

# Analgesic Effects of Ozone on Celiac Plexus Neurolysis, Reduced Need for Opioids, and Quality of Life in Patients with Pancreatic Cancer

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## Abstract

**Background:** Cancer pains are among high-severity pains that require multidimensional control and management, because such pains cause an urgent need for opioids that have undesirable side effects for patients. **Objective:** The present study aimed to investigate the analgesic effects of ozone on celiac plexus neurolysis (CPN), reduced need for opioids, and quality of life in patients with pancreatic cancer. **Methodology:** The present research was a cross-sectional descriptive study. The sample size was determined to be 40 and the participants were selected based on convenience sampling method. In the mediocostal approach, the anterior edge of L1 vertebra and then posterior aorta were caused to pass the aorta using the loss liquid method and the desired site was determined at the anterior aorta and posterior perineum by injecting a radiocontrast agent under fluoroscopic guidance. Then, ozone was administered to the desired site using 0.05% Marcaine (Bupivacaine) plus 40mg of Depo-Medrol (methylprednisolone). After confirmation of analgesia by the patient, CPN was done using 55 mg/l of ozone. The data were statistically analyzed using Pearson correlation coefficient, analysis of variance, chi-square test, Fisher's exact test, and logistic regression analysis in SPSS-19 at 0.05 level of significance. **Results:** The severity of pain significantly reduced over time in patients who received ozone ( $p < 0.001$ ). However, such a significant reduction was not observed in patients who were treated with alcohol ( $p = 0.029$ ). The results also showed that improvement in the quality of life over time was significantly higher in patients who received ozone ( $p < 0.004$ ) compared to those treated with alcohol ( $p = 0.019$ ). In addition, there was a significant difference in the opioid dosage administered to patients before and after the celiac plexus blockage ( $p < 0.001$ ). **Conclusion:** As a new medical treatment for celiac plexus blockage in patients with pancreatic cancer, ozone therapy was shown effective in reducing severity of pain and need for opioids and other analgesics and improving quality of life.

**Key words:** Celiac plexus blockage; Ozone therapy; Pain; Quality of life.

## Introduction

One of the most common and prevalent symptoms in cancer patients is pain that causes distress to patients and their families (Ovayolu et al., 2015). Hence, pain management is one of the main objectives of palliative care (Portenoy, 2011). Pain control and management in cancer patients are necessary both clinically and morally. Despite the availability of effective drugs and clinical guidelines for pain management, pain control is not properly done in many patients with cancer, which may reduce the quality of life and performance of patients and increase their stress (Puetzler et al., 2014).

Most cancer patients experience severe pains that are usually controlled by prescribing opioids. Although these drugs reduce the severity of pain, they cause adverse effects such as respiratory distress, reduced consciousness, severe nausea and vomiting, and dissatisfaction of patients and caregivers (Najafi et al., 2018).

Since cancer pains are a mixture of all three kinds of nociceptive, neuropathic, and idiopathic pains, their control requires further and more specific measures. The celiac plexus blockage is a common method for pain control and management in patients with visceral cancer, and CPN induces analgesia for three to six months. As the place where splanchnic nerves are connected to each other, the celiac plexus blockage induces complete analgesia for patients (Kaufman et al., 2010).

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A limited number of studies have been conducted around the world, especially in the northwest of Iran, to compare different type of celiac plexus blockers (e.g. ozone). This is mostly due to novelty of using this method and its uncertain results. In addition, few studies have been conducted in Iran or other countries about effects of neurolysis on celiac plexus.

### *Objective*

The present study aims to investigate the analgesic effects of ozone on celiac plexus neurolysis (CPN), reduced need for opioids, and quality of life in patients with pancreatic cancer. The results of this study can be a starting point for developing new methods to reduce pain and improve quality of life in such patients.

### **Methodology**

The present research was a descriptive study (Ethics no: 5/D/537795) conducted in the palliative care ward and pain clinic of Imam Reza Hospital affiliated to Tabriz University of Medical Sciences from March 21, 2017, to March 21, 2018. The study population consisted of all patients hospitalized in the oncology ward of this hospital who were referred to the palliative care ward. Considering the maximum error of 0.05, a statistical power of 50%, and an attrition rate of 10%, the final sample size was determined to be 40. The participants were selected based on convenience sampling method among patients who met the inclusion criteria.

The inclusion criteria were age of 18 to 80 years old, confirmation of pancreatic cancer by an oncologist and a pathologist, being under chemotherapy and radiotherapy, severe and intolerable pain during the last two weeks, and referral by an oncologist. The exclusion criteria also included unwillingness to participate in the study, death during the study, history of taking psychotropic drugs, drug addiction, history of cardiovascular disease or other cancers, allergy to drugs administered to patients in the study, coagulation disorders, history of fauvism, sepsis, and affliction with intraabdominal infection or ileus.

Before administering the drugs, a three-part questionnaire was completed for all patients. The first part of this questionnaire consisted of items about age, gender, weight, and symptoms of constipation, fatigue, insomnia, anorexia, ascites, dehydration, jaundice, and nausea. The second part included the VAS checklist that measures the severity of pain. Based on VAS, 0 denotes no pain and 10 represents intolerable severe pain (Cleeland and Ryan, 1994). The third part of this questionnaire was the 36-Item Short Form Health Survey (SF-36), which was developed to measure the quality of life in patients with physical conditions or mental disorders and also healthy individuals. This form consists of 36 items that measure the quality of life in 8 subscales as follows: physical function, social function, physical role, emotional role, mental health, vitality, physical pain, and general health. The items are scored based on a Likert scale and higher scores indicate more favorable conditions. The minimum and maximum scores obtainable on this scale are equal to 0 and 133, respectively (Ware and Sherbourne, 1992). The SF-36 has been used in many studies in Iran and its scientific validity has been confirmed. In addition, its Cronbach's alpha has been reported to be 0.82 (Montazeri et al., 2005).

After referral by an oncologist, all patients were examined by a palliative care specialist and a pain specialist in order to confirm the need for celiac plexus blockage. Then, patients received counseling for cardiovascular diseases, surgery, infection, internal medicine, anesthesia, oncology, and forensic medicine. If the counseling result was positive, patients were sent to the pain room for the celiac plexus release. An appropriate IV line was prepared for all patients and all of them received 500 CC of normal saline serum in one hour before entering the operating room. Then, they were asked to comfortably lie down on the bed in a prostrate position.

Before the celiac plexus blockage, P&D was performed for all patients through washing with green iodine in two stages. In the mediosefal approach, the anterior edge of L1 vertebra and then posterior aorta were caused to pass the aorta using the loss liquid method and the desired site was determined at the anterior aorta and posterior perineum by injecting a radiopaque agent under fluoroscopic guidance. Then, ozone was administered to the desired site using 0.05% Marcaine (Bupivacaine) plus 40mg of Depo-Medrol (methylprednisolone). After confirmation of analgesia by the patient, CPN was done by using 55 mg/l of ozone. Patients were transferred to the PACU in another bed and then the palliative care unit after their analgesia and hemodynamic status were stabilized. After 6 hours, patients were either discharged or sent to the origin (the oncology ward). In case of pain relapse in the PACU or the palliative care unit, all patients received a systemic analgesic regimen and then they were sent to the operating room after 24 hours for induction of analgesia with alcohol. Similar to the above-mentioned approach, neurolysis was done using 15 ml of 70% alcohol.

In the recovery unit, the severity of pain was measured using the VAS checklist at 2, 4, 12, and 24 hours after discharge from the PACU. In addition, the severity of pain was recorded weekly for up to three months. Those with intolerable pain in the oncology ward or at home intramuscularly received pethidine based on their body weight. The opioid dosage administered to patients was recorded as mg of morphine in the hours mentioned. The SF-36 was also completed for patients monthly for up to three months. If the patients were hospitalized, the SF-36 was completed for them by the assistant researcher in an in-person interview. For others, this questionnaire was completed through a telephone call by the assistant researcher.

The data were statistically analyzed in SPSS-19. Analysis of variance was used to determine the relationship between qualitative variables and compare the groups in the mean value of quantitative variables. In addition, chi-square test, Fisher's exact test, and the logistic regression analysis were employed for descriptive analysis of data. The level of significance was determined to be  $p < 0.05$ .

Ethical considerations were observed similar to other studies (Zomorodi et al., 2017; Movassaghi et al., 2015; Bakhshaei et al., 2010). The necessary permission was gotten from the Ethics Committee (Ethics no: 5/D/537795) and the relevant authorities. Moreover, the patients were briefed on the research objectives and procedure in a simple and understandable language and they were assured that they can leave the study at any stage.

## Results

The results showed that 70% of participants were male and the rest of them were female. The mean age and weight of participants were equal to  $62.20 \pm 8.61$  and  $73.79 \pm 5.73$ , respectively. The most common symptoms included constipation and fatigue, which were observed in 92.5% and 60% of patients, respectively. Table 1 shows the clinical information of patients based on the analysis of variance.

Table 1: Clinical information of patients

Age (year)	
Mean $\pm$ SD	62/20 $\pm$ 8/61
Minimum	45
Maximum	77
Gender (n, %)	
Male	(n=28- 70%)
Female	(n=12- 30%)
Weight (kg)	
Mean $\pm$ SD	73/97 $\pm$ 5/73
Minimum	60
Maximum	83
Symptoms	n( %)
Constipation	37(92/5%)
Fatigue	34(60%)
Fever	13(32/5%)
Anorexia	8(20%)
Insomnia	4(10%)
Dehydration	3(7/5%)
Jaundice	3(7/5%)
Nausea	2(5%)

The mean severity of pain in patients before the procedure was  $8.95 \pm 1.05$ , with a minimum of 6 out of 10 in one patient and a maximum of 10 out of 10 in 19 patients (47.5%). The mean quality of life was also equal to  $115.70 \pm 9.25$ .

Based on the type of drug received for celiac plexus blockage, it was shown that ozone reduced pain in only 16 patients (40%) and the other 24 patients (60%) needed to receive alcohol. In patients treated with ozone, the severity of pain on the first day after the procedure was significantly lower ( $p < 0.001$ ). By contrast, there was no significant change in the severity of pain on the first day after the procedure in patients who received alcohol. However, a significant reduction was observed in the severity of pain in these patients after the alcohol administration ( $p < 0.001$ ). The severity of pain on the first day after the drug administration based on the t-test are shown in Table 2.

Table 2: The severity of pain on the first day after drug administration

Time	Ozone	Alcohol
At the recovery	2/55 $\pm$ 1/33	3/03 $\pm$ 1/12
2 hours after the procedure	2/55 $\pm$ 1/37	3/65 $\pm$ 1/29
4 hours after the procedure	2/85 $\pm$ 1/56	3/98 $\pm$ 1/39
12 hours after the procedure	3/37 $\pm$ 1/62	4/12 $\pm$ 1/55
24 hours after the procedure	3/92 $\pm$ 1/81	4/31 $\pm$ 1/69
P-value	$P < 0/001$	$P < 0/001$

The mean severity of pain at regular weekly intervals before the procedure indicated that the severity of pain was lower in patients who received ozone for the celiac plexus blockage compared to those who were treated with alcohol. In addition, the difference in the severity of pain over time was significantly lower in patients who received ozone ( $p < 0.001$ ). However, such a significant difference was not observed in patients treated with alcohol ( $p = 0.029$ ). The results also demonstrated that there was no significant difference between the two groups at any time ( $p > 0.096$ ).

The mean morphine dosage administered to patients before the procedure was equal to  $26.50 \pm 7.69$ . The results indicated that there was no need for morphine administration at different hours of the first day after the procedure. In addition, no analgesic was prescribed for none of the groups during the study and there was a significant difference between before and after the celiac plexus blockage ( $p < 0.001$ ). Because of reduced severity of pain, none of the patients in the studied ward received opioids.

The quality of life also significantly improved following reduced severity of pain. However, this improvement over time was significantly higher in patients treated with ozone ( $p = 0.004$ ). The results also showed that there was no significant difference between the two groups at any time ( $p > 0.089$ ).

## Discussion

As the first time in Iran and one of the few ones in the world, the present study aimed to investigate the analgesic effects of ozone on celiac plexus neurolysis (CPN), reduced need for opioids, and quality of life in patients with pancreatic cancer. The study findings indicated that the severity of pain reduced more significantly in patients who received ozone compared to those treated with alcohol. In addition, the need for opioids minimized at different hours of the first day after the celiac plexus blockage. Following the reduction in the severity of pain and no need for opioids, there was a significant improvement in the quality of life of patients.

In a meta-analysis study conducted by Magalhaes *et al.* (2012), the results indicated positive effects of ozone on reduction of low back pain in patients with herniated disk. Tirelli *et al.* (2018) reported positive results of ozone therapy in reducing pain in cancer patients and stated that ozone reduces patients' fatigue without causing special complication. Bernardino *et al.* (2018) reviewed clinical trials about the effects of ozone on cancer patients and stated that ozone therapy has potentially positive effects on improvement of such patients. However, because of the paucity of studies on this subject, they recommended that further studies be conducted to investigate the exact effects of this substance (Clavo *et al.*, 2018).

Bernardino *et al.* (2015) studied the effects of ozone on rectal bleeding caused by radiotherapy in treatment of prostate cancer and reported that ozone can reduce rectal bleeding in such patients. However, more studies are needed in this regard (Clavo *et al.*, 2015). Tirelli *et al.* (2018) investigated application of ozone therapy for patients with fibromyalgia and concluded that ozone has positive effects on such patients without causing special complications.

Recent clinical trials on the effects of ozone therapy have revealed the beneficial effects and few side effects of ozone. However, since limited studies have been on conducted on human samples in this regard, researchers believe that is necessary to conduct more studies on this subject with long-term follow-ups.

### Research limitations

One limitations of this study was the shortage of time that did not allow the authors to conduct long-term investigations on the severity of pain and side effects of ozone. Therefore, it is recommended to conduct longer studies without the limitations of this study.

## Conclusion

As a new medical treatment for celiac plexus blockage in patients with pancreatic cancer, ozone therapy was shown effective in reducing severity of pain and need for opioids and other analgesics and improving quality of life.

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