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Ozone Chemyonucleolysis vs Microdiscectomy
Prospective Controlled Study with 18 Months Follow-up

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SUMMARY – This prospective control study with 18 months follow-up was designed to disclose the differences in outcome between intradiscal ozone chemonucleolysis and microdiscectomy in patients with non-contained lumbar disc herniations. Forty-five patients were enrolled on the basis of precise inclusion and exclusion criteria and divided into two treatment groups selected by the patients themselves. The patients were followed by Visual Analogic Scale (VAS), Roland-Morris Disability Questionaire (RMDQ) and Overall Patient Rating Scale (OPRS). Disc herniation volume morphology was evaluated for five months by control MRI scanning. Twenty-seven patients (90%) in the chemonucleolysis group showed a statistically significant improvement in pain ($P<0.001$, Wilcoxon test) and function ($P<0.001$, Wilcoxon test) and the same was true for 14 patients (93.3%) in the microdiscectomy group. The mean satisfaction with the treatment on OPSR was 79.3% for the chemonucleolysis group and 82.1% for the microdiscectomy group. There were no major complications related to procedures. This study indicates that patients from both groups achieved a statistically significant improvement in pain and disability at 18 months follow-up and that there is no statistically significant difference in results between the two treatments.

Introduction

Lumbar disc herniation is a pathologic condition most commonly responsible for low back pain and nerve root compression, and the major reason for lumbar surgery [25]. MOST patients with lumboradicular symptoms from a disc herniation will get better spontaneously and the herniation will eventually disappear in a few months without any treatment [16]. In a number of reports on the long-term outcome of lumbar discectomy for lumbar disc herniation the success rates were fairly consistent (between 76% and 93%), although evaluation methods varied, and approximately 10-12% of the patients underwent revisions [1,9,21,22,33]. Many authors agree that peridural scar formation with tension on neural tissue plays an important role in a substantial proportion of patients with gradually increasing symptoms after primary successful surgical treatment [10,11,27].

For these reasons a number of minimally-invasive percutaneous techniques have been developed. These techniques share the common principle of of acting directly on the disc content without accessing the spinal channel. Two main types of percutaneous treatments have been devised: mechanical removal (endoscopic discectomy, automatized discectomy, laser discectomy) and chemical disruption of the nucleus pulposus (chymopapain, collagen, hydrocortisone, aprotin).

In the last decade, experimental studies showed that epidural application of autologus nucleus pulposus can induce marked morphological and functional changes in the nerve roots due to the increased endoneural fluid pressure of the nerve root and decrease of blood flow in the dorsal root ganglia with a concomitant increase in its excitability and mechanical hypersensitivity [28,32], all in the absence of mechanical compression. Phospholipase A2, tumor necrosis factor a, metalloproteinases and other substances were found in great quantities in the degenerated nucleus pulposus. These were found able to cause nerve root injury by partial demyelination that increases nerve root mechano-sensitivity making the nerve root more susceptible to mechanical pressure. The mechanical

factor may then trigger hyperexcitability and the ectopic nerve impulses in primary afferent axons that cause neuropathic paresthesia and pain [8,23].

Medical ozone is a trivalent form of oxygen used in medical treatment from the early 20th century, mostly in European countries. In 1885 The Florida Medical Association published *Ozone* by Dr. Charles J. Kenworthy, M.D. detailing the use of ozone for therapeutic purposes. In 1911, Dr. Noble M. Eberhart published "*A Working Manual of High Frequency Currents*"*(New Medicine Publishing Co, chapter* IX*)* on the use of ozone for medical purposes. Numerous other medical reports describe the use of ozone in the treatment of different human diseases *(for a comprehensive review one should search the web pages at www.iaqara.us/mccabe/)*. Experimental studies performed to date indicate that ozone, at appropriate doses and concentrations, dissolves in the interstitial water and generates the formation of reactive oxygen species (ROS). These act differently when they are present in the nucleus pulposus, where they oxygenate proteoglycans and glycosaminoglycans. Indeed, histological studies demonstrated that the intradiscal application of ozone at high concentrations produces hydrolysis of the matrix, water release and consequently cell shrinkage [14,18]. However, ozone released in surrounding fluids apparently causes a "paradoxical effect" such as the induction of antioxidant enzymes which suppress the production of pro-inflammatory cytokines and inhibit the synthesis of prostaglandins, bradykinins and other algogenic compounds [3,26].

This prospective controlled study compared the results of ozone chemonucleolysis and microdiscectomy in patients with non contained lumbar disc herniations with 18 months follow-up.

Patients and Selection Criteria

From September 2001 till December 2002, 45 patients, 22 women and 23 men, aged between 19 and 77 years (mean 45 ± s.d.14.2) were enrolled in the study on the basis of the following inclusion and exclusion criteria.

Inclusion criteria:
- Acute or subacute pain for at least one month non responsive to pharmacological treatment.
- Non-contained disc herniation at levels between L3 and S1;
- level of disc herniation corresponding to the level of symptoms;
- confirmation of pathology by MRI scanning.

Exclusion criteria:
- moderate to severe motor palsy (Fisher < 4);
- contained disc herniation;
- other spinal pathologies such as tumours, lyses, fractures, deformities, stenosis, instability, etc.;
- previous spinal surgery;
- use of drugs or history of mental disease.

A physician not involved in the treatment gave all the patients a detailed explanation of both procedures, the possibilities of success and the risk factors entailed, and each patient independently chose which treatment to receive by signing an informed consent form.

On the basis of this kind of randomization, the patients were divided into two groups:
1) the first group, comprising 30 patients, 16 women and 14 men, underwent ozone chemonucleolysis treatment;
2) the second group, comprising 15 patients, 6 women and 9 men, underwent standard microdiscectomy.

Six patients in the ozone chemonucleolysis group (20%) underwent multilevel treatment while 24 patients (80%) underwent single level treatment. All the patients in the microdiscectomy group were operated at just one level. The symptom duration for both groups ranged from 21 to >365 days with a mean duration of 203.9 days (s.d. ± 129.6.) The straight leg raising test was positive for all patients with a mean angle of evocation being 51.3° (s.d. ± 20.5°). None of the patients had major motor dysfunction. All the patients had an MRI image positive for non-contained disc herniation whose outer diameter was larger than ~4 mm.

Procedures

Percutaneous Technique

The procedure was performed in the operating theatre under moderate sedation. No preventive antibiotic therapy was given. The patient was prepared by the anaesthesiologist with pharmacological sedation half an hour before the procedure and then brought to the operating room and positioned in lateral decubitus leaving the affected side upwards with legs folded. The operating table was also folded to assume an upwards convex shape. This facilitated the surgeon's access to the lower discal space (L5-S1) even in patients with a high iliac crest or major spondylo-arthrosic deformities. A Beckton-Dickinson, Chiba type 22 G, 27 cm needle was inserted by the standard posterolateral, extra-articular percutaneous approach. The whole procedure was performed under continuous fluoroscopic control. Once in place, the position of the needle was confirmed by laterolateral, oblique and anteroposterior imaging. The ozone-oxygen mixture was produced in real-time by a medical o-

zone generator Ozonline E 80 (Medica srl) CE certified. The gas concentration range was ~30 μg O_3/ml O_2 in quantities between 10-15 ml for a single level. The syringe used was a Terumo type –50 ml. A bacteriological Millipore filter was positioned between the syringe and the needle before infiltrating the gas mixture inside the disc space. The ozone-oxygen mixture was infiltrated inside the disc space at an approximate velocity of 10 ml/min. The gas mixture inside the disc space appeared on the fluoroscopic image as positive contrastography. Some of the gas mixture escaped from the disc space and ran into the epidural space in cranial and caudal directions. During gas infiltration the patient was sedated by Propofol. The patient was discharged the next morning. For the first two days patients were recommended not to assume the sitting position but walking was encouraged. Return to work was permitted seven days after surgery.

Microdiscectomy

The procedure was performed in a standard microsurgical fashion. Antibiotic therapy (3rd generation cephalosporin) was administrated on the same day as surgery and then continued for five days afterwards. The patients were given a spinal anesthesia and positioned on the operating table in the knee-chest position. A median 2-3 cm incision was made and the paravertebral musculature of the affected side was removed from the spinous process until reaching the interlaminary space. The yellow ligament was incised followed by standard approach to the disc space.

The herniated material was removed and just a small part of the disc itself was excised as much as necessary to have the entrance space through the anulus free of detached disc material. Then rigorous haemostasis was performed and the wound was closed in a standard three-layer fashion. The patient was allowed to get out of bed 12 hours later and discharged the day after the surgery. Sitting was not allowed for the first five days post-surgery. Return to work was permitted two weeks after the procedure.

Follow-up

Patients were followed prospectively by compilation of pre and post-procedure questionnaires. Pain was evaluated by Visual Analogue Scale (VAS). Dysfunction and disability were followed by self-administrated Roland-Morris Disability Questionnaire (RMDQ). Overall treatment satisfaction was evaluated by a 100 point Overall Patient Satisfaction Rating (OPSR).

The VAS was submitted to patients as a coloured scale divided into ten different shades of the same colour and each shade further divided into ten. The clearer the colour the lesser the pain and vice versa. The RMDQ used was in the form approved and validated for use in the Italian language. Pain Rating Scale of the same questionnaire was not used as it was found less valuable than the VAS evaluation for pain. The OPSR was used as a simple scale from 0 to 100 where the patient indicated the percent of his/her general sense of satisfaction with the treatment. The above ratings were made on the morning before treatment and then six, 12 and 18 months post-procedure.

Fifteen randomly chosen patients from the ozone chemonucleolysis group of treatment underwent control MRI between three and five months after the procedure. Volume reduction was measured by an independent observer and expressed in % of volume reduction.

Statistical Method

Statistical analysis was performed using STATA 7.0 software (Stata Corporation, USA). The significance of the difference of the VAS score and the RMDQ score at time 0 and 18 months was tested by non-parametric statistics (Wilcoxon sign-rank test).

Results

Two patients dropped out of the ozone chemonucleolysis group because of aggravating symptoms and were operated upon: one three months and the other seven months after the pro-

Table 1 **Results and statistical significance at 18 months follow-up**

Variable	N	Preprocedure value (T 0)	Postprocedure value (T 18)
VAS ozone	30	5.3 ± 2.2	0.9 ± 1.0
VAS microdiscectomy	15	6.1 ± 3.1	2 ± 1.3
RMDQ ozone	30	9.1 ± 3.5	2.4 ± 2.7
RMDQ microdiscectomy	15	12.4 ± 4.3	2.1 ± 1.9

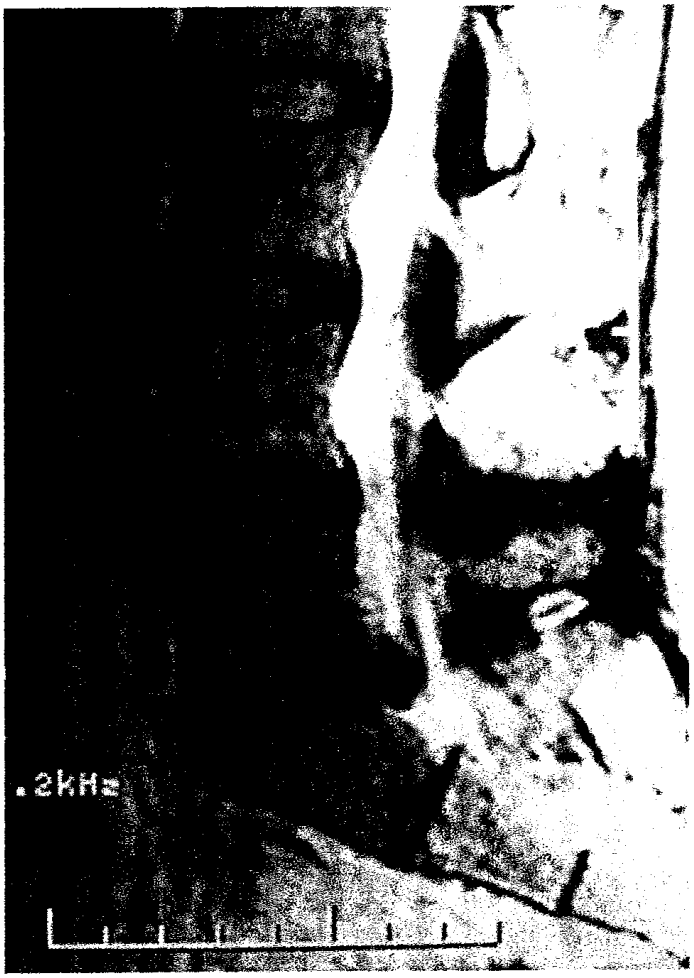

Figure 1

Figure 2

cedure. At 18 months follow-up 28 patients were available but the statistical analysis was performed on all 30 patients, regarding the two surgically treated patients as failures of the procedure. No patient from either group was lost to follow-up.

VAS – At 18 months follow-up, 27 patients (90%) in the ozone chemonucleolysis group showed improvement in pain, one patient (3.3%) remained unchanged whereas two patients (6.6%) had worsened (operated). The mean pre-treatment value for all patients was 5.3 ± s.d.2.2 and the overall mean 18 months follow-up value was 1.3 ± s.d. 1.6 with a change of 4.0 (95% CI = 2.9 – 5.0). The maximum improvement was seen inside the first two months.

At 18 months follow-up, 14 patients (93.3%) in the microdiscectomy group showed pain improvement whereas one patient (6.6%) had worsened. The mean pre-treatment value for all patients was 6.1 ± s.d.3.1 and the overall mean 18 months follow-up value was 2 ± s.d. 1.3 with a change of 4.1 (95% CI = 3.2 – 5.5). The maximum improvement was seen inside the first month.

Patients from both groups showed a statistically significant improvement in pain on 18 months follow-up ($p<0.001$). There was no statistically significant difference in pain improvement between the two groups of treatment ($p<0.001$).

RMDQ - At 18 months follow-up, 27 patients (90%) in the ozone chemonucleolysis group had improved in function, one patient (3.3%) remained the same whereas two patients (6.6%) had worsened (operated). The mean pre-treatment value for all patients was 9.1 ± 3.5 and the overall mean 18 months follow-up value was 2.2 ± s.d. 3.2 with a change of 6.9. The maximum improvement was seen inside the first three months.

At 18 months follow-up, 13 patients (86.6%) in the microdiscectomy group had improved in function, and two patients (13.2%) remained unchanged. The mean pre-treatment value for all patients was 12.4 ± 4.3 and the overall mean 18 months follow-up value was 2.1 ± s.d. 1.9 with a change of 10.3. The maximum improvement was seen inside the first three months.

Patients from both groups showed a statistically

significant improvement in function at 18 months follow-up ($p<0.001$). There was no statistically significant difference in function improvement between the two groups of treatment ($p<0.001$).

OPRS - Mean satisfaction with the treatment at 18 months was 79.3% ± 28.7 for the ozone chemonucleolysis group and 82.1% ± 31.2 for the microdiscectomy group.

Twenty-four patients (80%) in the chemonucleolysis group referred satisfaction equal to or greater than 80%, three patients (10%) referred satisfaction ranging from 50 to 80% whereas three patients (10%) were not satisfied with the treatment (two of these were operated upon by microdiscectomy). Twelve patients (80%) In the microdiscectomy group referred satisfaction equal to or greater then 80%, two patients (13%) referred satisfaction between 50 to 80% whereas one patient was not satisfied with the treatment.

Regarding satisfaction with treatment, there was no difference between the two groups.

Morphological changes (figure 1, figure 2) - Fifteen out of 30 patients from the ozone chemonucleolysis group, all of whom clinically improved, performed control MRI imaging. Eight of them had a substantial reduction, superior to 50%, of the herniation volume. Two patients showed volume reduction inferior to 50% whereas five patients had no substantial variation of the herniation volume. The mean volume reduction for 15 patients was 49% ± s.d. 42.5%.

Discussion

As the equation large herniation = major symptoms, small herniation = minor symptoms is not always true, it seems quite natural to assume that clinical signs and symptoms of disc herniation are not caused only or mainly by mechanical compression but that biochemical factors play an important role in inflammatory sensitization and immune response in the peridural environment of the nerve root [15,20,25,31]. For the same reason it seems logical to presume that mechanical removal of herniated tissue may not always be needed and that reducing the inflammatory process could essentially be sufficient to treat the symptoms. This study partially confirms this hypothesis because although only eight out of 15 randomly chosen patients from the ozone chemonucleolysis group showed a substantial volume reduction of the herniated material, all 15 had a significant improvement in pain and function.

Ozone chemonucleolysis for degenerative disc disease is a relatively new intradiscal treatment started in Italy some ten years ago. Pioneering reports mainly in form of case reports or case series published in Italian scientific journals and a few recent articles published in international peer-reviewed journals indicate that by reducing pain and improving functional status the treatment is useful in patients with disc herniations [2,7,34]. Basic research on ozone activity conducted in several Italian universities found that the mixture of ozone and oxygen has a potent, dose-related, biological activity[5,6,24,29,30]. At high concentrations (30-70 $\mu g0_3/ml0_2$), it may cause alteration and destruction of tissue structures. At medium concentrations (20-30 $\mu g0_3/ml0_2$) it seems to affect the regulation of the immune system while at low concentrations (<20 $\mu g0_3/ml0_2$) it improves the microcirculation by increasing the oxygen delivery to tissues.

At the level of the intervertebral disc in disc-root conflict, the effects of the ozone mixture application appear mainly related to the reduction of inflammation. Moreover, the improvement of the local microcirculation with reduction of venous stasis and ischemia at nerve root level certainly plays an important role [13,19]. Histological studies performed on animal models, demonstrated that the intradiscal application of ozone at high concentrations produces degeneration of cytosol and cell shrinkage in the nucleus pulposus [14,18]. If applied in adequate concentrations, ozone produced no toxic effects either in vitro or in vivo [26]. The critical parameters such as the concentration range and dose and the gas volume must not exceed the antioxidant capacity at the site of injection. Enzymes such as superoxide dismutase, catalase and GSH-peroxidase prevent the accumulation of superoxide anion (O_2-) and hydrogen peroxide (H_2O_2). The risk of free radical formation is minimal because at pH 7.5 the predominant mechanism is ozonolysis favouring the production of peroxides. Experimental tests in animals and humans showed a lack of negative effects [17]. The data from this study and the findings of other physicians using this method essentially confirm the lack of adverse effects on short and long-term follow-up. Experimental studies also indicate that the adequate doses and concentrations of ozone to the human body have no mutagenic properties [4]. Special attention should be paid to patients with hyperthyroidism, unstable arterial hypertension, cachectic patients and those with favism due to either hypermetabolism or an enzymatic defect of G6PD.

The results of this prospective controlled study are encouraging, but we still do not know why herniation volume diminishes in some patients and not in others despite clinical improvement. Further randomized studies with larger groups of patients are needed to confirm these initial findings.

Conclusion

This study indicates that there are no major differences in clinical outcome between ozone chemonucleolysis and microdiscectomy treatments in patients with non-contained disc herniations with predominant symptoms of pain and without neurological deficits. Treatment of disc herniation has to be proportionate to the severity of clinical signs and symptoms and the primary approach should not be surgical in patients with pain alone regardless of herniation volume.

Ozone chemonucleolysis may have a major impact on the treatment of symptoms of disc herniation as it seems to have a high clinical success rate and may also resolve the primary cause. It is a simple low-cost method both in terms of procedure and social cost with an almost total absence of risks and complications in short and long-term follow-up.

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