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Pain Relief and Functional Improvements after Spinal Ozone and PRP Injections for Symptomatic Lumbar Herniated Disc

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Abstract

Background and Objectives: Low back pain may be related to arthritic lumbar facet joints and painful intervertebral discs. Interventional pain management with intraarticular injections of corticosteroids is commonplace. Autologous platelet-rich plasma (PRP) has successfully treated inflammatory pain in large arthritic joints. Additional use of ozone may be beneficial.

Study Design: We conducted a prospective observational cohort study from January 2016 to March 2020 to assess the safety and therapeutic effectiveness of concomitant transforaminal, intradiscal- and intraarticular ozone and PRP injections in the management of symptomatic low back pain in patients with herniated disc and facet syndrome.

Setting: The outpatient clinic of a single academic medical center.

Methods: A total of 55 patients with painful lumbar herniated lumbar consisting of 24 women and 31 men with an average age of 48.63 ± 13.54 years and a mean follow-up of 25.84 ± 10.94 months were enrolled in our study. Under x-ray fluoroscopic control, patients received an injection of ozone combined with autologous PRP into the painful herniated disc. At the same time, patients were treated with bilateral lumbar facet joints blocks, transforaminal epidural injection, and a caudal block employing the same therapeutic mixture. Patients were followed up immediately, at one week, 12, 24, 48, and 96 weeks. Functional improvements were evaluated with low back pain visual analog scale (VAS) at rest for leg pain and during flexion, Oswestry Disability Index (ODI), and modified MacNab criteria for the pain relief.

Results: MacNab outcomes were reported excellent by 36.4% of patients, good by 49.1%, fair by 9.1%, and poor by 5.4%. VAS scores decreased from 7.98 ± 1.65 before the procedure to 2.72 ± 2.06 1 week, 2.85 ± 2.12 at 12 weeks, 2.76 ± 2.17 at 24 weeks, 2.58 ± 2.25 at 48 weeks, and 2.52 ± 2.35 at 96 weeks ($p < 0.001$). The ODI values showed similar reductions from an initial average of 72.65 ± 11.15 before the injection to 30.29 ± 15.67 one week after the procedure followed by 29.85 ± 16.02 at 12 weeks, 28.78 ± 16.74 at 24 weeks, 27.24 ± 17.57 at 48 weeks, 26.4 ± 18.35 at 96 weeks ($p < 0.001$).

Limitations: Observational cohort study without blinding or randomization.

Conclusion: Our prospective observational cohort study showed rapid pain reduction and functional gains in patients with acute lumbar herniated discs after spinal injections with ozone and activated PRP.

Keywords

Low back pain, Ozone, Autologous platelet rich plasma, Spinal injection.

Introduction

Chronic Lumbar pain, in most cases, is caused by the degeneration of the intervertebral disc and facet joints. However, acute low back pain may be due to a lumbar herniated disc which can present with acute onset of severe sciatica-type low back- and leg pain, seriously affecting patients' quality of life and work capacity. They may cause a substantial medical burden. Lumbar degenerative disc disease has become a global social and economic problem [1,2]. It is ubiquitous among middle-aged and older adults throughout the world. Existing treatment options include conservative approaches such as anti-inflammatory drugs, physical therapy, and microdiscectomy surgery. The latter may cause acceleration of the degenerative process requiring more spinal surgery [3-7].

Chymopapain was extensively used for chemical nucleolysis in the 1980ies in patients with unrelenting symptoms due to herniated disc. This proteolytic enzyme isolated from the latex of papaya – a cysteine protease that belongs to the papain-like protease group – was taken off the market because of complications and hazardous side effects [8]. Intradiscal oxygen/ozone injections into symptomatic lumbar disc herniations were first described in the 1980ies [9]. Since then, multiple, mostly retrospective observational cohort studies [10-23] and a few randomized trials [13,14,24-27] have been published supporting ozone therapy alone and in conjunction with steroids and other anti-inflammatory drugs. Periradicular, intraforaminal, intramuscular, and paravertebral ozone injections have also been shown to reduce pain associated with the lumbar herniated disc [22,24,26,28-33] The presumed primary mechanism of action is chemonucleolysis. Ozone is a strong oxidizer that quickly reacts with the proteoglycan GAGs responsible for maintaining the intradiscal osmotic pressure by breaking them down. The resultant dehydration of the nucleus pulposus reduces the intervertebral disc volume. Ozone is also a natural disinfectant for which reason prophylactic antibiotic use has been deemed unnecessary [34]. An additional anti-inflammatory response may result from interaction with intradiscal cytokines. The net effect is reduced sciatica-type low back- and leg pain [35]. The latter has been conclusively shown in an animal model

[36]. Reduction in size of the ozone-treated lumbar herniated disc has been shown by multiple volumetric CT and diffusion-sequence-based MRI studies [27,37-40].

Platelet Rich Plasma (PRP) contributes to pain relief in patients with symptomatic herniated and black lumbar degenerative discs [41]. The active composition can be divided into supra- and normal concentrations of autologous platelets in a small amount of plasma. It has been shown to stimulate the synthesis of the extracellular matrix and thereby may foster wound healing and intradiscal regeneration [42]. This healing effect of degenerative disc tissue is thought to alter cytokines release at a molecular level by upregulation of anti-inflammatory cytokines and downregulation of pro-inflammatory ones, 43 without provoking an immune response since the source is autologous [43]. Due to its anti-inflammatory and anti-microbial properties, similar to ozone, PRP injections into the spine are also associated with a reduced risk of infection [44,45]. The benefits of PRP on degenerative disc tissue are multiple and have been demonstrated *in vitro* in several tissue models [46]. Specific effects include restoring the denatured disc's mechanical properties by increasing the glycosaminoglycan content [47]. Latest clinical evidence shows a reduction of pain associated with painful lumbar discs. However, structural and functional improvements have not been conclusively demonstrated [48]. In this prospective observational cohort study, the authors investigated the benefit of ozone and activated autologous PRP preparations with the intent to maximize its beneficial role in patients with painful lumbar herniated discs.

Materials and Methods

Study Design & Patients

Patients were enrolled prospectively at a single study site from December 2017 to November 2018 at the Center for Neurological Diseases, La Paz Bolivia in an observational cohort study. There were 55 patients consisting of 24 (44%) females and 31 (56%) males with an average age of 48.63 ± 13.54 and average follow-up of 25.84 ± 10.94 months.

Inclusion/Exclusion Criteria

Patients with symptomatic lumbar disc herniation causing sciatica-type nerve root compression symptoms were the primary target group of this investigation. Inclusion criteria were 1) documented diagnosis of an acutely symptomatic lumbar herniated disc at one level from L1 to S1, 2) acute low back pain at least for six weeks months with a VAS for leg pain greater than 5, 3) 6 weeks of failed conservative treatment, 4) age 18-65 years old, 5) BMI <40, 6) a dermatomal distribution of pain consistent with advanced radiographic imaging findings, 7) a minimum retained disc height of at least 50% of adjacent disc levels, and 8) MRI signal intensity of the herniated disc equal or greater than the rest of the nucleus pulposus on T2-weighted sequences.

Patients were excluded from the study if they had 1) comorbid conditions affecting disc health such as metabolic diseases, 2) infection, 3) trauma, 4) spondylolisthesis, 5) radiculopathy or claudication symptoms from bony foraminal, lateral, or central canal stenosis, 6) herniations involving non–contiguous disc fragments or herniations extending past the facet joint, 7) tumors, 8) impairment of bladder or bowel function, 9) motor strength deficits in the lower extremity, 10) a recent epidural steroid injection in the past two weeks, 11) previous spinal surgery including discectomy, arthroplasty, or fusion at any lumbar level, 12) symptomatic sacroiliac joint disease, 13) pregnancy or female patients wishing to become pregnant during the study, 14) fibromyalgia, 15) more than three months sick leave, 16) known drug- or alcohol abuse, and 17) diagnosed psychiatric disease or psychological distress. These inclusion and exclusion criteria resulted in a study population of 55 patients. Statistical power analysis predicted that this study size was sufficient to assess ozone and activated PRP injections' safety and clinical outcomes in treating painful degenerative intervertebral discs.

Ozone-Preparation

The gas mixture is created by an oxygen-ozone generator system (Evozone basic Plus, Reutlingen, Germany) consisting of a sterile syringe cartridge and a console that accurately measures oxygen-ozone within a previously sterilized syringe containing a gas filter cartridge. Oxygen was converted to ozone directly in the syringe, minimizing the risk of dilution or contamination with a transfer from a non–sterile ozone generator to a sterile syringe. This system comprises oxygen-ozone resistant components lubricated with silicone minimizing any undesired byproducts or degradation of the oxygen-ozone mixture. The oxygen-ozone gas was prepared at a standardized concentration of 40 µg/mL. The concentration of ozone was measured inside the syringe using an ultraviolet photometer.

Autologous PRP Preparation

All study patients had laboratory testing including CBC, PT, PTT, INR, blood- and Rh-typing, glucose, creatinine, and HIV testing. A total of 300 cc of peripheral venous blood was drawn under sterile technique. It was first centrifuged at 3000 rpm for 8 minutes. The platelet-rich plasma (PRP) was obtained in a laminar flow hood and and was activated with ozone concentration of 80 µg/mL.

Injection Procedures

Patients were positioned in lateral decubitus on a pad placed in the lumbar region with the legs flexed on the abdomen without the knees interfering with the fluoroscopic images of the lumbosacral area, which was prepped with chlorhexidine (**Figure 1**). A 20F Chiba needle is introduced to the intervertebral disc through the oblique transforaminal approach for the intradiscal injection under conscious sedation and local anesthesia with 2% lidocaine. Approximately 3 to 5 ml of the oxygen-ozone mixture at a concentration of 40 µg/mL was injected, followed by three ccs of the activated platelet-rich plasma. The intraarticular facet injections were in the prone position. A 22 G spinal needle (Spinocam®) was introduced to the zygoapophyseal joint to inject 2 ml of the oxygen-ozone PRP mixture. The exact amount was injected through the sacral hiatus and transforaminal into the neuroforamina of the symptomatic level. Patients were monitored for any adverse events for one hour after the interventional procedure. Typically, they were sent home with acetaminophen 500mg every eight hours for 24 hours and instructed to avoid bending, twisting, and any weight lifting more than over 10 lbs for two weeks after the procedure.

Outcome Assessment & Statistical Analysis

Primary clinical outcome measures assessing the effectiveness of oxygen-ozone and activated PRP preparations in reducing acute herniated disc symptoms were the modified McNab criteria, [49] VAS low back pain, [50] and ODI [51]. These Patient-Reported Outcome Measures (PROMs) are most suitable for correlating clinical improvements with post-injection MRI image scoring of the

healing lumbar intervertebral disc. Patients were clinically evaluated at 3, 6, 12, and 24 months post-treatment. The post-procedure MRI scans were available in 10 of our 55 study patients in 4 and 12 weeks post intervention. Patients' outcome questionnaires included the Visual Analog Score (VAS) for low back pain, the Oswestry Disability Index (ODI) for overall function, and the modified MacNab criteria. Additionally, patients were interviewed to determine if any unfavorable or unintended signs, symptoms, or diseases had occurred. The treatment's ultimate success was determined if no post-injection interventions were directed at the treated disc level. Post-intervention MRI scans were evaluated whenever available for volumetric reduction of the herniated disc or any healing of annular tears. Descriptive statistics tests were performed on demographic and outcome data using the software SPSS™ version 27. Outcomes were tested for statistically significant improvements by employing the paired T-test.

Results

Most patients suffered from exclusive traversing nerve root pain syndromes since patients with extraforaminal herniations were excluded from the study. There were no adverse events, infections, or any other complications following the oxygen-ozone and activated PRP injection. Twenty-two percent of patients presented with isolated axial low back pain **Figure 2**. The remaining 78% of patients presented with a combination of sciatica-type low back and radicular leg pain matching the dermatomal distribution suggested by the pre-procedure MRI scan. The frequency of treated lumbar levels was as follows: L4-L5-7%; L5-S1-18%, L4-L5 and L5-S1-51%, and more than two levels - 24% **(Figure 3)**.

The VAS score for leg pain reduced from an average of 7.98 ± 1.65 before the procedure to 2.72 ± 2.06 after the first week ($p<0.001$). The rapid and statistically significant reduction in sciatica-type back and leg pain noted within one week from the intervention was maintained throughout the post-procedure follow-up to 96 weeks (1.841 years) without any statistically significant change in pain resolution throughout the entire study period. VAS scores decreased rapidly after the procedure and remained low for the remainder of the follow-up period: 2.85 ± 2.12 at 12 weeks, 2.76 ± 2.17 at 24 weeks, 2.58 ± 2.25 at 48 weeks, and 2.52 ± 2.35 at 96 weeks ($p<0.001$; **Figure 4**). The ODI values

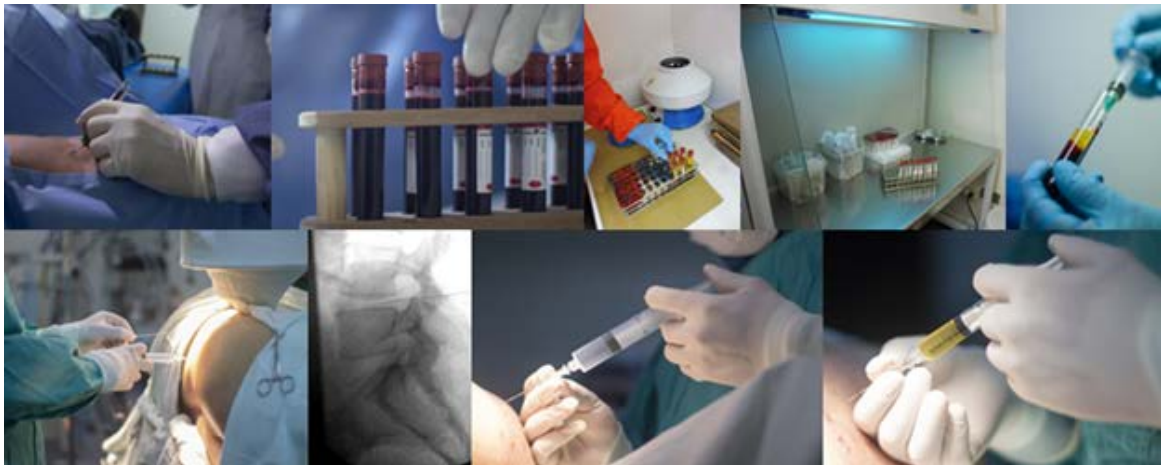

Figure 1: Ozone was prepared in an ozone concentrator, and the platelet-rich plasma (PRP) was prepared in a laminar flow hood from 300 ccs of peripheral venous blood centrifuged. Patients were positioned in lateral decubitus for the transforaminal intradiscal injection of oxygen-ozone and activated PRP 20F Chiba needle. Under conscious sedation and local anesthesia with 2% lidocaine, approximately 3 to 7 ml of the oxygen-ozone mixture at a concentration of 40 µg/mL was injected into the herniated disc, followed by three ccs of the activated platelet-rich plasma.

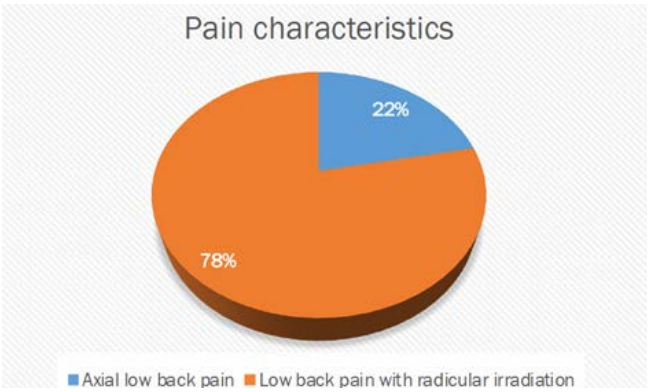

Figure 2: Our prospective observational cohort study included 55 patients consisting of 24 (44%) females and 31 (56%) males with an average age of 48.63 ± 13.54 and an average follow-up of 25.84 ± 10.94 months. Twenty-two percent of patients presented with isolated axial low back pain and 78% with sciatica-type low back and radicular leg pain matching the dermatomal distribution suggested by the pre-procedure MRI scan.

showed similar reductions from an initial average of 72.65 ± 11.15 before the injection to 30.29 ± 15.67 one week after the procedure ($p<0.001$). Dramatic functional improvements were reported by our patients with a nearly 68.3% of the ODI reduction (42.36 basis points) materializing within one week after the injections ($p<0.001$). Additional functional improvements were reported up until 96 weeks (1.811 years) without any statistically significant difference between the respective follow-up ODI numbers: 29.85 ± 16.02 at 12 weeks, 28.78 ± 16.74 at 24 weeks, 27.24 ± 17.57 at 48 weeks, 26.4 ± 18.35 at 96 weeks ($p<0.001$; **Figure 5**). Postoperatively, excellent MacNab outcomes were reported by 36.4% of patients, good by 49.1%, fair by 9.1%, and poor by 5.4%. Thus, 85.5% of patients reported favorable results.

Surveillance post-procedure MRI scans were available in 10 of our 55 study patients frequently up to 12 weeks post intervention **Figure 6**. After spinal injections with oxygen-ozone and activated PRP, a gradual volumetric reduction of the herniated disc could be observed on routine T2-weighted sequences using 1.5T routine MRI scanning without contrast from pre-intervention to 4 and 12 weeks post-intervention. Structural changes on MRI scan lagged behind symptom resolution, which occurred much sooner – in most patients within one week after the procedure.

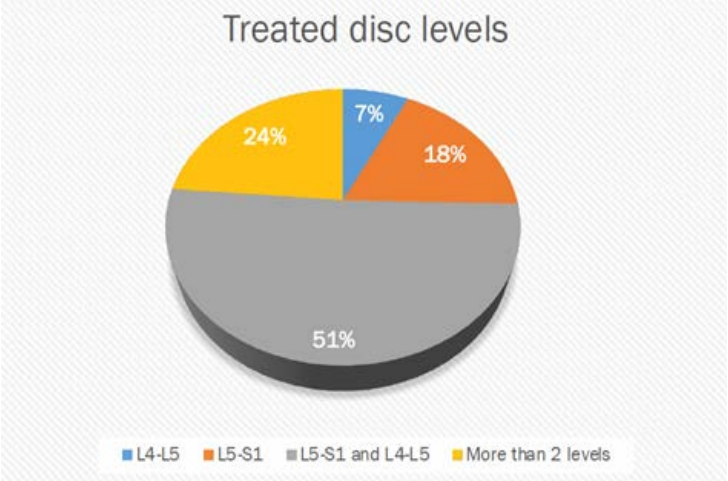

Figure 3: Frequency of treated lumbar levels in our study population of 55 patients.

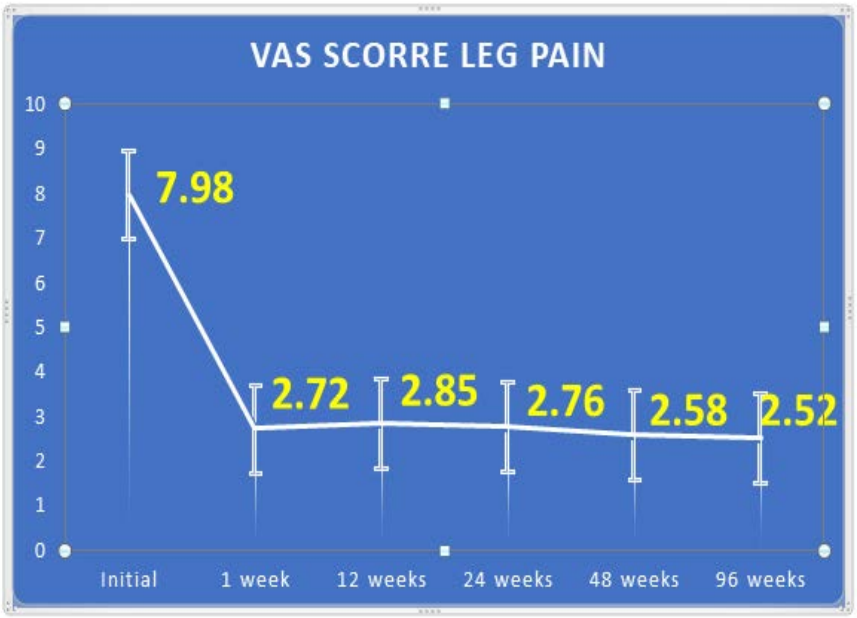

Figure 4: Initial and post-procedure reductions of VAS score for sciatica-type back- and leg pain with the standard deviation error bars observed in our study population of 55 patients after spinal injections with oxygen-ozone activated PRP. A rapid and statistically significant reduction in sciatica-type back and leg pain was noted within one week from the intervention, which then was maintained throughout the post-procedure follow-up to 96 weeks (1.841 years) without any statistically significant change in pain resolution throughout the entire study period.

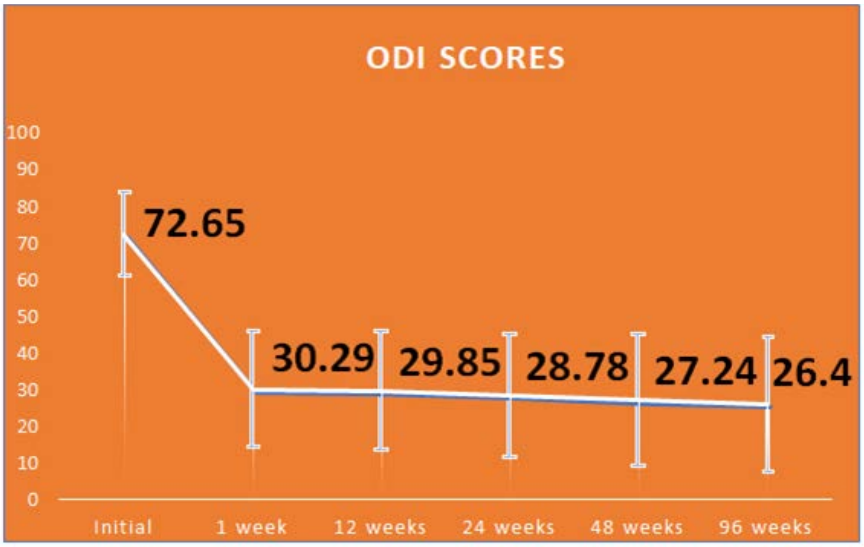

Figure 5: Initial and post-procedure reductions of ODI score shown here with the standard deviation error bars were observed in our study population of 55 patients after spinal injections with oxygen-ozone activated PRP. Dramatic functional improvements were reported by our patients, with nearly 68.3% of the ODI reduction (42.36 basis points) materializing within one week after the injections ($p < 0.001$). Additional functional improvements were reported up until 96 weeks (1.811 years).

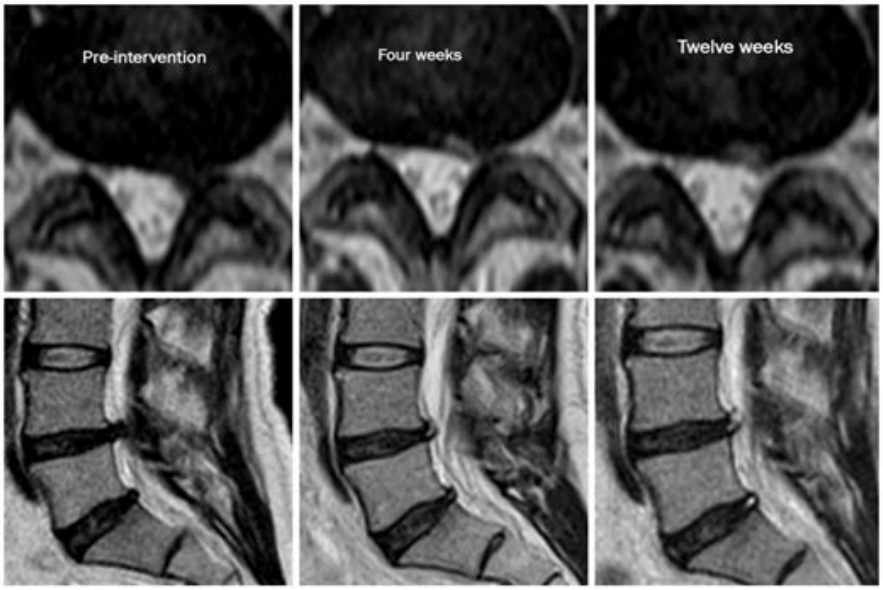

Figure 6: Surveillance post-procedure MRI scans were available on some of our 55 study patients. After spinal injections with oxygen-ozone and activated PRP, a gradual volumetric reduction of the herniated disc could be observed on routine T2-weighted sequences using 1.5 T routine MRI scanning without contrast from pre-intervention to 4 and 12 weeks post-intervention. Structural changes on MRI scan lagged behind symptom resolution, which occurred much sooner – in most patients within one week after the procedure.

Discussion

Interventional treatments of lumbar herniated disc causing acute pain syndromes are usually limited to epidural steroid injections. An array of percutaneous procedures ranging from radiofrequency [52] to non-visualized removal [53-56] of herniated disc tissue exist. However, the latter methods may be beyond the purview of postgraduate training for some physicians treating acute spine pain [57,58]. The emerging field of interventional pain surgery may fill this gap between pain management and traditional microdiscectomy surgery in the future [59-62]. In today's routine clinical context, many patients who do not want spine surgery go untreated or have ineffective treatments for their acute lumbar spine pain syndrome [63].

Regenerative medicine of an injured or degenerated lumbar intervertebral disc is in its infancy, [43,48,64-72] with few clinical studies conclusively demonstrating benefit. However, high-grade clinical evidence from double-blinded prospective randomized clinical trials supporting some regenerative anti-inflammatory

strategies that play out on the cellular level does exist for both ozone and platelet-rich plasma (PRP) [13,14,24-26,32,70,73]. A previous meta-analysis of the latest clinical evidence suggested that high-grade clinical evidence does not support functional improvements with PRP alone [48]. Additional studies of various PRP preparations in combination with other drugs or agents have been proposed to define further the role of spinal PRP injections in interventional spine care [48]. For example, PRP have been compared to steroid injections [13]. Further investigations into its regenerative effects were also suggested. 48 While the latter is beyond the scope of this study, the authors of this study were interested in assessing post-procedure pain reduction and functional improvements after injection of oxygen-ozone and activated PRP into acutely symptomatic lumbar herniated discs [48].

Our prospective observational cohort study provided convincing evidence that spinal injections with ozone and activated PRP, including those into the painful intervertebral disc, can significantly improve patients' functioning and reduce pain promptly – within one week in most of our study patients. Spine pain following acute herniated disc is complex and may not be limited to the herniated disc alone [74-79]. For this reason, the authors combined the intradiscal ozone and active PRP injection with injections of the same mixture into the facet joints, sacral hiatus, and transforaminal periradicular injections. These injections are well founded in the literature and are supported by many high-grade clinical trials [10,11,24,26,28-31]. Whether the pain relief combined with the functional improvements came from the intradiscal injections or some of the other concomitantly performed injections into the facet joints, sacral hiatus, or the foraminal injections is of little consequence to our patients. Others conclusively demonstrated shrinkage of lumbar herniated disc on MRI investigations after oxygen-ozone injections [9,18,27,38-40]. This is certainly corroborated by the sporadic MRI follow-up studies that available for some of our patients. A formal volumetric MRI-based analysis of disc shrinkage as a result of ozone and activated PRP injections into herniated discs should be done but was beyond the scope of our study.

One of the main limitations of our study is that it cannot be determined with certainty which component of our ozone and PRP interventional protocol produced the most significant benefit for our patients. Other limitations include patient selection bias by the proceduralists, [80] or hindsight reporting bias by the patients [81]. The substantial reduction in pain and improvement of patient function within one week, however, supports the feasibility concept of our ozone and activated PRP protocol. Further study is needed to validate our findings by large prospective double-blinded double-arm randomized controlled trials to diminish bias and overcome heterogeneity in outcome measures.

Conclusion

Our prospective observational cohort study showed rapid pain reduction and functional gains in patients with acute lumbar herniated discs after spinal injections with ozone and activated PRP. The addition of oxygen-ozone to PRP showed additional functional improvements, presumably due to the ozone-induced shrinkage of the herniated disc. The other foraminal and transforaminal injections and the sacral hiatus likely contributed to additional pain relief. Further detailed, ideally double-blinded randomized investigation into clinical protocols with varying doses of ozone and activated PRP are necessary to reduce bias and more clearly define clinically useful interventional spine pain management protocols involving ozone and PRP.

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