An observational retrospective/horizontal study to compare oxygen-ozone therapy and/or global postural re-education in complicated chronic low back pain

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Summary

Acute low back pain (LBP) is the fifth most common reason for physician visits and about nine out of ten adults experience back pain at some point in their life. In a large number of patients LBP is associated with disc herniation (DH).
Recently, oxygen-ozone (O_2O_3) therapy has been used successfully in the treatment of LBP, reducing pain after the failure of other conservative treatments.
The aim of this study was to assess the effects of O_2O_3 therapy in back pain rehabilitation, comparing three groups of patients suffering from chronic back pain associated with DH submitted to three different treatments: intramuscular O_2O_3 infiltrations, global postural re-education (GPR), or a combination of the two (O_2O_3+GPR). The data show that pain severity before treatment was significantly lower in the patients treated with GPR alone (VAS score 7.4) than in the O_2O_3+GPR patients (VAS score 8.5) and the O_2O_3 patients (VAS score 8.6). At the end of treatment, pain severity was lower in the O_2O_3 patients than in the GPR-alone patients. After some years of follow-up only the difference between O_2O_3+GPR and GPR-alone remained significant.

KEY WORDS: chronic back pain, combined treatment (O_2O_3+GPR), global postural re-education, intramuscular oxygen-ozone infiltrations, lumbar disc herniation, sciatica.

Introduction

Back pain is a major cause of functional disability, absence from work and need of healthcare services in western countries (Van Tulder et al., 2002).
In most patients suffering from back pain, the pain is located in lumbar regions (low back pain or LBP), with or without involvement of the anterior or posterior part of the lower limb, and/or in the cervical portion of the spine (neck pain), with or without involvement of the arm.
Up to 70-85% of the general population have reported at least one episode of LBP in their lifetime (Andersson, 1999). In accordance with data from several cross-sectional studies collected by Andersson (1997), the lifetime prevalence of LBP has been found to range from 49% to 70% (Van Tulder et al., 2002). Moreover, the prevalence of people suffering from sciatica has been found to range from 12% to 43% (Konstantinou and Dunn, 2008) and about two thirds of the population have suffered from neck pain at least once in their lifetime (Binder, 2007).
Disc herniation (DH) is a condition often associated with LBP (Modic et al., 2005). A significant association between DH and LBP was recently found in a general population of over a thousand subjects (Cheung et al., 2009).
The natural history of DH tends to be favorable in most cases: spontaneous regression of DH in longitudinal imaging studies has been reported (Sakai et al., 2007), and a spontaneous resolution of pain within the acute phase (from 6 to 12 weeks after pain onset) has been documented in 60-80% of patients with sciatica

(Peul et al., 2005). However, relapses (Häkkinen et al., 2007), recurrent episodes of pain and chronic LBP – namely, a "tolerable" and yet persistent pain which is resistant to conservative treatments – are not infrequent (Awad and Moskovich, 2006).

The traditional approach to the treatment of DH is surgery, which has been shown to be effective in 76-93% of cases (Häkkinen et al., 2007). However, various factors influence the surgical success rate. Relapses post-surgery occur with a probability ranging from 5% to 15% (Awad and Moskovich, 2006) and 5-12.5% of patients undergo surgery again (Häkkinen et al., 2007). Moreover side effects, such as discitis, osteomyelitis, adhesional fibrosis, and post-surgery complications, are frequent (Awad and Moskovich, 2006).

Nowadays, surgery is considered indicated only in patients who complain of intolerable pain, who present a progressive neurological deficit, or who risk developing a cauda equina syndrome (Awad and Moskovich, 2006). Minimally invasive methods have been developed (such as steroidal and non-steroidal anti-inflammatory injection and infiltration, acupuncture and mesotherapy), in addition to various non-surgical treatments, such as systemic oral anti-inflammatory treatments, skeletal muscle relaxants, physiotherapy, vertebral manipulation and postural re-education. Recently there has been increasing use, among the conservative treatments, of oxygen-ozone (O_2O_3) therapy. O_2O_3 is a gas mixture of medical oxygen and ozone which is produced from pure oxygen passing through a high voltage gradient (5-13mV) in a medical generator.

In the last few years, O_2O_3 therapy has been successfully used in the treatment of LBP. In patients affected by lumbar DH, O_2O_3 has also been found to be helpful in reducing pain after the failure of other conservative treatments. In this context, intradiscal and/or intraforaminal administration was initially used, whereas in routine clinical practice paravertebral intramuscular infiltration is now the technique mainly used (Paoloni et al., 2009) as it is much less invasive. Unfortunately, to date very few investigations have been carried out to study the effectiveness of this procedure in the treatment of LBP. A good reduction of pain and a significant improvement in daily-life activities was obtained in patients with lumbar DH treated with intramuscular infiltrations of O_2O_3 (Apuzzo, 1998). Much more recently Paoloni and colleagues (2009) conducted a double-blind randomized controlled trial in patients suffering from acute pain associated with lumbar DH and treated with O_2O_3 intramuscular infiltrations. These authors recorded, in a high percentage of subjects, short- and medium-term decreases in pain, disability and intake of analgesics.

Another branch of conservative treatment employed in the treatment of LBP is physical therapy. Indeed, postural deficit is a major cause of DH; furthermore, most patients assume an incorrect posture in response to pain, which results in the generation of muscular contractures and maintenance or worsening of the algogenic conditions.

Global postural re-education (GPR) is a specific method of physical therapy started by Souchard in the 1980s (Souchard, 1987). It consists of stretching anti-gravity muscles which are contracted and retracted within different postural muscle chains. This action reduces muscle tension which could be responsible for overloading joints. The principles of GPR can be summarised as follows:

- causality: all musculoskeletal problems depend on one primary cause (primary compensation), therefore, simply removing secondary compensations is not enough to obtain complete and long-lasting resolution of pain;
- overview: pain in a specific part of the body cannot be treated per se but must be treated taking into account its effects in related areas;
- individuality: the aim of GPR is to treat an individual with disability rather than a pathology.

For all these reasons this method is particularly indicated for the treatment of a wide-range of musculoskeletal and rheumatic diseases. Satisfactory results have been obtained in the reduction of LBP, even when it is associated with DH.

The present author provided evidence of the effectiveness, short- and long-term, of this combined therapy in reducing pain and improving quality of life (Apuzzo and Tomaiuolo, 2001; Apuzzo et al., 2003, 2004).

The present study was conducted to evaluate the effectiveness of intramuscular O_2O_3 infiltration in patients with chronic back pain associated with DH, comparing it both with GPR and with the two treatments combined (O_2O_3 +GPR).

Materials and methods

The population under study comprised patients with unilateral or bilateral DH or disc protrusion and associated pain, a clinical picture referred to as complicated low back pain.

Inclusion criteria were: i) DH or disc protrusion at lumbar and sacral level diagnosed on the basis of MR images, and ii) symptoms associated with the herniation/protrusion site as verified through clinical assessment.

Exclusion criteria were: i) severe vertebral osteoarthrosis, ii) calcified hernia, iii) major neurological deficits of the upper or lower limbs, and iv) unstable spondylolysis and/or spondylolisthesis. We had preliminarily excluded from O_2O_3 treatment all patients whose medical conditions could be worsened by O_2O_3 injections, such as pregnant women or patients affected by clinically diagnosed hyperthyroidism or heart failure. Therefore, subjects positive for any of these particular conditions who received only the GPR treatment were also excluded from the study.

From May 1995 to December 2007, a total of 923 patients satisfying these criteria were treated at the "SALUTE OK" clinic in Rome, Italy; even though this is a retrospective study every effort was made to choose similar patients for comparison.

In accordance with normal clinical practice all these patients were measured on pain and disability scales and investigated for the occurrence of side effects

both before and at the end of treatment. All complained of pain persisting for a period of time ranging from one month to five years. Most had received at least one (different) conservative treatment previously, without resolution of the pain. Only 35 patients had previously undergone surgery; surgery had also been recommended by an orthopedic specialist or neurosurgeon in a further 179 subjects, even though these patients did not have neurological disabilities constituting true indications for surgery.

In all, 546 patients agreed to be re-evaluated through a follow-up questionnaire. These were administered at varying intervals from the end of treatment (between six months and 11 years).

After a comprehensive baseline assessment patients were assigned to O_2O_3, to GPR, or to combined therapy (O_2O_3+GPR) on the basis of specific criteria aimed at defining the severity of their medical condition. These assignment criteria were as follows: i) pain intensity: patients who complained of the highest levels of pain were assigned to treatment with O_2O_3 infiltrations (with or without GPR) whereas subjects with a less intense level of pain were assigned to GPR treatment alone; ii) global posture: the subjects experiencing the highest level of pain included cases showing a markedly erroneous global postural pattern; these subjects were assigned to combined therapy (O_2O_3+GPR).

The O_2O_3 therapy group included 187 (20%) subjects. The clinical protocol involved bilateral intramuscular O_2O_3 infiltrations, injected at the disc lesion site with a paravertebral approach.

An ozone generator was used to produce an oxygen-ozone mixture at a level of 20 µg/ml. The injection site was then disinfected and 15 cc of the gas mixture was injected into each side using a 22-gauge spinal needle (length, 30 mm; size, 0.70 mm). In order to promote homogeneous distribution of the gas through the muscle fibers and avoid pain, the gas mixture was injected very slowly (at a rate of 2.50-3.75 cc/s) and the injection site was massaged gently at the end of the injection. The whole procedure was performed by a specialist physiatrist. The clinical protocol provided for 12 biweekly sessions of treatment, and 10 maintenance sessions (four performed at weekly intervals, followed by four at fortnightly intervals and finally one a month for two months).

Ninety-three (10%) subjects received GPR therapy alone. The treatment, administered by a team of physiotherapists, was based on breathing, stretching and proprioception exercises, to ease muscle contractures and, indirectly, help lengthen the spine. The protocol provided for 12 biweekly sessions of care followed by three maintenance sessions, the first after a week, the second a fortnight later, and the third after an interval of one month from the second.

The combined treatment (O_2O_3+GPR) was assigned to 643 (70%) subjects. It involved the concurrent administration of the above-described O_2O_3 and GPR protocols.

At admission, as in normal clinical practice, each patient underwent a baseline assessment (T0) which comprised: i) collection of *demographic* data, e.g. gender, age, ethnicity, marital status, educational level and occupation; ii) collection of *neuroradiological* data, such as type and location of disc lesions, on the basis of MR images provided by the patient; iii) collection of a *general and specific medical and pharmacological anamnesis*, in particular regarding previous non-surgical treatments of back pain, previous neurosurgery (or recommendation for), current diagnosed diseases and medications, daily life habits such as sports activity, intensity of physical activity, number of hours spent driving; iv) collection of *clinical* data by means of a comprehensive physical and neurological examination including the Lasegue test, the Wassermann test, Dandy's search, Valleix points, trigger points, pince roulé; muscle strength evaluation, sensory assessment and the ROT examination; v) a *global postural* evaluation, aimed at highlighting noticeable deficits in postural pattern.

After baseline assessment a clinical research technician, in accordance with what is done in normal clinical practice, explained the procedure and obtained the patient's written and signed informed consent.

The subjects were each administered a visual analog scale (VAS) to measure their overall perception of pain. They were asked to estimate their back pain by indicating a level on a 10-point (from 0 to 10) numerical rating horizontal line, where the point on the extreme left corresponded to pain that is "not noticeable at all" and the one on the right extreme to the "worst pain imaginable". Perceived daily functional status and disability were evaluated using the "Role limitations because of physical problems" (RL-p) scale, extracted from the Short Form-36 Health Survey (SF-36). This scale is composed of four items and it was used to measure, on a four-level Likert scale, the extent to which daily social life and work/study activities were impaired by pain. A final index (RL-pI) was computed from the single four scores (Table I).

Thus, on the basis of collected data and the treatment assignment criteria, patients were addressed to a spe-

Table I - Role limitations because of physical problems (RL-p) subscale from the Short Form-36 Health Survey (SF-36).

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?	
1. Cut down on the amount of time you spent on work or other activities	Yes / No
2. Accomplished less than you would have liked	Yes / No
3. Were limited in the kind of work or other activities	Yes / No
4. Had difficulty performing the work or other activities (for example, it it took extra effort)	Yes / No

cific therapy and informed about therapeutic mechanisms, possible adverse events and the administration procedure. If they agreed, they received the treatment assigned.
At the end of each session of treatment, the patients who received the O_2O_3 or O_2O_3+GPR treatments were asked how they felt and whether they had encountered any adverse effects since the previous session. Details of any reported side effects were recorded. At the end of treatment the patients were invited to contact the clinic in the event of health problems over the following month.
After an interval of about one month had elapsed since the end of the treatment the VAS and the RL-p were administered again (TI).
Patients were encouraged to repeat MRI scans three months after the end of treatment in order to check the post-treatment disc lesion status. To reinforce MRI data interpretation, two neuroradiologists independently and blindly evaluated the post- and the pre-treatment MRI data, comparing the dimensions of DH in the two scans. Patients' status was scored positive (+) if the MRI status had improved, unchanged (0), or negative (-) if had worsened. Disagreements were resolved by consulting a third neuroradiologist.
GPR treatment is indicated in the presence of a deficit in postural pattern, i.e. a disequilibrium of the patient's previous stabilized subjective postural pattern. This disequilibrium is supposed to be one of the possible effects of the inflammation caused by DH.
From January through May 2008 a seven-item follow-up questionnaire was mailed to all the 923 patients treated for disc hernia/protrusion and related pain (T2). Only the 546 patients who answered the questionnaire were considered for this analysis. The questions were designed to investigate the following variables: i) perceived current health status (4 items); ii) post-treatment surgery (2 items); iii) current overall perception of pain using VAS (1 item) (Table II). The subjects were informed about the purpose of the follow-up evaluation and informed that they would be contacted by telephone in a few weeks by a clinical research technician who would collect their answers and verbal informed consent. Accordingly, the patients were contacted by telephone and said whether they agreed to participate in the follow-up evaluation. Their answers to the follow-up questionnaire questions were tape-recorded and subsequently transcribed.

Statistical analysis

The statistical analysis was based mainly on ANOVA for repeated measures with Time as the within-subjects factor and Treatment as the between-subjects factor. Correlation was assessed by means of Spearman's coefficient. The SPSS (ver. 16.0) was used for statistical analysis.

Results

This retrospective/horizontal observational study was designed to track the evolution of patients with back pain, treated with GPR and/or O_2O_3 It was felt that the large sample and the comparison with published papers on effects of similar and alternative treatments could furnish useful information about O_2O_3 treatment.
A follow-up questionnaire was mailed to all the participating patients; 377 of the total 923 (41%) were not reached and this could be a first source of bias. Comparisons were performed in order to establish whether the available sample data are representative and homogeneous and to analyze possible biases. Patients who answered the follow-up questionnaire (n=546) were similar to those who did not answer (n=377) in terms of age (t-test=1.067, df=921, p=.286)

Table II - Follow-up questionnaire mailed to all 923 patients treated for disc hernia/protrusion and related pain (T2).

(a) Perceived current health status (4 items):	
1. How did you feel at the end of the treatment?	Fine, not too bad, bad
2. How do you feel right now?	Fine, not too bad, bad
3. If you are not feeling well, after how long did the pain come back?	Within 6 months, from 6 months to 1 year, after 1 year
4. After the treatment your life in general is:	Improved, the same, worsened
(b) Post-treatment surgery (2 items)	
1. After the treatment did you undergo surgery for the herniation or protrusion treated?	Yes / No
2. If so, after how long?	Within 6 months, from 6 months to 1 year, after 1 year

(c) Current overall perception of pain (VAS) (1 item):

Considering a scale ranging from 0 to 10, where 0 represents no pain and 10 the worst possible pain, how intense is your pain right now?

0	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
NOT NOTICEABLE AT ALL										WORST PAIN IMAGINABLE

and sex (chi-square=0.119, df=1, p=.730). In addition, pain (VAS score) was similar in the two groups (t=1.474, adjusted df=912.6, p=.110), as was the RL-p score (Mann-Whitney test, p=.715).
In the whole sample of 923 patients, the median number of sessions was 15 (interquartile range=10-25 sessions), while the median duration of the treatment was three months (interquartile range=1.5-14 months).
Baseline demographic and clinical characteristics of the 546 patients are summarized in table III.
When type of treatment was entered in ANOVA as a between-subjects factor, a significant interaction

Table III - Baseline demographic and clinical characteristics of all patients (*n*=546) and of the patients divided by treatment groups.

	Sample *n* 546	O_2O_3 *n* 109 (20.0%)	GPR *n* 54 (9.9%)	O_2O_3+GPR *n* 383 (70.1%)
Age, years				
• mean±sd	50±14	50.3±13.5	46.1±13.2	50.5±14.2
• range	17-91	27-81	19-77	17-91
Females, n (%)	267 (48.9)	32 (59.3)	51 (46.8)	184 (48.0)
Duration of back pain, n (%)				
• < 6 months	233 (42.7)	39 (35.8)	38 (70.4)	156 (40.7)
• 6 months-1 year	123 (22.5)	27 (24.8)	9 (16.7)	87 (22.7)
• 1-5 years	113 (20.7)	24 (22.0)	4 (7.4)	85 (22.2)
• >5 years	77 (14.1)	19 (17.4)	3 (5.6)	55 (14.4)
Previous treatment, n (%)				
• pharmacology	169 (31.0)	34 (31.2)	14 (25.9)	121 (31.6)
• physical therapy	183 (33.5)	45 (41.3)	11 (20.4)	127 (33.2)
• other*	43 (7.9)	2 (1.8)	2 (3.7)	39 (10.2)
• none	151 (27.7)	28 (25.7)	27 (50.0)	96 (25.1)
Pre-treatment surgery, n (%)	35 (6.4)	14 (12.8)	-	21 (5.5)
Indication for surgery, n (%)	179 (32.8)	53 (48.6)	-	126 (32.9)
Disc lesion type, n (%)				
• protrusion	283 (51.8)	52 (47.7)	45 (83.3)	186 (48.6)
• contained herniation	136 (24.9)	29 (26.6)	8 (14.8)	99 (25.8)
• extruded/migrated herniation	41 (7.5)	7 (6.4)	-	34 (8.9)
• different types of herniation	83 (15.2)	21 (19.3)	1 (1.9)	64 (16.7)
Disc lesion location, n (%)				
• C3-C7	77 (14.1)	6 (5.5)	18 (33.3)	53 (13.8)
• L1-L5	176 (32.2)	46 (42.2)	9 (16.7)	121 (31.6)
• L1-S5	135 (24.7)	28 (25.7)	8 (14.8)	99 (25.8)
• L5-S1	154 (28.2)	28 (25.7)	19 (35.2)	107 (27.9)
• C3-S1**	4 (0.7)	1 (0.9)	-	3 (0.8)
Symptoms, n (%)				
• cervicalgia	29 (5.3)	1 (0.9)	15 (27.8)	13 (3.4)
• cervicobrachialgia	46 (8.4)	5 (4.6)	3 (5.6)	38 (9.9)
• lumbalgia	118 (21.6)	21 (19.3)	16 (29.6)	81 (21.1)
• sciatalgia	44 (8.1)	11 (10.1)	2 (3.7)	31 (8.1)
• lumbosciatalgia	252 (46.2)	62 (56.9)	15 (27.8)	175 (45.7)
• lumbocruralgia	29 (5.3)	4 (3.7)	1 (1.9)	24 (6.3)
• lumbalgia+sciatalgia+cruralgia	23 (4.2)	4 (3.7)	1 (1.9)	18 (4.7)
• cervicalgia+ lumbalgia or sciatalgia	5 (0.9)	1 (0.9)	1 (1.9)	3 (0.8)
Valleix, positive, n (%)	243 (44.5)	56 (51.4)	11 (20.4)	176 (46.0)
Wassermann, positive, n (%)	53 (9.7)	8 (7.3)	3 (5.6)	42 (11.0)
Lasegue, positive, n (%)	62 (11.4)	17 (15.6)	3 (5.6)	42 (11.0)
Absent or reduced deep tendon reflexes, n (%)				
biceps	11 (2.0)	1 (0.9)	1 (1.8)	9 (2.3)
triceps	9 (1.6)	1 (0.9)	1 (1.8)	7 (1.8)
knee-jerk	73 (13.4)	18 (16.5)	2 (3.7)	53 (13.9)
ankle-jerk	132 (24.2)	35 (32.1)	5 (9.3)	92 (24.0)

Abbreviations: O_2O_3=oxygen-ozone treatment; GPR=global postural re-education; O_2O_3+GPR=combined treatment.
*chiropratic, mesotherapy, acupuncture, paravertebral infiltration; **more than one herniation, at different spinal levels

"Treatment X Time" was found [F(4,1075.0)=9.800, p<.001]. This interaction is represented graphically in figure 1, which depicts the trends of pain across time according to type of treatment. The main reason for the significant interaction is the lack of parallelism between decreases occurring between T0 and T1 (p<.001): pain in the GPR group decreased less than in the other two groups, which instead showed very similar changes.

In the period between the end of therapy and the follow-up visit (i.e. T1-T2), type of treatment did not show a marked effect (p=.216), although the decrease observed in the whole sample could be ascribed mainly to the O_2O_3+GPR group.

Figure 1 also shows that pain severity before treatment (T0) was significantly lower (p<.001) in patients treated with GPR alone (7.4, 95% CI=6.9-7.5) than in the O_2O_3+GPR patients (8.5, 95% CI=8.4-8.7) and in the O_2O_3 patients (8.6, 95% CI=8.3-8.8). However, at the end of treatment these differences were reversed, pain severity being found to be lower in the O_2O_3 patients (with or without GPR) than in the GPR-alone patients. At follow-up, the difference between O_2O_3+GPR and GPR-alone remained significant (p=.005). As a matter of fact, GPR showed clearly lower efficacy during treatment but seemed to have a beneficial effect in the long-term, since the only group that did not show a decrease at follow-up was the one not submitted to GPR.

Age did not exert any effect on baseline pain [F(1,539)=0.010, p=.919], whereas a sex effect could be documented [F(1,543)=5.570, p=.019], with the women showing higher mean values (8.7; 95% CI=8.5-8.8) than the men (8.2; 95% CI=8.0-8.4). Instead, as regards changes in pain during follow-up, while no effect of gender was found (p>.20), age seemed to play a role. More precisely, the pain reduction observed soon after the end of the treatment was not modulated by age, while the reduction observed between the end of the treatment and the follow-up evaluation was lower in older than in younger patients. Although the age effect size was quite low (around 2% of pain reduction variance could be attributable to age) and its significance was due to the large sample size, it was noted that the pain reduction after the end of treatment occurred only in youngest group (under 40 years). This age effect was not a spurious effect of the assignment of patients to treatments according to their age: in fact, there was no association between age and type of treatment (p=.475) and the percentages in the three age groups that underwent the treatment without GPR were very similar (21% in the 20-40 year olds, 20% in the 41-60 year olds and 18% in the 61-80 year olds.

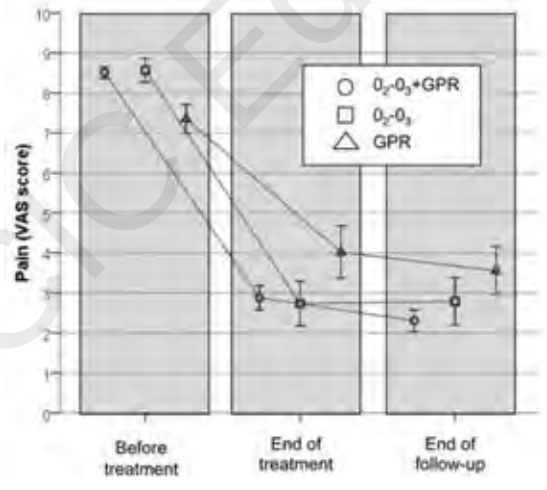

Figure 1 - Comparison of the treatments at three time points.
T0 represents pain status at the beginning of therapy, T1 (p<.001) pain status at the end of treatment, T2 pain status after 1 to 5 years of follow-up after the end of treatment.

A high percentage of patients (72%) had received other therapies in the past. As shown in figure 2, the pain reductions observed after the three treatments were similar in patients who had previously been treated with other approaches and in *de novo* patients. This finding indicates that the gain for O_2O_3 therapy vs GPR-alone was confirmed even in patients who had not benefitted from previous treatments ("refractory" patients).

Since changes in RL-p and in VAS scores were strongly associated with each other (r=-.58, p<.001), we expected similar effects of treatment on these functional measures. In fact, a 41% increase in RL-p was recorded in the GPR-alone patients (95% CI: 33-50), versus 56% in the O_2O_3 (95% CI: 49-63) and 54% in the O_2O_3+GPR (95% CI: 50-58) groups.

Similarly, high correlations were found between VAS score and the global evaluation provided by patients about their status at the end of treatment (Spearman's rho=.71, p<.001) and at the time of follow-up interview (Spearman's rho=.74, p<.001).

The percentage of patients without recurrence of previous symptoms was 64.2% in the O_2O_3+GPR group, 59.6% in the O_2O_3 group and 24.1% in the GPR-alone group (chi-square, p<.001). In the cases with recurrence, the percentage experiencing recurrence within the first six months was higher in the GPR-alone (80.5%) than in both the O_2O_3 groups (48.2% with GPR, 38.6% without GPR; p=.001). Again, no evidence of difference was found between the O_2O_3 groups (p=.272).

Of the patients who repeated MRI at the end of treatment (*n*=130), the herniation was found to be reduced in 47 (36%), while it was stable or enlarged in 83 (64%) (Fig. 3a). It is to be noted that only three patients in the GPR-alone group underwent MRI examination and they were excluded from the subsequent analysis. As shown in figure 3b, the VAS reduction was observed in both MRI groups. More precisely, in the group with improvement on MRI the pain was reduced by 5.3 points (SE=0.4) and in the group with stability or worsening on MRI it was reduced by 4.1 (SE=0.5). This difference was not strictly significant (p=.071).

The incidence of side effects during and soon after O_2O_3 treatments was low (7 cases, 1.4%). In particular, side effects were reported by six patients in the O_2O_3+GPR arm (1.6%) and by one in the O_2O_3 treatment group (0.9%), without significant difference (chi-

square=0.255, p=.614). Considering the total number of O_2O_3 infiltrations, the incidence of side effects was 3 x 1000 infiltrations. The side effects reported were insomnia, itching and papules around the point of infiltration, gastritis, dizziness, tachycardia, hot flush and trigeminal neuralgia.

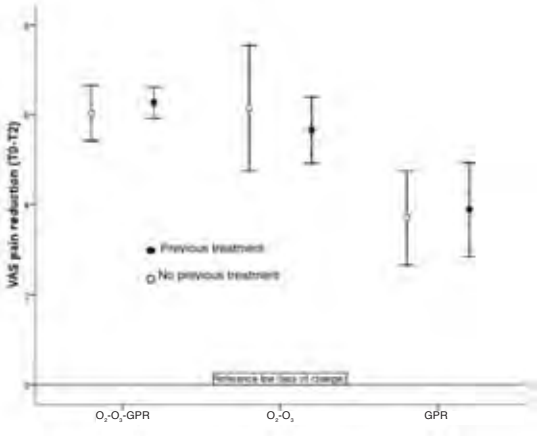

Figure 2 - Comparison, in three different treatment groups, between patients who had (72%) and had not been submitted to other treatments in the past.

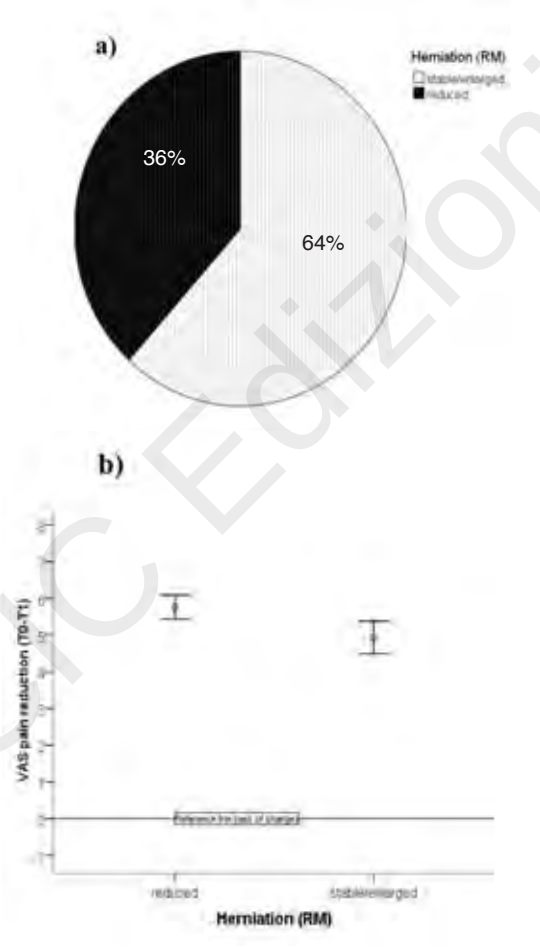

Figure 3 - Outcome of the 130 low back pain patients who repeated MRI at the end of treatment.

The patients who had had surgery prior to receiving the O_2O_3 treatments numbered 35 (21 entered the O_2O_3+GPR arm and 14 the O_2O_3 arm). In these patients, too, a significant decrease in pain (VAS) was found: -5.0 (95% CI: -3.3; -6.6) after O_2O_3+GPR treatment and -3.6 (95% CI: -1.5; -5.6) after O_2O_3 treatment.

The patients who had been advised to undergo surgery numbered 179. Of these, 126 entered the O_2O_3+GPR arm and 53 the O_2O_3 arm. A significant decrease in pain (VAS) was also recorded in these patients: -5.8 (95% CI: -5.2; -6.3) after O_2O_3+GPR and -5.6 (95% CI: -5.2; -6.1) after O_2O_3 treatment.

A low incidence (17 out of 179=9.5%) of post-treatment surgery was found in the patients advised to undergo surgery (9.5% after O_2O_3+GPR treatment and 9.4% after O_2O_3 treatment). It must be remembered that the median follow-up was 2.4 years (interquartile range: 1.1-4.8).

Discussion

These data showed that O_2O_3, GPR and O_2O_3+GPR were effective in the treatment of pain associated with DH, both in the short and the long term. In all the samples, the pain was found to have significantly decreased at the end of treatment and was further reduced at follow-up.

Analysis of changes in pain in each treatment group revealed an approximately 6-point reduction in VAS score at the end of the treatment in the groups that underwent ozone therapy, as opposed to a reduction of 3.3 VAS points in the GPR group, which, in addition, had significantly lower baseline pain severity. These results in the GPR patients remained unchanged at follow-up, whereas pain in the O_2O_3 and O_2O_3+GPR groups was found to have decreased further, significantly so in the latter arm.

Summarizing, ozone therapy, alone or in combination with GPR, seems to be associated with the best short-term effects on pain, whereas GPR, alone or in combination with ozone therapy, seems to be associated with a further reduction in pain over time. These findings seem to suggest that ozone could produce a sharp decrease in pain in the short term, and that this effect could be maintained, if not further increased, by the corrective and long-lasting action of GPR on postural deficits.

It should be noted that this further improvement in pain at follow-up was observed only in patients younger than 40 years. This result is likely to be due to the fact that correcting an incorrect and ingrained postural pattern is harder in older people because of the effects of aging on joint structure and cartilage.

For most people affected by DH who undergo ozone therapy, this therapy is their last option before surgery; others try ozone after post-surgery recurrences. In the present sample, 72% of the patients had, in the past, undergone at least one different conservative treatment, while 35 had previously had surgery. These data show that most

of them, on admission to the clinic, suffered from chronic pain, and that this pain was also resistant to a wide range of conservative treatments. Notwithstanding this, after having received our treatments, these patients did not show less reduction of pain than the subjects who had never been treated. Even patients who had previously undergone surgery showed a significant decrease in the level of pain, in a similar way to those who had never been operated on. This trend was observed in all three treatment groups, showing that each of the treatments is effective even in "difficult patients", such as those with chronic and treatment-resistant pain. Moreover, a high percentage of patients (33%) had previously been advised by an orthopedic specialist or neurosurgeon to have surgery (even though none of them presented a true indication for neurosurgery such as neurological disability); only about 10% of them actually underwent surgery after our treatments.

Thanks to the pain reduction obtained, the patients' health status at the end of the treatment and their perceived quality of life both appeared to be improved. This was true in the sample as a whole, but particularly in the O_2O_3 groups.

Disc herniation, as observed on MRI, was found to stable or enlarged in most patients at the end of treatment (64%). Furthermore, no difference in pain reduction was found in the patients with a reduced DH size compared with those showing no change. These findings suggest, as shown in the literature, that pain is not necessarily correlated to herniation size and therefore a consequence of compression.

It has been proposed that chemical components, too, can play a role in generating symptoms in sciatica associated with DH. The intervertebral disc has been demonstrated to be potentially immunogenic: when a disc is herniated, the nucleus pulposus (normally isolated from the immune system) may secrete substances capable of eliciting an autoimmune response, which in turn may induce chronic inflammation (Mulleman et al., 2006). In fact, disc tissue from patients undergoing discectomy for neck pain, LBP and sciatica produces proinflammatory mediators, cytokines and metalloproteinases (Burke et al., 2002). Thus, both mechanical and chemical factors play a role in generating pain, and when they are present in combination, they probably act in a synergistic way. It is also proposed that the chemical component may be predominant early on in the process (Mulleman et al., 2006). The mechanical component is usually associated with symptoms of neurological dysfunction.

These findings offer an explanation as to why ozone therapy is so effective in reducing pain in patients suffering from discopathy. We hypothesize that the O_2O_3 gas mixture induces a change in the biochemical composition of the affected disc. This change could be ascribed to i) elimination of toxic metabolites produced by inflammation through a process of oxidation, ii) stimulation of fibroblasts and lymphocytes to arrive at the site (Paoloni et al., 2009). The latter phenomenon might in turn promote the generation of connective tissue for disc repair. Such biochemical modifications could inhibit the production of irritant substances caused by discopathy and released onto sensitive ganglia, thus counteracting the process of inflammation. This hypothesis would explain the beneficial effects observed in patients without any reduction of herniation.

However, the question of how O_2O_3 induces pain relief in subjects affected by DH is still controversial. Iliakis and colleagues (2001) suggested that O_2O_3 can improve the local micro-vascularization at the level of cartilaginous plates and promote neo-angiogenesis. This mechanism could improve the intervertebral disc trophism, reduce ischemia and inflammatory edema in the periradicular area and, as a result, lessen hypoxia at the level of sensory nerve roots.

Portolano et al. (1996) suggested that the O_2O_3 mixture might have an oxidant action on mucopolysaccharides constituting the external portion of a herniation or deformed annulus. In turn, oxidation might increase dehydration and consequent disc shrinkage. It has also been suggested that the O_2O_3 mixture might have an antiseptic and an antibacterial action (Bocci, 1996).

A very encouraging finding is that the O_2O_3 mixture is very well tolerated. Indeed, only a very small percentage of the sample presented side effects. With respect to the total number of O_2O_3 infiltrations, the incidence of side effects was 3 x 1000 infiltrations, data confirmed at follow-up.

Of course this retrospective study can be only used as a promising invitation to invest in a randomized perspective study to further investigate the effects of ozone therapy and its possible combinations. Nevertheless the large sample drawn from an experience of more than a thousand patients and the accuracy of the data keeping found in normal clinical practice have provided us with a strong basis for working out new studies that might allow, in the future, the identification of specific indications and the development of recognized guidelines.

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