Low back pain related to a sacral insufficiency fracture: role of paravertebral oxygen-ozone therapy in a paradigmatic case of nociplastic pain

Alessandro de Sire[a, b]
Alessio Baricich[a, c]
Marco Alessandro Minetto[d]
Carlo Cisari[a,c]
Marco Invernizzi[a]

[a] Physical and Rehabilitation Medicine, Department of Health Sciences, University of Eastern Piedmont "A. Avogadro", Novara, Italy
[b] Rehabilitation Unit, "Mons. L. Novarese" Hospital, Moncrivello, Vercelli, Italy
[c] Physical Medicine and Rehabilitation Unit, University Hospital "Maggiore della Carità", Novara, Italy
[d] Division of Physical Medicine and Rehabilitation, Department of Surgical Sciences, University of Turin, Turin, Italy

Correspondence to: Alessandro de Sire
E-mail: alessandro.desire@gmail.com

Summary

We describe the case of a 68-year-old woman with an acute episode of severe low back pain (LBP) resistant to opioids, who had experienced a sacral insufficiency fracture (SIF) two years earlier. At clinical examination, patient reported constant, dull, non-localizable pain at lumbar and sacral level, exacerbated by paravertebral palpation, particularly at L4-L5 and the sacroiliac joint, with a concomitant and remittent neuropathic component, difficult to localize at lumbar and sacral level.
The latest magnetic resonance imaging study revealed disc herniations at L3-L4, L4-L5, and L5-S1 levels. The patient was treated with intramuscular-paravertebral injections of oxygen-ozone (O_2O_3) mixture for 4 weeks (once a week), using a O_3 concentration of 20 mcg/mL (5 mL in L4-L5 zone and 5 mL in L5-S1 zone, bilaterally). At 1 week after the first injection, the pain (assessed by Numerical Pain Rating Scale and Brief Pain Inventory) was considerably reduced and the patient's health-related quality of life (assessed by Short Form 12-Item Health Survey and European Quality of Life Index) had improved; these findings were confirmed at follow-up 1 month after the last injection. This paradigmatic case of nociplastic pain successfully treated by paravertebral O_2O_3 therapy might be a starting point for further studies on the effects of this treatment in terms of decreasing pain and improving HRQoL in patients affected by opioid-resistant LBP.

KEY WORDS: fracture, low back pain, oxygen-ozone, oxygen-ozone therapy, pain, quality of life.

Introduction

Low back pain (LBP) is one of the leading causes of long-term disability and one of the most burdensome health problems worldwide (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016), with an estimated recurrence rate of approximately 50% within 1 year (Stanton et al., 2008). Sacral insufficiency fractures (SIFs) are stress fractures and they are a frequently undetected cause of LBP and sciatica (Hatgis et al., 2017; Tamaki et al., 2017).
LBP could be a hybrid of both nociceptive and neuropathic pain with a concomitance of tissue damage and neural dysfunction, although the neuropathic component is often under-recognized (Baron et al., 2016).
At present, it is considered mandatory for physicians to prevent episodes of acute LBP in high-risk patients and to choose the most effective therapeutic options, according to the pain etiology (Tousignant-Laflamme et al., 2016).
The American College of Physicians recently recommended that pharmacological therapies, particularly opioids, should be avoided in the treatment of acute or subacute LBP, highlighting the role of non-pharmacological conservative therapies in these patients (Qaseem et al., 2017). Among the available non-pharmacological treatments, oxygen-ozone (O_2O_3) therapy, a mixture of medical oxygen and ozone, is a promising therapeutic tool in LBP treatment (Zanardi et al., 2016). Recent studies have demonstrated that paravertebral intramuscular infiltration of O_2O_3 can reduce pain and improve activities of daily living (ADLs) in patients affected by LBP (Apuzzo et al., 2014; Paoloni et al., 2009). However, to date, no cases of LBP with a concomitant SIF treated with O_2O_3 therapy have been reported in the literature.

Case report

We describe the case of a 68-year-old Caucasian woman (BMI of 31 kg/m^2) with an acute episode of severe LBP resistant to opioids, referred in March 2017 to the Outpatient Clinic for Musculoskeletal Pain Management, University Hospital "Maggiore della Carità", Novara, Italy.

Clinical history

Five years previously, this patient had experienced a severe osteoporotic wedge fracture of D11 and two years previously a SIF.
The last dual X-ray absorptiometry examination (performed in 2015) showed a lumbar spine bone mineral density (BMD) of 0.798 g/cm^2 (T-score = -3.2 SD; Z-score = -1.4 SD) and a femoral neck BMD of 0.619 g/cm^2 (T-score = -3.0 SD; Z-score = -1.6 SD).

She had thus been treated with subcutaneous denosumab (60 mg once every 6 months).
However, due to recurrent self-limiting LBP episodes treated with NSAIDs and spinal mobilization without consistent beneficial effects, and progressive limitations in ADLs combined with a worsening of her emotional status, the patient had subsequently had a lumbar magnetic resonance imaging (MRI) scan, in November 2016. MRI showed a severe wedge fracture of D11 and a mild osteoporotic biconcave fracture of L2 (Fig. 1). Furthermore, a signal alteration in the left wing of the sacrum (hypointense on T1-weighted images and hyperintense in T2-weighted short-tau inversion recovery sequences), consistent with SIF was observed. A mild L3-L4 disc protrusion without focal disco-radicular conflicts, a severe L4-L5 disc herniation, and a mild L5-S1 disc protrusion without focal disco-radicular conflicts were also present.
In March 2017, while doing housework, the patient suffered a severe acute LBP episode and was thus referred to an Emergency Department. Analgesic treatment with oxycodone/paracetamol, 10 mg/325 mg, twice a day for three days, then increased to 20 mg/650 mg twice a day for two weeks, was ineffective. After 7 days of therapy, the patient experienced dizziness, nausea, and constipation; these symptoms spontaneously resolved after therapy suspension. Therefore, given the persistence of the pain, the patient was referred to our Outpatient Clinic for Musculoskeletal Pain Management by her general practitioner.

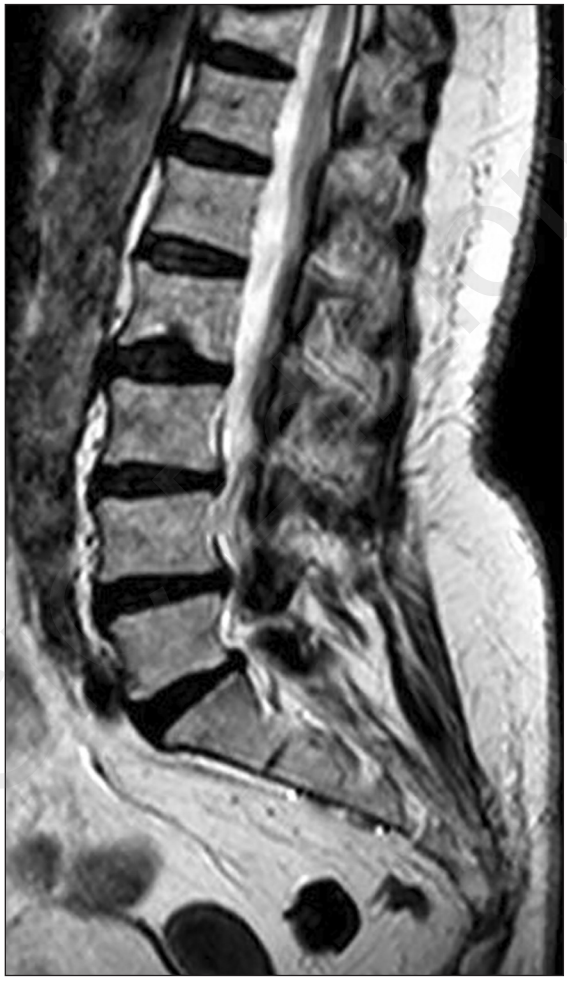

Figure 1 - Lumbar magnetic resonance imaging.

Clinical evaluation
At the clinical examination, the patient reported constant, dull, non-localizable pain at lumbar and sacral level, exacerbated by paravertebral palpation, particularly at L4-L5 and the sacroiliac joint, with a concomitant and remittent neuropathic component, difficult to localize at lumbar and sacral level. Neurological examination did not show any abnormalities or signs of sciatica. She reported severe constant pain localized at lumbar and sacral level without modifications between night and day, but exacerbated by movements. The patient needed physical assistance to walk and was unable to perform sit-to-stand alone, reporting an exacerbation of pain symptoms in the lying position.
We assessed the patient's pain using the Numerical Pain Rating Scale (NPRS) (Childs et al., 2005), on which she scored 8.5, and the Brief Pain Inventory (BPI) (Keller et al., 2004), with its two components: severity index and interference index, on which she scored 7.5 and 7, respectively.
The severe pain she was experiencing negatively influenced her functional status and health-related quality of life (HRQoL), as shown by her Short Form 12-Item Health Survey (SF-12) (Cheak-Zamora NC, 2009) score, and by her Physical Composite Score (PCS) and Mental Health Composite Score (MCS): 25.2 and 35.7, respectively. The European Quality of Life - 5 Dimensions - 3 Levels (EuroQol-5D-3L) index (EQ-5D-3L index) (EuroQol Group, 1990) and EuroQol-Visual Analogue Scale (EQ-VAS) scores were 0.45 and 42.0, respectively.
The patient had very low expectations regarding the possibility of obtaining pain resolution and was discouraged and exhausted, both physically and emotionally. Moreover, the degree of pain and the functional impairment were so severe as to preclude any kind of physical exercise or rehabilitation treatment. The patient refused to undergo any other kind of per os pharmacological therapy (e.g. tapentadol or NSAIDs) due to the occurrence of adverse events after previous oxycodone/paracetamol treatment.

Treatment
Therefore, also in view of the lack of evidence on the long-term efficacy of opioids in acute LBP (Abdel Shaheed et al., 2016), the patient was treated with intramuscular-paravertebral injections of an O_2O_3 mixture (20 mL) with an O_3 concentration of 20 mcg/mL (5 mL in the L4-L5 zone and 5 mL in the L5-S1 zone, bilaterally) using a 27-gauge needle (Sterican, B. Braun Melsungen AG, Germany), under sterile conditions, with a maximum injection time of 15 seconds.
The gas mixture was obtained by means of an Ozonline E80 generator (Eco3 s.n.c., Brandizzo, TO, Italy) connected to a pure O_2 source (the O_3 generator uses O_2 through high-voltage tubesì and has output values of 5% O_2O_3 ranging from 4,000 to 14,000 liters). The patient repeated the intramuscular-paravertebral O_2O_3 treatment once a week for 3 consecutive weeks (T_1, T_2, T_3). She did not take any analgesics, except for parac-

Table I - Clinical assessments before each weekly intramuscular-paravertebral injection of O_2O_3 mixture (T_0, T_1, T_2, T_3) and at 1 month after the last injection (T_4).

T_0	T_1	T_2	T_3	T_4	
NPRS	8.5	5.5	4.0	3.0	1.0
BPI Severity Index	7.5	5.5	4.5	3.5	2.0
BPI Interference Index	7.0	5.0	4.0	3.5	2.0
SF-12 PCS	25.2	30.4	35.6	41.2	45.0
SF-12 MCS	35.7	43.2	45.7	46.8	52.0
EQ-5D-3L index	0.45	0.59	0.63	0.69	0.81
EQ-VAS (mm)	42.0	58.0	60.0	62.0	74.0

Abbreviations: NPRS, Numerical Pain Rating Scale; BPI, Brief Pain Inventory; SF-12, Short Form 12-Item Health Survey; PCS, Physical Composite Score; MCS, Mental Health Composite Score (MCS); EQ-5D-3L index, European Quality of Life - 5 Dimensions - 3 Levels index; EQ-VAS, European Quality of Life Visual Analogue Scale.

etamol 1000 mg if needed, throughout the O_2O_3 treatment period.

We assessed all the outcome measures (NPRS, BPI, SF-12, EQ-5D-3L index and EQ-VAS): at baseline, at each O_2O_3 administration (T_1, T_2, T_3), and at 1-month follow up (T_4).

At 1 week after the first injection, the pain was considerably reduced (NPRS: 5.5 *vs.* 8.5) and the patient's HRQoL had improved (SF-12 PCS: 30.4 *vs.* 25.2), testifying to her good response to intramuscular-paravertebral O_2O_3 therapy. These findings were confirmed at the follow-up visit (T_4) (NPRS: 1 *vs.* 8.5; SF-12 PCS: 45.0 *vs* 25.2) (see Table I for further details).

Discussion

In this study, we have described the clinical characteristics of a patient affected by multifactorial LBP successfully treated with O_2O_3, after opioids had been found to be ineffective in achieving pain control.

LBP is a highly disabling and recurrent condition with important health and socioeconomic implications (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016).

In this case report, the concomitant presence of SIF, multiple disc herniations, previous osteoporotic fractures, and spondyloarthritis determined a complex clinical picture in which pain genesis might be multifactorial. The various characteristics of pain previously described by this patient and her history of multiple acute LBP episodes in recent years suggest a hybrid of both nociceptive and neuropathic pain, due to both tissue damage and subsequent neural dysfunction (Baron et al., 2016; Tousignant-Laflamme et al., 2016). In particular, in this patient we observed a frequently under-detected (Baron et al., 2016) neuropathic component of LBP.

These considerations are in line with the terminology used by the International Association for the Study of Pain (2017), which recently introduced the following definition of "nociplastic pain": "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain".

Furthermore, the patient reported an insufficiency fracture, which is a stress fracture subtype that is caused by normal stress applied to abnormal bone that has lost its elastic resistance. In particular, SIFs most commonly involve the sacral ala and often present as LBP or sciatica which may radiate to the buttock, hip, or groin in the absence of any antecedent trauma. SIFs are often underdiagnosed because of a lack of appropriate imaging and a tendency to focus on different pain etiologies at lumbosacral level. The overall incidence of SIFs is higher in patients with previous or concurrent lumbar vertebral osteoporotic fractures (Hatgis et al., 2017). Different treatment options have been proposed for the treatment of SIFs, including analgesics, teriparatide, and sacroplasty in more severe cases (Tsiridis et al., 2006). Regrettably, specific treatment protocols and guidelines are lacking to date (Simon et al., 2017).

Recently, the American College of Physicians recommended that acute LBP should not initially be treated with pharmacological treatments, such as opioids (Qaseem et al., 2017), whose efficacy in the long term is still controversial (Abdel Shaheed et al., 2016).

Here, we have illustrated a possible conservative treatment, namely intramuscular O_2O_3 therapy, in a case of LBP with concomitant SIF resistant to opioids. This therapeutic approach has been shown to induce analgesia and anti-inflammatory effects, probably due to the properties of O_3 which might modulate cytokine activity, stimulating pro-inflammatory cytokine antagonists and inhibiting pro-inflammatory prostaglandins (Zanardi et al., 2016). In our opinion, O_2O_3 treatment represents a useful and promising therapeutic option in LBP resistant to analgesic drugs such as opioids, especially in patients with several concomitant pathological conditions. The short-term improvement in pain severity suggests a rapid effect of O_2O_3 treatment in this condition, as shown by the 50% NPRS score reduction obtained in our patient at T_2. Lastly, it should be underlined that O_2O_3 is, overall, a safe technique associated with extremely low occurrence of adverse events and low medication, procedure and personnel costs (Paoloni et al., 2009).

In conclusion, this study could be the starting point for further investigations of the effects of intramuscular-paravertebral O_2O_3 therapy for short-term pain management and quality of life improvement in patients affected by multifactorial LBP with both nociceptive and neuropathic components.

References

Abdel Shaheed C, Maher CG, Williams KA, et al (2016). Efficacy, tolerability, and dose-dependent effects of opioid analgesics for low back pain: a systematic review and meta-analysis. JAMA Intern Med 176: 958-968.

Apuzzo D, Giotti C, Pasqualetti P, et al (2014). An observational retrospective/horizontal study to compare oxygen-ozone therapy and/or global postural re-education in complicated chronic low back pain. Funct Neurol 29: 31-39.

Baron R, Binder A, Attal N, et al (2016). Neuropathic low back pain in clinical practice. Eur J Pain 20:861-873.

Cheak-Zamora NC, Wyrwich KW, McBride TD (2009) Reliability and validity of the SF-12v2 in the medical expenditure panel survey. Qual Life Res 18:727-735.

Childs JD, Piva SR, Fritz JM (2005). Responsiveness of the numeric pain rating scale in patients with low back pain. Spine 30: 1331-1334.

EuroQol Group (1990) EuroQol—a new facility for the measurement of health-related quality of life. Health Policy 16: 199-208.

GBD 2015 Disease and Injury Incidence and Prevalence Collaborators (2016). Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 388: 1545-1602.

Hatgis J, Granville M, Jacobson RE, et al (2017). Sacral insufficiency fractures: recognition and treatment in patients with concurrent lumbar vertebral compression fractures. Cureus 9: e1008.

International Association for the Study of Pain (2017). IASP Terminolgy. Available at: http://www.iasp-pain.org/ Education/Content.aspx?ItemNumber=1698. Accessed on: 5th October 2018.

Keller S, Bann CM, Dodd SL, et al (2004). Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. Clin J Pain 20: 309-318.

Paoloni M, Di Sante L, Cacchio A, et al (2009) Intramuscular oxygen-ozone therapy in the treatment of acute back pain with lumbar disc herniation: a multicenter, randomized, double-blind, clinical trial of active and simulated lumbar paravertebral injection. Spine (Phila Pa 1976). 34: 1337-1344.

Qaseem A, Wilt TJ, McLean RM, et al (2017). Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. Ann Intern Med 166: 514-530.

Simon JI, Surrey DE, Kitei P, et al (2017). Successful repeat sacroplasty in a patient with a recurrent sacral insufficiency fracture: a case presentation. PM R 9: 1171-1174.

Stanton TR, Henschke N, Maher CG, et al (2008) After an episode of acute low back pain, recurrence is unpredictable and not as common as previously thought. Spine (Phila Pa 1976) 33: 2923-2928.

Tamaki Y, Nagamachi A, Inoue K, et al (2017) Incidence and clinical features of sacral insufficiency fracture in the emergency department. Am J Emerg Med 35: 1314-1316.

Tousignant-Laflamme Y, Martel MO, Joshi AB, et al (2017) Rehabilitation management of low back pain - it's time to pull it all together! J Pain Res 10: 2373-2385.

Tsiridis E, Upadhyay N, Giannoudis PV (2006). Sacral insufficiency fractures: current concepts of management. Osteoporos Int 17: 1716-1725.

Zanardi I, Borrelli E, Valacchi G, et al (2016) Ozone: a multifaceted molecule with unexpected therapeutic activity. Curr Med Chem 23:304-314.