

## Long-Term Improvement in Refractory Headache Following Ozone Therapy

Bernardino Clavo, MD, PhD,<sup>1,2,3</sup> Norberto Santana-Rodriguez, MD, PhD,<sup>2</sup> Dominga Gutierrez, RN,<sup>2,3</sup>  
Juan C. Lopez, MD,<sup>4</sup> Gerardo Suarez, RN,<sup>2,3</sup> Laura Lopez, RN,<sup>2,3</sup>  
Francisco Robaina, MD, PhD,<sup>1</sup> and Velio Bocci, MD, PhD<sup>5</sup>

### Abstract

**Background:** Headache afflicts approximately 10%–15% of the general population. Mixed results are obtained from various therapies, usually drugs, but also oxygen inhalation, behavioral psychology, physical therapy, and peripheral or central neurostimulation. When refractory to treatment, it has severe impact on quality of life.

**Objectives/subjects:** Five (5) patients are presented who had suffered from severe/persistent headache refractory to standard management (including 5-HT<sub>1</sub> agonist triptan drugs) and were treated with ozone therapy.

**Interventions:** Ozone administration was by major autohemotherapy. The procedure involved venous blood drawn into a sterile single-use glass bottle containing anticoagulant, gently mixed with an equal volume of O<sub>3</sub>/O<sub>2</sub> gas mixture (prefiltered through a sterile 0.20- $\mu$ m filter) and slowly reinfused back into the donor patient via the antecubital vein.

**Outcome measures:** The analyzed parameters were analgesia requirements, days of sick leave due to headache, number of headache events, and pain intensity according to the visual analogue scale (VAS); these recorded at three time points: pre-ozone therapy, post-ozone therapy, and before the last follow-up (mean: 64.6  $\pm$  36.8 months).

**Results:** The number of headache episodes pretreatment ( $n=80$ ; range 5–200) was significantly decreased during the first 6 months post-treatment ( $n=0$ , range 0–1;  $p=0.042$ ) and over the 6 months before the last follow-up visit ( $n=1$ , range 0–2;  $p=0.043$ ). The corresponding VAS scores were 8.7  $\pm$  0.8 pretreatment versus 1.1  $\pm$  2.5 the 6 months post-treatment ( $p=0.003$ ) and versus 3.1  $\pm$  3.3 the 6 months before last follow-up visit ( $p=0.036$ ).

**Conclusions:** Ozone therapy decreased headache episodes and pain severity over a protracted period. This novel approach is effective and merits further research.

### Introduction

HEADACHE AFFLICTS APPROXIMATELY 10%–15% of the general population. Migraine is a frequent type of primary headache. When chronic or severe, headache has high social impact related to direct and indirect financial costs (sick leave and loss of productivity) and is associated with decreased quality of life.<sup>1</sup> Concerning pathophysiological explanations of migraine, several authors have suggested that migraine results from a spreading depression of cortical electrical activity with an increased blood flow and activation of trigeminal meningeal afferents. Brainstem dysfunction, or alterations in the neurotransmitter systems, may also be a relevant factor in the evolution of a migraine.<sup>2,3</sup> Other studies

have presented data indicating that migraine is a genetically transmitted syndrome.<sup>4</sup> Several treatments have shown benefit in the relief of pain, but the benefits that accrue and the reduced frequency of attack are often not very substantial. Hence, prevention strategies are important components of therapy aimed at reducing the attack frequency and severity. Several drugs have been evaluated for use in the treatment (or prevention) of headache<sup>2,3</sup> as well as nonpharmacological treatments,<sup>5–7</sup> all with varying degrees of success.

The use of ozonated major autohemotherapy (m-AHT) in headache has not been thoroughly investigated, to date. However, the increasing use of ozone therapy in different pain syndromes has been supported by a recent meta-analysis in disc herniation.<sup>8</sup> In 1997, ozone therapy was

<sup>1</sup>Chronic Pain Unit, <sup>2</sup>Research Unit, <sup>3</sup>Departments of Radiation Oncology and <sup>4</sup>Neurology of the Dr. Negrin University Hospital, Las Palmas, Spain.

<sup>5</sup>Department of Physiology, University of Siena, Siena, Italy.

introduced in our Chronic Pain Unit (CPU) as a complementary therapy or as a palliative approach in the management of ischemia-related syndromes<sup>9-11</sup> and pain.<sup>12</sup> Currently, the authors are enrolling patients in a randomized clinical trial to compare ozone therapy against standard treatment (microdiscectomy) to evaluate pain reduction in patients with disc herniation (ClinicalTrials.gov Identifier: NCT00566007). This present report highlights preliminary experience in a small group of patients with severe, refractory headache.

## Methods

Between April 2001 and March 2007, 5 patients with a diagnosis of severe headache that was resistant to standard treatment were referred to the authors' CPU. In all cases, patients and/or referral physician requested ozone therapy in this CPU. This therapy is used in the authors' hospital for complementary and palliative pain management. The procedures are in accordance with the Helsinki Declaration of 1975, with specific Ethical Committee approval being obtained for specific clinical studies. Ozone therapy (O<sub>3</sub>T) was administered to these patients as a preliminary protocol on compassionate grounds, and patients provided informed written consent to the therapy.

The patients (3 female and 2 male; age 44±11 years) had suffered persistent headache for 21±11 years. Headache was classified according to the Headache Classification Committee of the International Headache Society.<sup>13</sup> All had been under previous management by neurologists or specialists in internal medicine, without much success. Treatment had included 5-HT<sub>1</sub> agonist triptan drugs as well as standard analgesia in all the patients. Prophylaxis had also been used unsuccessfully (with verapamil in patient 2 and with  $\beta$ -blockers in patient 5). The severity of headache had been such that extensive periods of sick leave had been taken during the year prior to ozone therapy (90, 15, and 113 days for patients 2, 4, and 5, respectively). Patient's data are summarized in Table 1.

The following data were recorded pre- and post-O<sub>3</sub>T: requirements for analgesia and 5-HT<sub>1</sub> agonist triptan drugs; days of sick leave due to headache; number of headache events "over the 1 month" and "over the 6 months" pre-O<sub>3</sub>T, post-O<sub>3</sub>T, and before the last follow-up; pain intensity according to the visual analogue scale (VAS). Periods of assessment during study are depicted in Figure 1.

The ozonated m-AHT procedure involves venous blood (220–300 mL) drawn into a sterile single-use glass bottle containing heparin (25 IU/mL per mL of blood). The blood is mixed with an equal volume of O<sub>3</sub>/O<sub>2</sub> gas mixture (pre-filtered through a sterile 0.20- $\mu$ m filter) at progressively increasing O<sub>3</sub>/O<sub>2</sub> concentrations from 30 to 60  $\mu$ g/mL per mL of blood. After gentle mixing (approximately 5 minutes), the blood is slowly re-infused back into the patient via the antecubital vein. The O<sub>3</sub>/O<sub>2</sub> (4%/96%) gas mixture is prepared from clinical-grade oxygen using medical ozone generators.<sup>14,15</sup> Initially, the m-AHT was scheduled for 2 sessions/week. When there was clinical improvement, the sessions were progressively reduced to 1 session/week, then 2 sessions/month and, finally, 1 session/month for 2–3 additional months.

The SPSS® software package (version 15) was used for all statistical analyses. Variables with normal distributions are

presented as mean±standard deviation and non-normally distributed variables as median and range. Comparisons of differences were with the two-sided paired *t*-test (VAS variable) or two-sided Wilcoxon test for "events" or "days off work." The  $\chi^2$  test was used to analyze categorical variables such as 5-HT<sub>1</sub> agonist triptan drug use. Statistical significance was set at  $p < 0.05$ .

## Results

Mean follow-up post-O<sub>3</sub>T was 64.6±36.8 months. During the follow-up period, no patient sought absence from work (sick leave) because of headache, nor was there any 5-HT<sub>1</sub> agonist (triptan drugs) prescription solicited from the attending physician ( $p = 0.011$ ). Standard analgesia was sufficient to control any new episodes of headache. The mean time-lapse to a debilitating headache episode (similar to pre-O<sub>3</sub>T) was 32.6±27 months. Individual data are summarized in Table 1.

Pre-O<sub>3</sub>T, the median number of severe headache episodes over a 1-month period was 20 (range 2–60) and over a 6-month period was 80 (range 5–200). Post-O<sub>3</sub>T, these rates were significantly reduced at 1 month post-treatment (0 events, range 0–0;  $p = 0.042$ ) and at 6 months post-treatment (median 0, range 0–1;  $p = 0.042$ ). Before the last follow-up the median rate for 1 month was 0 (range 0–1;  $p = 0.043$ ) and for 6 months was 1 (range 0–2;  $p = 0.043$ ). Pain intensity assessed by the VAS pre- and 6 months post-treatment was significantly reduced (8.7±0.8 versus 1.1±2.5;  $p = 0.003$ ). This control was maintained even during the 6 months before the last follow-up (3.1±3.3;  $p = 0.036$ ). Further details of pain intensity data distribution are depicted in Figure 2.

The mean number of O<sub>3</sub>T sessions was 27±16. Mean number of months under ozone treatment was 8±5.7. No adverse effects were observed with m-AHT except ecchymosis at the site of injection. Conversely, all patients described a feeling of well-being postprocedure.<sup>16</sup>

## Discussion

Migraine is a disorder with a complex pathogenesis. It is often refractory to treatment and has an adverse impact on the patient's quality of life.<sup>1</sup> The group of patients in this study had suffered severe persistent headache, of high-intensity pain and high frequency of episodes despite the systematic use of 5-HT<sub>1</sub> agonist triptan drugs, analgesics, and even prophylaxis with verapamil (patient 2) and treatment with  $\beta$ -blockers (patient 5). Following the m-AHT, and over long-term follow-up, the frequency of headache episodes was significantly reduced, as was the pain intensity experienced. Patients no longer required 5-HT<sub>1</sub> agonist triptan drugs, nor did they solicit leave to be absent from work. Although with respect to sick leave the differences were not statistically significant, of note is that 3 of the 5 patients (60%) required sick leave secondary to headache during the year before ozone therapy and no sick leave was needed during the 5 years of follow-up.

To the best of the authors' knowledge, this is the first report indicating the efficacy of ozonated m-AHT in the management of headache, albeit the potential role as a preventive therapy had been reported as early as 1991.<sup>17</sup> The biologic effects of ozone in blood, and the consequent therapeutic effects, need some explanation. While oxygen

TABLE 1. PATIENT CHARACTERISTICS AND OUTCOMES OF O<sub>3</sub> TREATMENT

	Patient no.					p <sup>a</sup>
	1	2	3	4	5	
Age	33	55	54	47	31	
Gender	Female	Male	Female	Female	Male	
Headache classification <sup>b</sup>	Migraine without aura	Cluster headache	Migraine without aura	Migraine without aura	Migraine without aura	
Family history of headache	Yes	No	Yes	Yes	No	
Years with headache	26	25	26	25	1	
Events during 1st month	20	60	2	3	60	
	0	0	0	0	0	
Pre-O <sub>3</sub>	1	0	0	0	0	0.042
Post-O <sub>3</sub>	80	120	5	15	200	0.042
Events over 6 months	0	0	0	1	0	
Pre-O <sub>3</sub>	2	0	1	2	0	0.043
Post-O <sub>3</sub>	8	10	8	8.5	9	0.043
VAS (0–10) worst event during 6 months	0	0	0	5.5	0	0.003
Pre-O <sub>3</sub>	3.5	0	8	4	0	0.036
Post-O <sub>3</sub>	0	90	0	15	113	
Sick leave due to headache, days	0	0	0	0	0	0.109
During follow-up	Yes	Yes	Yes	Yes	Yes	
Pre-O <sub>3</sub>	No	No	No	No	No	0.011
During follow-up	78	24	24	6	No events	
5-HT <sub>1</sub> agonist triptan drugs required	8	13	32	36	46 <sup>c</sup>	
Months up to the first severe episode	1	4	15	9	12 <sup>c</sup>	
Number of O <sub>3</sub> sessions	121	82	43	46	31 <sup>c</sup>	
Months with O <sub>3</sub>						
Follow-up, months post-O <sub>3</sub>						

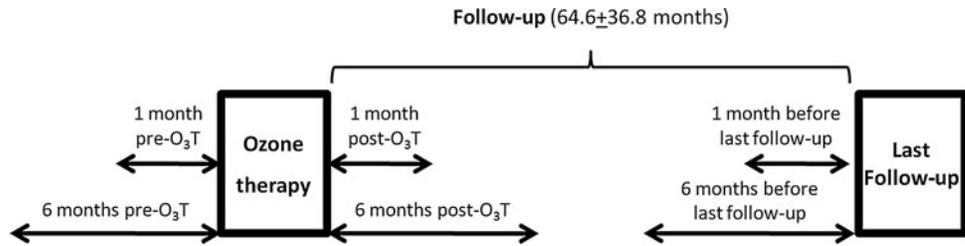
<sup>a</sup>p-values are relative to pre-O<sub>3</sub> values.

<sup>b</sup>According to Headache Classification Committee of the International Headache Society (Ref #13).

<sup>c</sup>Patient 5 was treated with ozone therapy at two different times: for 8 months initially and, after a period of 9 months, repeat treatment for a period of 4 months. In this patient, data in the Table summarizes the complete ozone therapy treatment (both treatment cycles together). The data "post-O<sub>3</sub>" represent the values at the end of the second ozone therapy treatment.

VAS, visual analogue scale.

**FIG. 1.** Periods of assessment during study. Number of headache episodes and pain intensity were recorded as occurring "over 1 month" and "over 6 months" in three periods: pre-ozone therapy (O<sub>3</sub>T), post-O<sub>3</sub>T, and before the last follow-up.

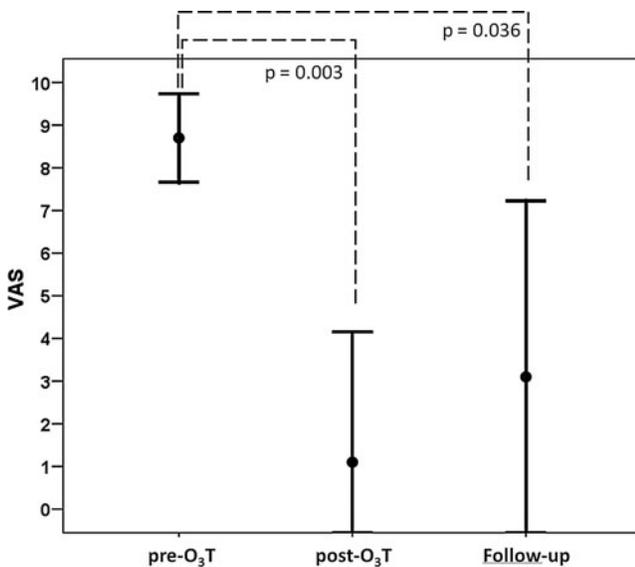


hyperoxygenates the blood *in vitro*, ozone dissolves very rapidly in the aqueous environment of plasma where it is partly quenched by hydrophilic antioxidants (e.g., ascorbic acid, uric acid, and reduced glutathione) and the bulk of the ozone reacts with polyunsaturated fatty acids bound to albumin. This critical reaction is extremely rapid and generates two essential ozone messengers: 1 mol of hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) and 2 mol of alkenals, of which the major constituent is 4-hydroxynonenal (4-HNE). H<sub>2</sub>O<sub>2</sub>, at concentrations below 30 μmol, acts as an anionized molecule. It enters into all blood cells and triggers a number of biochemical reactions that can have therapeutic value. Submicromolar amounts of alkenals form adducts with the cysteine-34 of albumin or with any of the other 11 nucleophilic groups present in albumin. Indeed, this protein complex is the main antioxidant and protective molecule in plasma.<sup>15</sup> After 5 minutes of *ex vivo* mixing, the blood is infused slowly into the donor patient and will proceed to exert several actions, one of the most important of which is the vascular effect. Ozone can

induce regulation of cerebral blood flow<sup>10,11</sup> and oxygen delivery in ischemic tissues<sup>9</sup> partly due to a regulation of 2,3-diphosphoglycerate (2,3-DPG) in erythrocytes, and the local release of nitric oxide (NO) and carbon monoxide (CO) by the endothelium.<sup>18</sup> Other relevant effects of ozonated blood are (1) a broad immuno-enhancement due to release of cytokines from lymphocytes; (2) an upregulation of intracellular antioxidant enzymes due to cell stimulation by 4-HNE, which is able to reduce chronic oxidative stress; and (3) a feeling of well-being<sup>16</sup> that is due, most likely, to release of endorphins. Overall, ozonated m-AHT acts as a biologic response modifier. An extensive review of this topic, including vascular effects, has been published recently.<sup>15</sup>

The mechanisms of action of ozone for the observed effect in persistent migraine are unknown. However, based on the biologic effects highlighted above, the hypothesis is that O<sub>3</sub> could enhance self-regulatory functions in the cortical electrical activity and the neurotransmitter systems as well as in the metabolism of sensitive brain tissues. Glutamate is an important excitatory neurotransmitter, and it is implicated in spreading cortical depression, trigeminovascular activation, and central sensitization. Glutamate receptor subtype antagonists seem effective in preclinical as well as clinical models of migraine.<sup>3,19</sup> The protective effect of O<sub>3</sub> against oxidative stress has been related to the enhancement of A1 adenosine receptors in rat models,<sup>20</sup> and the activation of these receptors can reduce glutamate release. Conversely, as demonstrated by positron emission tomography (PET) studies, chronic migraine has been associated with brain hypometabolism in several cerebral areas such as insula, thalamus, anterior cingulate, and parietal.<sup>3</sup> In addition to regulation of blood flow and oxygenation by O<sub>3</sub>T described by ourselves and other authors, we recently described a patient with brain ischemia and hypometabolism with clinical and radiological improvement post-O<sub>3</sub>T (assessed by PET and single photon emission computed tomography),<sup>11</sup> which extends the potential usefulness of this therapy in patients with chronic migraine.

However, in the blood (where there are antioxidant systems present), ozone administered at appropriate concentrations will produce a weak, and controlled, pro-oxidant status. This in turn will induce an adaptive enhancement of antioxidant mechanisms. Such a response has been well documented in animal models and includes the protection against free-radical damage in renal<sup>21</sup> and hepatic tissue.<sup>22,23</sup> The effect has been documented in patients with heart<sup>24</sup> and vascular diseases.<sup>15</sup> For pain treatment, the most relevant example is the use of O<sub>3</sub>T in disc herniation. A recent meta-analysis of randomized clinical trials has shown a clinical effect similar to that obtained with surgery, but with significantly lower toxicity.<sup>8</sup> Of note is that most of the reported



**FIG. 2.** Evolution of pain intensity. The figure shows the maximum pain intensity assessed by the visual analogue scale (VAS) during the 6 months before ozone therapy (pre-O<sub>3</sub>T), during the 6 months after ozone therapy (post-O<sub>3</sub>T), and during the 6 months before the last follow-up (Follow-up). The values are presented as mean (circles) and the 95% confidence intervals. There was a significant decrease in pain intensity ( $p=0.003$ ) over the 6 months post-O<sub>3</sub>T, and this was maintained even up to the 6 months before the last follow-up ( $p=0.036$ ). Mean follow-up was  $64.6 \pm 36.8$  months.

serious side-effects with ozone therapy have been secondary to the technical–medical procedure and not a function of the O<sub>3</sub> administration *per se*.<sup>25</sup>

Usually, the follow-up of patients with headache is performed by the neurologist. The available drugs for treatment include ergot alkaloids, triptan drugs affecting 5-HT<sub>1</sub> receptors. Drugs for prevention include serotonergic or  $\beta$ -adrenergic antagonists, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, cortisone, botulinum toxin type A, and anti-epileptics.<sup>2</sup> Nonpharmacological treatments can include behavioral psychology, psychosomatic medicine, physical therapy, and acupuncture.<sup>5</sup> Finally, only the most refractory cases are referred to a CPU, where interventional approaches including peripheral<sup>6</sup> or central<sup>7</sup> neurostimulation are being increasingly favored. Our patients came to us as, perhaps, the last resort before invasive procedures, because they had suffered headaches despite several years of pharmacotherapy.

There are several limitations to this report. It is an open-label case study that involved only 5 patients. Not all were homogeneous with respect to type of headache or previous treatment, although all of them had used at least standard analgesia 5-HT<sub>1</sub> agonist triptan drugs. Prophylaxis with  $\beta$ -adrenergic antagonists was documented only in 2 patients. There was no “control group” for the study, and, potentially, the spontaneous resolution of the headache and/or placebo effects cannot be discounted. However, the number and intensity of episodes recorded during the 6 months pre-O<sub>3</sub>T were high in our patients, with 3 patients requiring leave-of-absence from the workplace due to the headaches. It would appear unlikely that the clinically relevant decrease in number and intensity of episodes would have been due to the natural evolution of the headache, or to the placebo effect. It would appear even more unlikely that any placebo effect would be maintained over the 5 years of follow-up in the patients in the present study. Nevertheless, further research is warranted to explore these findings.

## Conclusions

This study shows that, following ozone therapy, a long-term, clinically relevant reduction in the number and severity of headache episodes accrues. It is hoped that the encouraging results will elicit interest and stimulate other clinical investigators to explore and extend this study’s findings in a randomized, double-blind, placebo-controlled, multicentered, clinical trial in order to validate this treatment.

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## Disclosure Statement

No competing financial interests exist.

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Address correspondence to:  
*Bernardino Clavo, MD, PhD*  
*Department of Radiation Oncology*  
*Chronic Pain Unit and Research Unit*  
*Dr. Negrin University Hospital*  
*C/ Barranco la Ballena s/n*  
*35010 Las Palmas (Canary Islands)*  
*Spain*

*E-mail: bernardinoclavo@gmail.com*

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