

Intradiscal Ozone Therapy in Lumbar Discogenic Pain

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Abstract

Introduction: Lower back pain is one of the health problems that most afflict adults worldwide. It is estimated between 40-70% of adult population seek medical help at some point in their lives. Because the existence of a large number of patients who do not respond to conventional pharmacological treatment, percutaneous procedures with intradiscal ozone are beginning to be used, obtaining good results.

Objectives: To evaluate intradiscal ozone therapy as an effective treatment of discogenic pain.

Methods: A retrospective and cross-sectional study was conducted at the Institute of Neurology and Neurosurgery in Cuba where 99 patients with discogenic pain undergoing percutaneous therapy with intradiscal ozone were analyzed using Oswestry Disability Index(ODI) and Visual Analog Scale(VAS), between years 2015 and 2019.

Results: The mean age of the patients was 49 years, being the most prevalent pain in the male sex and finding a moderate disability when patients arrived at the consultation. 66.6% of patients were treated in 3 sections with ozone concentrations that oscillated between 12% and 43%. The number of treatment sections or ozone concentrations were not concluding for the outcome. Three months after intradiscal ozone treatment, there was improvement in VAS and ODI $Z=5.511$; $Z=5.303$ respectively.

Conclusions: Percutaneous therapy with intradiscal ozone is an effective and safe method in the treatment of discogenic pain. Evident improvement was found after this therapy in the studied population.

Keywords: discogenic pain, intradiscal ozone therapy

Introduction

Lower back pain, low back pain or lumbosacral pain is one of the health problems that most afflict adults worldwide, with an estimated 40-70% seeking medical help at some point in their lives and that the severity of the pain will often continue to increase [1].

In other reports it is estimated that more than 30% of the population presents low back pain with different degrees of intensity, so the pain is not necessarily in all patients, reason for consultation [2, 3, 4]. Patient reports by age group vary by country. However, those who most seek medical help are between the ages of 20 and 34 years old. Adolescents figures as high as 40.9% are reported in Turkey and 30% in Germany, while in Spain in a survey conducted in Mallorca with a total of 16,394 participants, it was found that 50.9% of boys and 69.3% of girls had had low back pain at some point in their lives [1, 5].

The serious economic problem that it currently represents can be perceived if we consider that the expenses generated in care related to this pathology reach 50 billion dollars annually. Moreover, low back pain is considered the most frequent cause of absenteeism in the population under 45 years of age: it is a common condition in all countries. Some publications show that 50% of workers suffer from low back pain every year and that 80-90% of adults will suffer from it sometime in their lives. According to updated information, low back pain is among the first five diagnoses established in the consultation on the first level of care [6].

In Cuba, an analysis of statistical care records found that of the 501 diagnoses recorded between 1991 and 2003, 303 (60.4%) they had pain as their main or important symptom. In that period, low back pain was the most attended problem [6, 7].

In 2000, a study was conducted on epidemiological aspects of low back pain of somatic and mechanical causes in cimeq hospital workers, finding a prevalence of 70.6%. In a survey conducted in three municipalities of

Havana, which included a sample of 1179 people over the age of 15, it was found that among a 78-81% manifested lower back pain at some point in their lives, predominating the female sex. The age group was 31-40 years and the occupations most affected were technicians and workers. The working days lost in the most enduring crises were between 22 days and a month (54%) [6].

Low back pain and sciatica, in all its clinical forms and stages, are among the diagnostic and therapeutic challenges of greatest magnitude and importance [8]. In most of patients, low back pain does not come from a herniated disc, but from undue overloads of the ligaments and paravertebral muscles, chronic inflammatory and degenerative vertebral processes. When patients report that the pain radiates to the lower limb, in many cases it is about radicular symptoms due to compression or irritation. Because of this are derived the concepts of facet pain, discogenic pain and radicular pain; to focus treatment on the cause of pain and not just analgesia [9, 10].

Facet pain is a common consultation pain. Its origin is settled in the rear arch and its characteristics are explained by the innervation of the region. The segmental nerve root has a posterior branch that innervates the articular and spinous processes, as well as a synovial ramus that innervates the intervertebral disc. The degenerative phenomenon affecting the triarticular structure compromises the intervertebral space and the posterior arch. Possibly the loss of the height of the intervertebral space generates a microinstability and biomechanical changes in the posterior arch, which produces a destabilization and inflammatory changes of the zygoapophyseal joints that will present an osteoarthritic phenomenon on an arthrosic basis. The discogenic pain is due to a degenerative process of disc with migration of nuclear material through the fissure of the ring. It produces pain through chemical mediators by stimulating adjacent ligamentous structures. The invasion of neofunctional vessels and granulatory tissue into the damaged disc is accompanied by nociceptors, which will result in a discogen-type pain that is easily evaluated with contrasted Magnetic Resonance Imaging (MRI). It should be mentioned that not all imaging alterations are related to pain. High-signal foci of the fibrous ring are extremely

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common in the normal population. Only some foci are associated with pain, those that compromise the medial third would have a clinical significance. Radicular pain is the most well-known and most sought after pain, however, it is not the most common. Fundamentally it is triggered by stimulation of chemical mediators and in the case of compressions, by inflammation, edema and neural ischemia [10].

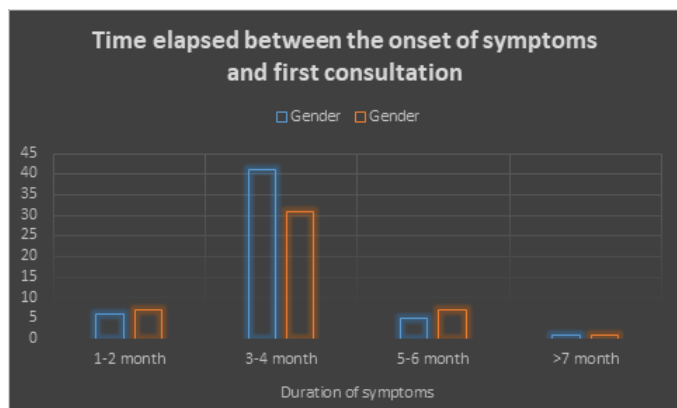


Figure 1: Symptoms and time

Within minimally invasive therapies, intradiscal ozone therapy has proven useful in the treatment of herniated disc (HD) pain. This technique consists of administering ozone inside the nucleus pulposus, with the aim of reducing the volume of the intervertebral disc and therefore the protrusion or symptomatic disc herniation [11, 12, 13, 14].

The efficacy of ozone (O₃) in the treatment of HD has been demonstrated in several studies [16]. In the American Journal of Neuroradiology, a randomized study was published in 306 patients and the analgesic effect of ozone was demonstrated in a percentage close to 80% [14].

Discogenic pain is one of the great diagnostic and therapeutic challenges faced by neurosurgeons and other specialists. Over the past few decades, treatment modalities have changed, and surgical treatment for degenerative disc disease has been increasing. However, reoperation rates reach between 12-19% of patients at 5 years of surgery. Pseudoarthrosis, degeneration of the adjacent segment and non-resolution of low back pain are reported as the most frequent complications. It is also recommended to design a study that compares intradiscal ozone therapy, intersomatic fusion and total disc replacement, evaluating the patient's recovery time, hospital stay, cost, relief of symptoms and complications. Intervertebral fusion necessarily sacrifices the motility of the segment, which results in increased stress on adjacent levels with the consequent degeneration of the same. For these reasons, artificial devices were developed to perform a total replacement of the intervertebral disc and replace it with these devices that allow motility to the segment. In many reports it is found as an even higher reference to lumbar interbody fusion procedures. The goal of this technique as an alternative to fusion, is to relieve pain and maintain range of motion to restore stability [15, 16, 17]. In a controlled study published in Spine where the results of 5 years of this technique for the degeneration of a single segment are shown, it is concluded that it is a safe procedure and with evident improvement in the Oswestry Scale after treatment. In addition, no degeneration of the adjacent segment is observed [18]. So far only three generations of devices have been approved for total replacement of the disc by the Food and Drug Administration, the Type Charité Artificial Disc in 2004, the type ProDisc-L in 2006 and a last generation of Implants Asculap, activL. Clinical and biomechanical studies show that the use of the Asculap activL system improves patient outcomes when compared to previous versions [18, 19, 20]. In a meta-analysis that included 4 studies comparing total disc replacement with intervertebral fusion, no improvement was found in lower back pain. If improvement in the Oswestry scale was found in patients who underwent total disc replacement above those who underwent lumbar intersomatic fusion [21].

The development of a peptide that interferes in the NF- κ B route that is responsible for the degeneration of the intervertebral disc, has been developed.

The NEMO-Binding domain peptide (NBD) prototype has been tested in vitro and in animal models, yielding promising results by reducing interleukins 1 β and IL-6. These results are corroborated by checking with MRI images to attenuate the dehydration response of the intervertebral disc after administered the NBD [22].

Research's justification

Low back pain is a condition that affects a large part of the adolescent and adult population. One of the most common causes of it is discogenic pain, which is usually addressed with conservative medical treatment. This focuses only on achieving the patient's analgesia, but without really treating the cause of it; degeneration of the intervertebral disc. This results in us finding patients who evolve due to crises of up to more than 10 years, requesting medical help for an analgesic and anti-inflammatory therapy that relieves pain. These same patients after a while arrive at consultation with a change in the characteristics of their pain, from one of discogenic type to one radicular by herniation of the disc material; surgical treatment is then imposed after years of analgesic therapy. The development of percutaneous therapies to access the intervertebral disc and produce a lysis of it either by radiofrequency or with ozone in degenerative disc pathology in general, reports good results in Europe. Microsurgical fusion techniques for discogenic pain report 5-year reoperation rates in the United States. The total removal of the disc and its replacement with devices that maintain the full range of motion of the segment reports very encouraging results, but it is an expensive therapy for countries with limited economic resources. Intradiscal ozone therapy has been developed for 6 years in the INN so it is proposed to carry out a study that evaluates this technique on lumbar discogenic pain.

Scientific problem: Analgesic and anti-inflammatory treatment on discogenic pain relieves the patient for periods of time that are shortened as the degeneration of the intervertebral disc continues, since the consequence is treated and not the cause. Intradiscal ozone therapy could be effective in discogenic pain, decreasing the number of annual consultations in treated patients and thus delaying the appearance of herniated discs that present as a radicular syndrome.

Objective

To evaluate intradiscal ozone therapy as an effective treatment of discogenic pain.

Ozone Action Mechanisms

The mechanism of action by which ozone manages to decrease the volume of the disk is due to the output of water molecules and the cellular degeneration of the matrix through the oxidation of proteoglycans, which is replaced by fibrous tissue. This conditions a loss of volume and less venous compression that produces a reduction in blood stasis, improving local microcirculation and increasing the supply of oxygen to the nerve root, which decreases neuropathic pain. This has been studied in animals by Steppan et al. in 2009, observing histological changes and in the concentration of cytokines at 2 and 28 days after ozone injection. In addition, Iliakis et al., in 2001, justified the analgesic and anti-inflammatory effect of ozone by inhibiting the synthesis of prostaglandins and bradykinin, stimulating immunosuppressive cytokines (IL-10) or growth transforming factor -1, and inhibition of the synthesis of inflammatory cytokines such as IL-1, IL-2, IL-8, IL-12, IL-15, interferon or tumor necrosis factor [23, 24, 25].

Methods

A retrospective, analytical and observational cross-sectional study was conducted in the Neurosurgery service of the Institute of Neurology and Neurosurgery of Cuba Dr. José Rafael Estrada González in the period from January 2015 to January 2019. The universe of the study consisted of patients with lower back pain who attended the neurosurgery consultation of the INN. The sample was composed of 99 patients from the study universe, who presented low back pain resistant to pharmacological treatment with semiological characteristics of discogenic pain. Those who had a radicular

syndrome or extruded disc herniation in the imaging studies were excluded from the study. Each patient was given VAS. and ODI pretreatment and 3 months after treatment with intradiscal ozone. The number of sick spaces of each patient was also taken into account, and the procedure was practiced in the most affected segment, defining the same one by which the most loss of height presented. The analysis of the variables to obtain the results was performed in the statistical program SPSS-19.

Results and Discussion

According to age, gender and race, most of the patients were aged between 41 and 60 years for a frequency of 66 patients accumulating 83.8% being the average age of 49 years and predominating the male sex with a total of 53 patients, representing 53.5%. Similar results were obtained in their investigations Torres LM, Terrero MJ [14], and Kieran Murphy et al [17] Anuj Bhatia et al [52]. In the study conducted by Torres LM, Terrero MJ the age of the patients was between 26 and 77 years with an average of 52 ± 7 and also predominated the male sex. On the other hand, the clinical study conducted by Anuj Bhatia, of the 39 cases operated by ozone therapy were between 20 and 64 years of age. However, in Sweden figures are reported, for the diagnosis of low back pain, of 254 patients per 10000 women and 200 per 10000 men; reaching a higher prevalence in the UK: 500 and 300 per 10000 women and men respectively, A systematic review of low back pain behaviour showed that the average prevalence of low back pain was higher in women; individually in age ranges between 40 and 80 years [1,12], in turn, it is proposed that it may be influenced by psychosocial factors, as well as by the hormonal process of the menstrual cycle that makes women more sensitive to pain[8].

Regarding skin color, 77 patients were white and although no study evaluating this variable was found in the literature, it is considered that this behavior is due to the fact that in Cuba the population is mostly white (64.1%) and the structure by skin color varies markedly by province. Thus, in the province of Havana, the population with white skin color is larger and represents 58.4% [26].

Table 1: Patients age

Age	Frecuency	Percentage %
20-40	17	17,2
41-60	66	66,7
>61	16	16,2
Total	99	100,0

Table 2: Patients Gender

Gender	Frecuency	Percentage %
male	53	53,5
female	46	46,5
Total	99	100,0

According to the relationship that exists between the time of evolution of symptoms with respect to gender and the number of sick intervertebral spaces. The most frequent time in which patients attended the consultation ranged between 3 and 4 months after starting discogenic pain, being the majority of male gender and only two patients attended the consultation after 7 months of pain evolution. Curious fact we find in table 3 where we see that of the 99 patients who attended the consultation with discogenic pain, 98 presented 3 sick intervertebral spaces. This is undoubtedly related to the degeneration suffered by the nucleus pulposus over time, since most of the patients ranged in an age of 41-60 years of age, a group that is also active. In a study published in Spine, the imaging changes associated with low back pain were evaluated,

98% had osteophytes and 67% had loss of height of the intervertebral space, however, there was no statistical significance in association between low back pain and the presence of osteophytes. Loss of height of the intervertebral space was associated with low back pain [26].

Table 3: Relationship between the duration of symptoms and the number of sick spaces

Relationship between the duration of symptoms and the number of sick spaces		Duration of sintoms			
		1-2 month Patients	3-4 month Patients	5-6 month Patients	>7 month Patients
Diseased intervertebral spaces	2	0	1	0	0
	3	13	71	12	2

As for the intensity of pain according to the VAS, a study conducted by Borroto et al. found that the mean on the scale of VAS values before ozone treatment was 8.4 with a minimum of 7 and a maximum of 10 [27], finding very different values in our study, because the minimum was 3 points and the maximum was 10, with an average of 6.73.

64.6% of the patients arrived with a moderate disability to the consultation and 20.2% had a minimal disability. In a report of 10 cases published in the Spanish journal of pain, to which ozone annuloplasty was performed, initial mean values of 8.9, and 50.1, were found for VAS and Owestry disability index respectively [28], which means that these patients had a higher degree of disability and pain before treatment than those who attended a neurosurgery consultation for intradiscal ozone therapy in this study. 10, with an average of 6.73. Figure 4 better shows the relationship between the time of evolution of symptoms and disability according to the Owestry Disability Index score.

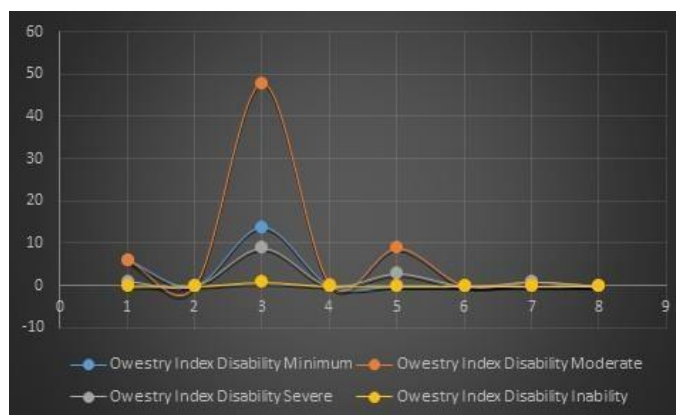


Figure 2: Relationship between the evolution of symptoms and disability

Regarding the concentration of ozone and the number of intervertebral spaces diseased, it was found that the most frequent ozone concentration used was 32% for a total of 53 patients, followed by a concentration of 43%. The minimum number of sessions performed in the patients was 1 and the maximum of 4, with the highest frequency being 3 sessions for the treatment of low back pain with intradiscal ozone.

Table 7 shows a comparison between pretreatment and posttreatment. A significantly higher average is found before treatment than that found after treatment with ozone. The range between maximum and minimum values after ozone therapy decreased considerably. This achieves a significant standard deviation and demonstrates the efficacy of the method for the treatment of discogenic pain.

Table 4: Relationship between the evolution of symptoms and VAS

Relationship between the evolution of symptoms and VAS		Duration of symptoms			
		1-2 month	3-4 month	5-6 month	>7 month
		Patients	Patients	Patients	Patients
VAS	3	0	1	1	0
	4	1	6	1	0
	5	4	13	1	1
	6	1	12	3	0
	7	3	15	1	1
	8	2	16	2	0
	9	0	3	0	0
	10	2	6	3	0

Table 5: Disability of patients treated according to ODI

Disability of patients treated according to ODI		Patients	%
Owestry Disability Index	Minimum	20	20,2%
	Moderate	64	64,6%
	Severe	14	14,1%
	Inability	1	1,0%

Table 6: Relationship between O3 concentration and number of sessions

Relationship between O3 concentration and number of sessions		Ozone concentrations							
		12	15	18	21	24	30	32	43
		Patients	Patients	Patients	Patients	Patients	Patients	Patients	Patients
Number of sessions	1	1	0	1	0	4	1	5	7
	2	0	0	1	0	1	0	10	4
	3	0	1	0	1	6	5	36	11
	4	0	0	0	1	1	0	2	0

Table 7: Comparison of VAS.

Comparison of VAS	N	Minimum	Maximum	Media	Desv. tip.
VAS pretreatment	99	3	10	6,73	1,806
VAS 3 month later	99	0	4	0,39	0,843
Valid N	99				

The VAS at 3 months of treatment reported a score of 0 in 80 of the 99 patients treated. Only one patient obtained a value of 4 points after treatment. In all groups according to ozone concentration there was improvement in discogenic pain, however there was great variability in the distribution of patients by each group, so it can not be asserted in this study that the concentration of ozone influences the results of treatment. Regarding the number of sessions, patients who were treated 3 times, 48 of them had 0 points in the VAS at three months and 11 patients reported 2 points. In the study conducted by Borroto et al. that evaluates intradiscal ozone therapy and compares it with other treatment modalities, it found that the mean VAS of all ozone treatments was 1.8 at three months. All therapies were effective by more than 88.06% after treatment. However, in the deep paravertebral that only reached 35.98% later and 39.63% at three months. The most effective technique according to the VAS scale, was intradiscal ozone therapy, followed by microdiscectomy, there were no statistically significant differences between any of the applications points in the VAS at three months and 11 patients reported 2 points [27]. Similar results were obtained in a study conducted in India where intradiscal ozone therapy is compared with ozone therapy plus radiofrequency thermocoagulation, being observed in both techniques a decrease in pain according to VAS by more

than 50% [29]. A meta-analysis carried out by Steppan et al. evaluating the effectiveness and safety of this technique also yields promising results, as significant differences were found between pretreatment and aftertreatment [30]. In the study by Casanova et al. which compares intradiscal ozone therapy, radiofrequency annuloplasty and radiofrequency annuloplasty plus intradiscal ozone therapy; it is shown that the latter yields more favorable results for pain relief. However, it is equally demonstrated that intradiscal ozone therapy is superior to radiofrequency annuloplasty [31].

According to the relationship of owestry disability index with the frequency of treatment sessions, it was found that most patients came to the consultation with moderate or severe disability, being treated with intradiscal ozone in three treatment sessions. Owestry's disability index at 3 months showed significant improvement. Of the 99 patients, only 4 reported moderate post-treatment disability, representing only 4.04%. No severe disability or disability was reported after intradiscal ozone therapy. If these results are closely observed, the number of sessions does not seem to significantly influence the improvement of symptoms because in the 4 groups it was reduced to a minimum disability, only in group three was where there was a greater number

of patients treated. In the research conducted by Das et. al, in a 2-year follow-up, it was confirmed that 65.17% of the patients, treated by intradiscal ozone therapy, presented an improvement in the visual analog scale of pain with a single session of intradiscal and periradicular ozone injection [32]. No other research was found to evaluate this variable, nor the concentration of ozone, so it will be necessary to design a study where these two variables are evaluated to clarify the importance of them.

The reduction of disability after ozone treatment was demonstrated when it was evaluated at three months of evolution, since before treatment only 11 patients presented a minimum disability index, 45 moderate, 12 severe and 1 with disability, the highest percentage being patients with moderate disability, for 45.5%. After treatment a marked improvement was observed, in fact, most of

the patients, 95.9%, were within the range of minimum disability. These results are corroborated by previous research [14,23,25,32,33,34,35,36] in which it is confirmed, in humans, that ozone improves 79.7% of treated patients and reduces at least one category of the modified Macnab pain test and improves functional capacity. This is because this therapy leads to the reduction of the size of the intervertebral disc by the action of a dehydration mechanism of the Extra Cellular Matrix and the Nucleus Pulposus [23]. This mechanism of dehydration is carried out through interactions with proteoglycans. In an experimental work in animals, it has been found that a drop of intradiscal ozone decreases by 0.3 ml the volume of the disc, since the proteins of the nucleus pulposus are reduced by one third and thus, the intradiscal pressure (10 psi) [14].

Table 7: Comparison of VAS.

Relationship of the pre- and post-treatment ODI and the number of sessions		Sessions' s number			
		1	2	3	4
		Patients	Patients	Patients	Patients
Owestry Disability Index	Minimum	11	6	3	0
	Moderate	7	9	45	3
	Severe	1	0	12	1
	Inability	0	1	0	0
Owestry Disability Index at 3 months	Minimum	18	15	58	4
	Moderate	1	1	2	0
	Severe	0	0	0	0
	Incapacidad	0	0	0	0

Wilcoxon's paired test showed a highly significant decrease in visual analog scale scores for pain and owestry disability index after application of intradiscal ozone therapy.

Table 9: Wilcoxon paired test

VAS	Z=5.511	p=0.0000	0
ODI	Z=5.303	p=0.0000	0

Treatment with intradiscal ozone is safe, taking into account that in 99.15% of the cases no complications were evident. Only one patient presented a vasovagal crisis during the procedure. This is corroborated by most studies conducted. In 2015, The Canadian Association of Radiologists Journal published a study confirming the results obtained in a meta-analysis of approximately 8,000 patients in which no adverse effects associated with ozone administration were evidenced. They concluded that the risk of complications associated with this procedure is 0.003%, much lower than that of conventional surgery [23].

Conclusion

The largest number of patients attending the consultation with discogenic pain have an evolution of approximately three months. If intradiscal treatment with ozone is performed, significant improvement is found at three months of both the pain and disability suffered by the patient. We cannot claim that the number of sessions and the concentration of ozone influence the results. It is an effective and safe procedure.

Recommendations

It is recommended to apply intradiscal ozone treatment to reduce clinical manifestations in those patients with discogenic pain refractory to drug treatment as an alternative to intersomatic fusion and total disc replacement. However, it is necessary to take into account the number of sessions to be applied in each case, as it could influence the result, as well as the concentration of ozone used. We suggest concentrations of 32% in 3 treatment sessions,

separated from each other by 21 days. It is also recommended to design a study that compares intradiscal ozone therapy, intersomatic fusion and total disc replacement, evaluating the patient's recovery time, hospital stay, cost, relief of symptoms and complications.

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