month (VAS)	Medication	Successful Remission
1	6	5	5	5	5	Ibuprofen	No
2	8	6	6	6	6	Ibuprofen	No
3	8	3	3	2	1	Compound lidocaine cream	Yes

Successful remission was defined by a decrease in pain of 50% or greater as measured by the VAS scores at 6 months posttreatment; First month = 1 month posttreatment; Third month = 3 months posttreatment; Sixth month = 6 months posttreatment.

VAS scores for pain intensity were 3.00 ± 1.80 in group A, 2.13 ± 1.14 in group B, and 2.56 ± 1.10 in group C ($P > 0.05$) (Fig. 4). In group A, the 1-, 3-, and 6-month posttreatment VAS scores for pain intensity were 3.21 ± 1.51, 3.00 ± 1.49, and 3.05 ± 1.72, respectively. In group B, these were 1.78 ± 1.38, 1.78 ± 1.38, and 1.87 ± 1.46, respectively. In group C, these were 2.17 ± 1.43, 1.78 ± 1.17, and 1.67 ± 1.46, respectively (Fig. 4). Group A had much higher VAS scores than group B and C at 1, 3, and 6 months posttreatment, whereas there was no significant difference between group B and C over the same time intervals following treatment (Fig. 4). The injection pain during the therapeutic period was similar between groups B and C but were significantly higher than group A (Fig. 5).

At 6 months posttreatment, the SF-36 questionnaire in all cases showed statistically significant changes in all domains (Table 3). However, the HAMA and HAMD scores did not demonstrate significant changes (Table 4).

Table 2. *Characteristics for all patients*.

Characteristics	Value (n = 60)
Age, median (IQR), years	45 (33–54)
Pain duration, median (IQR), months	24 (12–48)
History of abdominal surgery	32
History of PID	34
History of abdominal surgery and PID	15
No established local or infectious cause	9
Successful remission	47
Injection pain	54

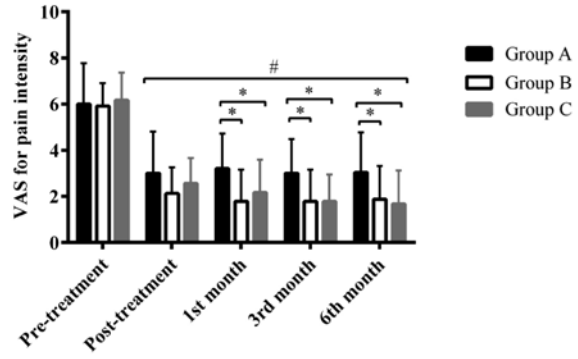

Fig. 4. *Pain level as measured by the VAS scores in patients who presented with CPP. The VAS scores for pain intensity of the 3 groups decreased significantly over time following treatment. The pre- and posttreatment VAS scores for pain intensity of the 3 groups were not significantly different ($P > 0.05$). Group A shows a much higher VAS scores than group B and C at 1, 3, and 6 months posttreatment ($P < 0.05$), whereas there was no significant difference between group B and C ($P > 0.05$). #The VAS scores for pain intensity of the 3 groups decreased significantly over time following treatment, $P < 0.05$. *Group A vs. group B, $P < 0.05$; group A vs. group C, $P < 0.05$. First month = 1 month posttreatment; Third month = 3 months posttreatment; Sixth month = 6 months posttreatment.*

Discussion

Ozone therapy is a novel approach for pain management (15,16). It has been considered that the origin of all pain is inflammation (25). Ozone performed its analgesic actions by modulating the immune system (balancing inflammatory and anti-inflammatory cytokines), increasing production of red blood cells and 2,3-diphosphoglycerate (stimulating more oxygen delivery) (15,16). Other probable mechanisms of ozone-induced pain relief could be activating the descending antinociceptive system and increasing the release of endorphins (26). In this report we recorded and reviewed 55 cases of patients with CPP with a previous history of abdominal surgery or PID. In animal experiments with female rats, the administration of ozone injected into the pelvic cavity demonstrated inhibition of pelvic inflammation (27). It revealed that the proinflammatory cytokine of tumor necrosis factor alpha was decreased, whereas the neutralizing proinflammatory cytokines of interleukin-2 increased, and the blood immunoglobulin content and immune function were improved (27). Oxidative stress may play an important role in the formation of intraabdominal adhesions caused by abdominal surgery or PID (28). Ozone can favorably modify those processes by altering reactive oxygen species production (17,29). What is more, ozone can also effectively break down inflammatory tissue and quickly promote the healing of wounds (30). These might be the possible mechanisms of ozone in the therapeutic benefit of CPP caused by adhesions or PID.

At present, the typical clinical O3 concentrations range from 10 to 60 mcg/mL (31). In our study of the 2 concentrations of ozone, the 15 mcg/mL ozone dosage was associated with a lowering in VAS scores for pain. The animal experiment with female rats showed that the higher the ozone concentration was, the lower the interleukin-6 content detected (20). However, we only analyzed 2 concentrations of ozone for patients with CPP and could not conclude that the higher ozone concentration was more effective than the

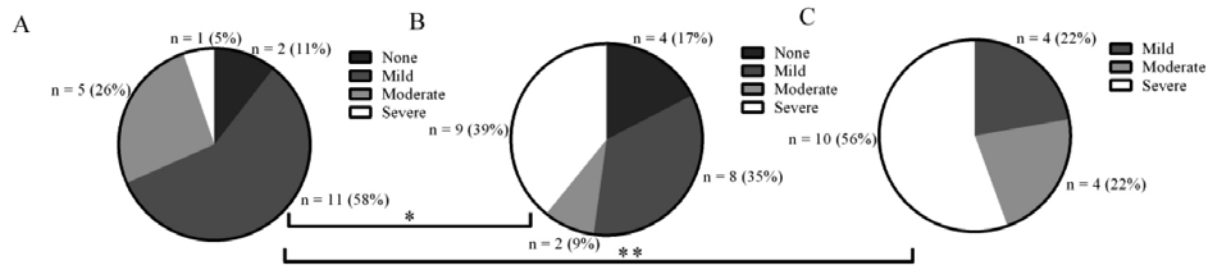

Fig. 5. *Pie charts depicting the severity of injection pain in the 3 groups of patients with CPP. The injection pain between groups B and C were significantly higher than group A, whereas there was no difference between the 2 groups. (A) Group A; (B) group B; (C) group C. Values are expressed as number (percentage); n = number of patients in each section; *Group A vs. group B, P < 0.05; **Group A vs. group C, P < 0.01.*

lower ozone concentration for long-term pain relief. Additionally, there is no clear evidence to explain the similar VAS scores for pain intensity of the 3 groups at posttreatment. It is necessary to design a multicenter large-sample study in the future to explain the reasons for this result. Although the 15 mcg/mL ozone dosage showed better pain relief at 6 months of follow-up, it also caused problems such as severe injection pain. Occurrence of injection pain was common in our study. The injection pain of 15 mcg/mL ozonated water and oxygen-ozone mixture were shown to be significantly higher than 10 mcg/mL ozonated water. Previous research indicates that the oxidative effects of ozone on the endothelial cells of veins (veins lack catalase protection) cause venous irritation and the higher concentrations of ozone are more vein irritating (16), however, there are few reports on injection pain. We hypothesize that the injection pain may be related to ozone-induced peritoneal surface oxidation and inflammatory tissue breakdown. Therefore we recommend that sedative and analgesic drugs can be added in the near future to alleviate the injection pain, which will undoubtedly increase the cost of treatment. Fortunately, the ozone therapy is quite inexpensive, predictable, and conservative with few side effects (14). However, ozone therapy also has the possible risks. For example, the intestinal wall was penetrated during the puncture, and the intestinal fluid extravasated into the abdominal cavity resulting in acute peritonitis. Second, ozone gas has a risk of provoking gas embolism resulting from injection into blood vessels. However, the most common side effect of ozone therapy is injection pain in our study.

In our analysis, we did not find a significant difference between 15 mcg/mL ozonated water and oxygen-ozone mixture in terms of the improvement of VAS scores for pain intensity over time following treatment. Therefore dosage forms may not impact the clinical effectiveness of ozone. Ozone disappears in a few seconds (31), and its effect is accomplished by ozone's induction of reactive oxygen species and lipid oxygen products known as ozonide (16). Finally, comparing the

Table 3. *The SF-36 score in all cases before and after 6 months treatment.*

SF-36 Score	Pretreatment	6 Months Posttreatment	*P* value
PF, median (IQR)	90 (68–95)	95 (80–100)	0.001
RP, median (IQR)	50 (0–75)	100 (50–100)	< 0.001
BP, median (IQR)	61 (51–72)	79 (66–84)	< 0.001
GH, median (IQR)	53 (40–70)	75 (55–80)	< 0.001
VT, median (IQR)	69 (45–75)	75 (65–85)	< 0.001
SF, median (IQR)	69 (53–88)	88 (75–100)	< 0.001
RE, median (IQR)	33 (0–100)	67 (33–100)	< 0.001
MH, median (IQR)	68 (51–80)	76 (64–84)	< 0.001

At 6 months posttreatment, the 8 items of the SF-36 in all cases increased compared with pretreatment. PF = physical functioning; RP = role physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role emotional; MH = mental health.

Table 4. *The HAMA and HAMD scores in all cases before and after 6 months treatment.*

Scale	Pretreatment	6 Months Posttreatment	*P* value
HAMA, median (IQR)	4 (1–9)	4 (1–7)	0.126
HAMD, median (IQR)	5 (1–12)	5 (2–11)	0.371

The HAMA and HAMD scores in all cases did not demonstrate significant differences.

15 mcg/mL ozone and the 10 mcg/mL ozone dosages, the former showed better results with regard to VAS scores for pain intensity at long-term follow-up. Also, when comparing between the different ozone forms, ozonated water is safer than gaseous ozone, which avoids the problem of air embolism caused by straying into the blood vessel. Taken together, we strongly suggest the 15 mcg/mL ozonated water for patients with CPP.

In our analysis, the VAS scores for pain intensity decreased in all cases at 6 months posttreatment. Concomitant with pain remission was a noticeable improvement in QoL. Our study showed an improvement in all 8 items of the SF-36 at the 6-month follow-up. These findings were basically consistent with other reports (32). However, our study found that the anxiety and depression of patients with CPP was not improved. Some studies have pointed out that for women with a long-term history of CPP, amelioration of pain had little impact on mood and was particularly insignificant on relieving depression (33). Moreover, prolonged painful states alter neuronal plasticity and induce conformational changes in the brain that are not easily reversed by pain improvement. Thus it is possible that improvement in the chronic pain state requires more time to modify mood (34,35). However, we did not study the brains of patients with CPP, and thus we can only hypothesize that the lack of changes in the mood of the patients in our study may be related to such a mechanism.

Limitations

First, reduced statistical power with a total of 60 patients and the follow-up time was insufficient. Second, this analysis was retrospective in nature, and some data were missing or incomplete. Third, there are several confounders in this study including medication use after the study intervention. Finally, as a bicenter retrospective analysis, there may be heterogeneity in procedural technique.

Conclusions

Most patients (78%) with CPP are successfully treated with ozone therapy, concomitant with pain remission, and an improvement of the QoL of patients. Ultrasound-guided peritoneal perfusion with ozone may be a safe, feasible, and effective modality for the treatment of CPP.

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