



## Review paper

# Review of intervertebral hernia disease treatment methodologies: Key emphasis on the oxygen-ozone therapy as a method with multifactorial influence

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## ABSTRACT

**Introduction:** Low back pain is one of the most common causes of short-term, and sometimes long-term, disability in the population younger than 45 years old. Approximately 60% to 80% of the population in developed countries experience back pain in various locations (neck, mid and lower back) at least once in their lifetime. Guidelines regarding back pain treatment are undergoing constant modifications and improvements. The relevance of dorsalgia as a significant medical problem and its management is shown by the increased number of recently published papers, which has tripled in the past several years (from 22% to 65%).

**Aim:** To analyze the most critical risk factors of the degenerative intervertebral disk disease, and to review the effectiveness of invasive and noninvasive methods of treatment of the lower back pain syndrome.

**Material and methods:** Recently published papers focusing on invasive and noninvasive treatments of low back pain syndrome.

**Results and discussion:** Surgical intervention as a single method of back pain treatment is indicated in a small number of cases. The risk of repeated surgeries for intravertebral disk herniation should be considered before any surgical intervention. A wide variety of treatment options allows to choose the most effective approach based on individual needs.

**Conclusions:** Conservative, noninvasive approach has shown to be an effective alternative for lower back pain and radiculopathy treatment. It has been determined that ozone therapy is an appropriate, relevant, and affordable treatment method for patients with vertebral degenerative changes and intravertebral disk diseases.

## 1. INTRODUCTION

Lower back pain is known to be one of the most common causes of short and long-term disability among young and middle-aged people; this syndrome occurs in 60–80% of the Europe population.<sup>1–3</sup> In Ukraine, dorsalgia accounts for nearly 76% of all medical visits and 72% of disability claims in the outpatient setting.<sup>4</sup> Recent statistical analysis show that about half of inpatient hospitalizations were connected to muscle-skeletal problems. Prevalence of chronic back pain in different age groups has a minor gender difference – 24% of men and 32% of women aged 20–64 years old.<sup>5,6</sup> In most cases, acute episodes of back pain resolve within 6 weeks. However, in one third part of adult patients, such acute pain becomes chronic.<sup>6,7</sup>

The financial burden associated with medical expenses and social benefits for patients with a temporary or permanent disability resulting from chronic lower back pain remains significant over the world. The largest one-time budget spending (about 31%) is associated with surgical treatment of acute back pain syndrome – discectomy.<sup>8</sup> However, at the same time, studies have shown that more than half of the cases of intravertebral disk herniations (IVHs) had no clinical manifestations and were incidental findings on MRI that did not require further medical treatment.<sup>6,9,10</sup>

Despite the considerable number of studies on pain management, the reasons why the asymptomatic course of the disease changes to acute radicular pain syndrome are not well understood.<sup>5,11</sup> Increasing attention of scientists to the research and discussion on new nonpharmacological treatment methods of the degenerative disk disease further indicate relevance and importance of this issue.<sup>4,10,12</sup>

## 2. AIM

To analyze the most critical risk factors of the degenerative intervertebral disk disease, and to review the effectiveness of invasive and noninvasive methods of treatment of the lower back pain syndrome.

## 3. MATERIAL AND METHODS

The data from controlled and non-controlled randomized studies and meta-analysis from 2000 to 2018 that investigated various methods of invasive and noninvasive treatments of the intravertebral degenerative disk pathology. We searched through Medline, Cochrane, Embase, DARE, NIH, PubMed and Springer, and choose the studies and trials with robust designs and sample sizes. Authors did not focus on comparing the effectiveness of different kinds of treatment. The presented studies were comparable in the age brackets of patients, duration of illness and an intensity of the pain syndrome. In all cases, the IVH was confirmed by magnetic resonance imaging (MRI).

## 4. RESULTS AND DISCUSSION

The main risk factors for developing a degenerative disk disease range in the following order, from the most prevalent to the least: age, excessive physical activity, prolonged work in an uncomfortable position, height of the person, obesity and smoking.<sup>13,14</sup> It was found that in 75% of young patients, the development of the degenerative process in the vertebral column is associated with specific genetic markers. The pathological mechanism in intravertebral discs (IVDs) is associated with the dysplasia of the connective tissue and is clinically manifested by joint hypermobility. Potential genetic markers of the IVD damage are dominated by genes encoding collagen 9A2 and 11A1, vitamin D3 receptors, various types of the metalloproteinases, intermediate cartilage protein, thrombospondin (THBS2), asporin (ASPNs) and sulphotransferase carbohydrate.<sup>11,13</sup> An excessive development of adipose tissue affects microcirculation and, as a result, accelerates degenerative processes in the IVDs, cartilage, and ligaments. Therefore, obesity is one of the major factors that complicate the course of the disease and treatment given it contributes to both primary and recurrent protrusions and hernias.<sup>15–17</sup>

Based on the study results conducted in Australia from 1995 to 2015 with 742 329 participants, the average body mass index (BMI) increased in both men and women and corresponded to different degrees of obesity. The study demonstrated that the number of adults with various severity of obesity doubled in the last 20 years, and more than half of the population born from 1971 to 1979 has a BMI more than 35 kg/m<sup>2</sup>.<sup>16</sup>

### 4.1. The main methods of treatment of dorsalgia

It is estimated that only 5%–10% of patients with acute or chronic low back pain require a surgical intervention.<sup>17,18</sup> Kokina and Filatov (2011) conducted a retrospective cohort study to determine the effectiveness of surgical treatment of the acute pain syndrome. Based on the results of MRI, 71% of patients had recurrent intravertebral hernias (IVHs) at a previously operated site and/or in adjacent segments. In the group of patients with satisfactory and good results of surgical treatment, a recurrence of IVHs was detected in 50% of patients one year following the surgical intervention. According to the experts, the rate of recurrence of IVH is not associated with the duration of the last exacerbation, clinical manifestation of the disease, MRI data or the frequency of exacerbations of the disease in the past.<sup>13,18</sup> In every 3rd patient, this condition was associated with comorbidities such as: diabetes, dysplastic connective tissue disease, and obesity, which have complicated operative and postoperative recovery periods. In order to prevent complications, some authors recommend performing a preoperative risk analysis.<sup>10,18,19</sup>

A risk stratification before the second discectomy includes a preoperative size, localization of the hernia, degree of traumatic disk damage (protrusion or sequestration), patient's age, duration of the pain syndrome, degree of neurological defi-

cits, duration of smoking (PPY) and presence of concomitant metabolic disease (diabetes mellitus).<sup>14,19,20</sup> The sources of information about recent randomized and nonrandomized trials used in this article are presented in Tables 1 and 2.

The effectiveness of surgical treatment of IVHs depends on the correct surgical approach. It is proven that endoscopic microdiscectomy is associated with a lower number of post-operative complications and significantly reduces the risk of recurrent surgery for IVD disease in adjacent segments.<sup>18,20</sup>

Weinstein et al. (2006) compared surgical vs. conservative treatment outcomes of patients with IVD hernias complicated by sciatica.<sup>21</sup> The authors noted that most patients

preferred the conservative approach as a modality of treatment of IVD, and it was associated with a significantly lower rate of complications than discectomy.<sup>22–24</sup>

Gugliotta et al. (2016) evaluated different treatment approaches for acute and chronic low back pain in 370 patients in a prospective cohort study. At weeks 3 and 12, and 1 year after the treatment, patients were assessed for neurological status, quality of life, physical activity and complaints. The authors noted that patients achieved a significantly faster improvement of symptoms (3 weeks) after discectomy and microdiscectomy than conservative management. However, only a minimal difference in the outcomes after treat

**Table 1. Characteristics of included observational cohort study and meta-analysis (n = 19).**

Authors and country	Period of investigation	Type of back pain	Sample size (patients)	Method of treatment	Level of evidence (evidence-based medicine)	Prospective/retrospective study
Artus M, et al., UK <sup>23</sup>	2010-2012; a 52 week follow up	Mixed	1787	Surgical and nonoperative	2	Prospective
Atlas SJ, et al., USA <sup>7</sup>	Date not specified; a 12 months follow up	Mixed	507	Surgical and nonoperative	3	Retrospective
Gugliotta M, et al., Switzerland <sup>6</sup>	2003-2007; a 24 months follow up	Mixed	370	Surgical and nonoperative	3	Prospective
Belykh E, et al., Russia <sup>17</sup>	2008-2012; a 24 week follow up	Acute	350	Surgical intervention	3	Prospective
Buric J, et al., Italy <sup>25</sup>	2002-2003; a 12 months follow up	Acute	30	Nonsurgical treatment	3	Prospective
Hegarty D, et al., Ireland <sup>11</sup>	Date not specified; a 3 months follow up	Mixed	53	Surgical and nonsurgical treatment	3	Prospective
Korhonen T, et al., Finland <sup>26</sup>	2002; a 12 months follow up	Acute	17	Nonsurgical treatment	3	Prospective
Morselli A, et al., Italy <sup>27</sup>	2013; a 2 months follow up	Acute	25	Nonsurgical treatment	3	Prospective
Murphy ME, et al., USA <sup>19</sup>	2010-2014; a 6 months follow up	Acute	23583	Surgical intervention	3	Retrospective
Oba H, et al., Japan <sup>13</sup>	Date not specified; a 6 months follow up	Acute	140	Surgical intervention	2	Prospective
Tu Z, et al., China <sup>14</sup>	2008-2011; a 6 months follow up	Acute	152	Surgical intervention	3	Prospective
Tschugg A, et al., Austria <sup>20</sup>	Date not specified; a 12 months follow up	Mixed	52	Surgical intervention	3	Prospective
Shin JS, et al., Korea <sup>22</sup>	2006; a 5 year follow up	Mixed	150	Nonsurgical treatment	3	Prospective
Thackeray A, et al., USA <sup>28</sup>	2010-2012; a 12 months follow up	Mixed	363	Nonsurgical treatment	3	Prospective
Ucar D, et al., Turkey <sup>29</sup>	2018-2019; a 6 months follow up	Acute	72	Nonsurgical treatment	3	Prospective
Vivekananda SP, et al., UK <sup>3</sup>	2009-2012; a 12 months follow up	Mixed	68	Nonsurgical treatment	3	Prospective
Weinstein JN, et al., USA <sup>21</sup>	2000-2003; a 6 months follow up	Mixed	743	Surgical and nonsurgical treatment	2	Retrospective
Yao Y, et al., China <sup>30</sup>	2005-2016; a 5 year follow up	Acute	111	Surgical intervention	3	Retrospective
Zhong M, et al., China <sup>31</sup>	1990-2015; a 5 year follow up	Mixed	587	Nonsurgical treatment	2	Retrospective

**Table 2. Characteristics of included randomized controlled trials (n = 6).**

Authors and country	Period of investigation	Type of back pain	Sample size (patients)	Method of treatment	Level of evidence (evidence-based medicine)	Prospective/retrospective study
Ackerman WE, et al., USA <sup>24</sup>	2004-2006; a 24 week follow up	Mixed	90	Nonsurgical treatment	2	Prospective
Cohen SP, et al., USA <sup>32</sup>	2005-2006; a 6 months follow up	Mixed	36	Nonsurgical treatment	2	Prospective
Isner-Horobeti M-E, France <sup>33</sup>	2014; a 28 day follow up	Acute	17	Nonsurgical treatment	2	Prospective
Freeman BJC, et al., USA <sup>34</sup>	2004; a 26 week follow up	Acute	49	Nonsurgical treatment	2	Prospective
Magalhaes FN, et al. <sup>35</sup>	1995-2011; a 6 months follow up	Mixed	861	Nonsurgical treatment	2	Prospective
Tuakli-Wosornu YA, et al., USA <sup>36</sup>	2010-2012; a 12 months follow up	Mixed	47	Nonsurgical treatment	2	Prospective

ment was noted when evaluating the intermediate results (3 months). The long-term effect of treatment was significantly better in the group with conservative treatment.<sup>6</sup> These study results correspond to similar research projects conducted in other countries.<sup>22,31</sup> As an alternative multimodal approach, conservative treatment includes physical therapy, medications, paravertebral block and other methods of conservative rehabilitation.<sup>10,19,24</sup>

Local corticosteroid injections are a well-known pain treatment technique, and its efficacy rate ranges from 20% to 95% of the cases. At the cellular level, the mechanism of action is achieved by reducing cytokine concentration in the area of inflammation. However, the analgetic effect and improvement of sensation in the affected area are usually short-lasting. According to observations, the use of corticosteroid epidural blocks does not reduce the potential need for surgery and does not affect the recovery of neurological deficits in radiculopathies.<sup>24,31</sup>

Several ongoing studies focus on different types of dorsalgia where the corticosteroid injections are an appropriate and effective treatment method. Kim et al. (2016) and Altun et al. (2017) proposed that one of the important conditions for a positive treatment outcome is the size of the intravertebral hernia, where transforaminal epidural blocks of hernias up to 6.23 mm demonstrated a success rate of almost 100%. According to the experts, hernias larger than 6.31 mm are more appropriate for the surgical treatment.<sup>37,38</sup>

TNF is a known molecular mediator in the pathogenesis of radiculopathy. Korhonen et al. (2004) followed a pathogenetic approach and used TNF-inhibitor-infliximab to treat lower back pain.<sup>26</sup> Later, Cohen et al. (2007) confirmed the positive effect from subcutaneous and epidural injections of infliximab in patients with lower back pain. However, small-dose injections did not demonstrate satisfactory results.<sup>32</sup> Freeman et al. (2013) conducted a placebo-controlled randomized trial with a transforaminal administration of TNF-inhibitor. Within 3 to 6 months after the treatment, patients reported a significant improvement in an overall wellbeing and control of lower back with sciatica.<sup>34</sup> However, the study did not consider the demographic characteristics of patients and did not report the dose-dependent effect of the treatment.

There is also a long-standing debate over the use of nontraditional treatment (dietary supplements, acupuncture, homeopathic pharmacopuncture, chiropractic care). A study by Shin et al. (2016) demonstrated 5-year positive results from the nontraditional treatment as evidenced by scales of Visual Ache Scale (VAS), 36-Item Short Form Survey (SF-36), and others.<sup>22</sup> In 66% of the cases, a regression of IVH was noted after repeated conservative courses of treatment. Zhong et al. (2017) described the results of a meta-analysis where most the patients experienced spontaneous resorptions of IVH after using traditional Oriental (acupuncture) treatment.<sup>31</sup>

Traction therapy has some limitations, but it is also one of the conservative treatment methods. This method leads to decreased edema and pressure on the nerve root,

which are the main factors contributing to the pain. The Isner-Horobeti et al. (2016) study aimed to determine the effectiveness of the traction therapy using different weights as the primary treatment method. The study demonstrated that the low weight traction (10% of body weight) was more effective than the high weight one (50% body weight). The results of the study were determined to be statistically significant but the design itself had some flaws (a small number of patients, 17 people).<sup>33</sup>

The traditional physical therapy is based on the course of long-term exercises that aim to strengthen core muscles thus increasing local and general mobility and reducing clinical manifestations of IVHs.<sup>19,31</sup> Thackeray et al. (2016) studied the efficacy of a physical therapy vs. surgical treatment, and according to the researchers, after 6 weeks of the treatment, there was no significant clinical difference between the two groups. A year later, the conservative treatment with physical therapy demonstrated better outcomes compared to the surgical approach. It was particularly emphasized that patients who took part in regular physical therapy had minimal use of opioids and muscle relaxants for pain control.<sup>28,39</sup>

Current studies have started to discuss the possibility of mesenchymal stem cell injections, a PRP-therapy in the treatment of IVHs in patients with a long-standing back pain syndrome (>6 months). Several prospective randomized studies have shown improvements in pain, quality of life, and physical activity within 1–2 weeks of therapy based on the analysis of the questionnaires/scales used in studies. A distinctive feature of the treatment was absence of side effects. However, a small number of studies conducted using stem cells and a platelet-enriched plasma is not sufficient for the widespread use of these methods in clinical environment.<sup>36,40</sup>

The ozone therapy is a relatively new alternative treatment widely used to treat the back pain syndrome. It is known for its anti-inflammatory properties. The pathophysiological mechanism of action of the ozone therapy works towards reducing the activity of biologically active substances (BAS – histamine, serotonin, bradykinin, cytokines) and concentration of inflammatory subtypes of prostaglandins. The direct anti-inflammatory effect on the pain is achieved by affecting inflammatory mediators, such as the tumor necrosis factor, interleukin-1, and interleukin-6.<sup>41</sup> The secondary analgesic effect is ensured by the reduction of lipid peroxidation, oxidative stress and improvement of microcirculation in the zone pathological process.<sup>29</sup>

#### 4.2. The use of ozone in the treatment of pathology of the intervertebral discs

A considerable number of articles have been devoted to the treatment of neuropathic pain with ozone therapy. Thus, intradiscal injections of various depth enriched with oxygen-ozone gas mixture demonstrated a significant anti-inflammatory effect for the treatment of IVD. A number of publications have highlighted a strong analgesic effect of the O<sub>2</sub> / O<sub>3</sub> infiltration.<sup>25,29,35,42,43</sup>

Lamberto et al. (2012) presented the results of a paravertebral subcutaneous injection with a low concentration oxygen-ozone mixture (8–12 mg/L). The total volume of the gas mixture administered per pain zone was 25–30 mL in total and did not exceed 2–3 mL per one injection spot. To compare the local changes and efficacy of the method, the same concentration of the solution was injected into the symmetrical part of the body. It was noted that after the administration of the oxygen-ozone mixture, the treated area was different compared to the healthy one as shown by more prominent erythema around the injection site. This difference was explained by an increased concentration of inflammatory markers BAS, interleukins, tumor necrosis factor, bradykinin, and other compounds in the intercellular space of the affected area. The appearance of more intense erythema around the injection sites occurs during the interaction of the oxygen-ozone solution with pain mediators, inflammatory factors and pain receptors, respectively. After  $16 \pm 7$  minutes, the erythema gradually decreased and disappeared, followed by the development of an analgesic effect in the treated area.<sup>44</sup>

A daily paravertebral administration of the low-concentration oxygen-ozone mixture for 1–2 weeks in the affected area of the spine demonstrated a steady decrease or complete resolution of the pain. According to the authors of the technique, the injection of an ozone solution into the affected area and the contralateral side prevented 'phenomenon of pain migration'.<sup>29,42</sup>

The hypothesis expressed by Lamberto et al. (2012) is that an immediate short-term analgesic effect is associated with the improvement of local microcirculation, and a long-term persistent analgesic effect occurs after the activation of the antioxidant system.<sup>44</sup>

A multicenter, randomized, double-controlled trial evaluated the effectiveness of ozone therapy in patients with a long-term lumbosacral pain. After paravertebral administration of the oxygen-ozone mixture, 62% of patients achieved a complete resolution and only 5% of patients still required surgical treatment. The effectiveness of the paravertebral ozone therapy is explained by the increase in pain threshold by affecting the spinal pain receptor arch.<sup>45</sup>

However, the paravertebral ozone injections might be associated with secondary side effects due to excessive tissue infiltration with a therapeutic gas solution.<sup>46</sup> The occurrence or an increase of a muscular or deep visceral pain, impaired gait, fatal cases of embolism were observed after an incidental injection of a large volume of the gas mixture into the vessels during deep (intradiscal) injections. Another reported side effect is a burning sensation at the area of innervation of spinal root related to the injection technique mistakes or high concentration of the oxygen-ozone mixture at the site of infiltration.<sup>27,29</sup>

Morselli et al. (2015) set the goal to reduce the likelihood of adverse effects associated with ozone therapy. They studied outcomes of the paravertebral administration of a smaller volume of the ozonated mixture (10 mL) and the possibility to use ultrasound-guided injections. There were 50 patients in the age group between 39 and 77 years un-

der observation with suboptimal and short-term response to pharmacotherapy. The treatment course consisted of weekly ultrasound-guided injections of 5 mL of the ozone mixture (ozone concentration of 20  $\mu\text{g}/\text{mL}$ ) in the area of the facet joint, which corresponded to the trigger zone, with total duration of 10 weeks. The study demonstrated a significant improvement of treatment outcomes by using the ultrasound-guided deep injection with a smaller volume of oxygen-ozone solution into the area of the affected IVD.<sup>27</sup>

The data from numerous published studies have confirmed the effectiveness of the ozone therapy for lower back treatment with or without sciatica.<sup>3,25,47,48</sup> Other studies compared the efficacy of analgesia and the duration of remission in patients with different courses of treatment: the use of ozone therapy-only vs. pharmacotherapy.<sup>27,35</sup> Thus, the first group underwent a local intra-foraminal or a peridural administration of steroids, and in the second group – a local administration of the oxygen-ozone mixture.<sup>45</sup>

Vivekananda et al. (conducted a clinical study to determine the impact of the chronic spinal pathology complicated by IVH. The prospective clinical study included 68 patients with a lower back pain complicated by IVH, as confirmed by an MRI. The treatment method consisted of a nucleolysis of hernias by administering an oxygen-ozone mixture under the MRI guidance.<sup>3</sup>

Ozone is known to have dose-dependent biological effects. At high concentrations (30–70 mg/mL), it can damage the structure of the tissue; at medium concentrations (20–30 mg/mL), ozone potentiates the response of the immune system, and at low concentrations (<20 mg/mL) it improves microcirculation. The unique property of ozone is due to the dehydration of the fibrillar matrix and the effect on collagen fibers, which explains the process of mummification of the IVH.<sup>46</sup>

A fluoroscopic guidance was used to achieve more precise administration of the gas mixture and prevent local tissue damage during the injection into the intravertebral space. Published data showed that over 85% of cases associated with IVH were treated conservatively with ozone hernialysis.<sup>3,25,35</sup> The success rate of the deep ozone therapy was 88% compared to 50%–90% after a surgical treatment with a disc microdiscectomy. Also, the ozone therapy was associated with fewer side effects or complications compared to the ones appearing after the surgery. The studies provided a sufficient evidence of both short- and long-term pain control with minimal side effects.<sup>3,29,48</sup>

## 5. CONCLUSIONS

- (1) The multiple studies demonstrated the possibility of non-surgical, cost-effective treatment methods for common complications of degenerative-dystrophic diseases of the spine.
- (2) An individualized approach continues to be the most important factor is the choice of the treatment tactic.
- (3) Newer trend is minimal invasive technique which is cost effective with minimal hospital stay and least complications.

(4) The ozone therapy has shown its effectiveness as one of the modern, minimally invasive procedures with a lower rate of recurrences and remarkably fewer side effects for patients with a chronic back pain.

### Conflict of interest

Authors declare no conflict of interest.

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