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Evaluation Study

INTRADISCAL INJECTION OF OXYGEN-OZONE GAS MIXTURE FOR THE TREATMENT OF CONTAINED CERVICAL DISC HERNIATIONS

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ABSTRACT

For disc herniations, open surgical approaches are reduced since new percutaneous methods allowing shrinkage of the disc and improvement of the radicular function are gaining interest. Studies on the spontaneous disappearance of disc fragments have demonstrated autoimmune responses with a chronic inflammatory reaction. Also, radicular pain is due mainly to biochemical mechanisms. Researchers in different fields surprisingly noticed that a brief, calculated oxidative stress by ozone administration might correct a persistent imbalance due to excessive, chronic oxidative injury. Oxygen-ozone gas injection in painful patients has a dramatic effect on clinical symptoms. On these bases, the intradiscal injection of oxygen-ozone gas has been conceived. We report the treatment on a series of patients affected by cervical disc pathology, treated by intradiscal injection of an oxygen-ozone gas mixture. The effects both on pain and on radicular dysfunction are impressive. The morphological effect of the treatment was also evaluated by pathological examination.

KEYWORDS: *intradiscal injection, contained disc herniation, oxygen-ozone, tinnitus*

INTRODUCTION

In cases of radicular dysfunction due to disco-radicular conflict, the treatment has evolved in the last two decades since methods that allow shrinkage of the herniated or protruded disc have been preferred to open tissue removal. Many percutaneous non-invasive techniques have been conceived. The common principle is to provoke morphological modification of the disc and its deformities. Simultaneously many studies have highlighted that pain may be due to biochemical mechanisms somehow independent of the mechanical problem. A situation of ischemia, acid intoxication of the

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nerve, and chronic inflammatory response are understood to combine causes of dysfunction. The spontaneous mechanisms of disc shrinkage and elimination of herniated fragments have been carefully studied, and a chronic inflammatory reaction has been developed (1). An autoimmune reaction may participate in physiopathology (2). Biochemical treatments may correct these problems, reducing the need for surgical intervention (3-7). The mixture of oxygen and ozone gases has been employed in medicine since the 30s to treat pain and dysfunction in patients affected by thrombotic and ischemic diseases. After experience in these fields, the empirical observations of powerful and long-lasting effects of this gas mixture injected in paravertebral muscles for treating pain and radicular dysfunction due to a disco-radicular conflict have led to detailed studies on the subject.

Working in different fields, researchers surprisingly noticed that a brief calculated oxidative stress achieved by ozone administration might correct a permanent imbalance caused by excessive or chronic oxidative injury. Bocci et al. have highlighted that modest, repeated ozone administration increases the activity of superoxide dismutase, catalase, and glutathione peroxidase, inducing a state of oxidative stress adaptation with very important therapeutic implications (8). The mixture is produced by an apparatus (ozone generator) that activates diatomic oxygen molecules in a voltaic arch. Ultraviolet spectrophotometry allows precise quantification of ozone percentages in the obtained mixture. The absence of side effects in over five million ozone therapy sessions for different pathologies has been reported since 1982 by Jacobs (9). The injection of an oxygen-ozone mixture in the intervertebral disc and the conjugation foramen (3, 4, 10) is combined with the paravertebral intramuscular treatment.

Several techniques have been developed to treat disc herniation. Percutaneous techniques such as percutaneous discectomy, laser discectomy, and nucleoplasty have minimised the invasive nature of these surgeries and decreased complications such as postsurgical infection (5, 11, 12). Among these, only ozone treatment has the characteristic of acting on morphology and biochemical functions. We present the progress (4) of our experience by this method in a series of 1268 contained cervical disc herniations.

Specific attention is paid to dizziness and tinnitus, symptoms which have been observed in 317 out of our cervical herniation patients.

Tinnitus is the perception of sound without an external acoustic stimulus (13). Its prevalence is roughly estimated as being between 10% and 17% of the population, afflicting around a third of North Americans over 55.3 years. For many years, tinnitus was thought to arise almost exclusively out of abnormal neuronal activity within the auditory pathways. However, accumulated evidence suggests that tinnitus-related neural activity is much more complex and multimodal than previously thought.

More often than ever, researchers conclude that tinnitus can be evoked or modulated by inputs from the individual's somatosensory, somatomotor and visual–motor systems; this means that the psychoacoustic attributes of tinnitus (loudness and pitch) might be changed immediately –though only temporarily – by different stimuli, such as the following: forceful muscle contractions of head, neck and limbs; eye movements in the horizontal or vertical axis, pressure on myofascial trigger points; cutaneous stimulation of the hand/fingertip region and the face; electrical stimulation of the median nerve and hand; or finger movements as well as orofacial movements.

This specific subgroup is called somatosensory tinnitus, and it seems to be a good example of central integration of the central nervous system because an auditory symptom like tinnitus may be modulated immediately after various non-audiology stimuli are presented. The modulation phenomenon is yet to be fully understood, but there is scientific evidence of existing neural connections between somatosensory and auditory systems, and their "activation" may play a role in this type of tinnitus.

In clinical practice, tinnitus is still considered an untreatable symptom, and many professionals tell patients that "there is nothing to be done" or that "you have to learn to live with it".

MATERIALS AND METHODS

In eight years, from 2013 to 2020, 2417 patients were admitted to our Service because of clinical symptoms bespeaking a cervical disc pathology. These underwent clinical, electrophysiological, and neuroradiological investigations to establish a precise diagnosis.

Those 1149 patients who were affected by cervical spinal canal stenosis, discarthrose processes, osteophytes, myelopathy, or concomitant CSN pathologies were not included in the series.

In this paper, we present the series of 1268 cases in which a contained disc herniation has been demonstrated by CT scan or RMI and EMG has demonstrated radicular dysfunction corresponding to the metameric level.

The mean patient age was 38 years, and 47% were males. C3-C4 herniation was observed in 76 of the 1268 patients, C4-C5 in 88 cases, C5-C6 in 570, and C6-C7 in 531. Among these patients, multiple-level herniation was observed in 491 (38.7% of cases). The double level distribution was in 460 patients as C5-C6 and C6-C7 levels combination and 31 patients as C4-C5 and C6-C7 combination.

Patients enrolled had received pharmacological and physical therapy without remedial of the clinical picture. The perspective of solving the problem of reducing drug administration without conventional surgical treatment was offered to the patients, who consented after a detailed explanation. Dexamethasone administration, if pre-existing, was interrupted when starting O_2-O_3 injections. It was never associated with O_2-O_3 treatment. Non-steroid drugs were allowed if occasionally needed. The treatment - EUNI Method - consisted of an intradiscal injection of O_2-O_3 preceded and followed by 6 paravertebral injections.

– paravertebral injection consisted of administration of 20 ml of O_2-O_3 at 10 micrograms/ml concentration, divided into 2 sites of injection: 3 cm deep in the paravertebral muscles bilaterally, at the metameric level of the pathology.

– intradiscal injection: introducing the needle in the disc through the anterolateral approach corresponds to the classical open surgery approach. The procedure was carried out with a high-resolution C-arm. The procedure was performed with the patient in a supine position under mild sedation, with complete anesthesiological assistance and continuous vital signs recording. The procedure modalities are as follows: the patient's neck is extended, and a thin pillow is under the interscapular region. The approach is right anterolateral. The operator displaces the carotid sheath laterally and trachea-oesophagus medially between the second and third fingers of the left hand. The right hand then inserts the needle, passing between the two left fingers, though the soft tissue window between the carotid sheath and trachea-oesophagus. Local anaesthesia is not required in this location. 22G spinal needle with a length of 3.5 inches was used. The needle tip is directed toward the centre of the disc. The position of the needle is checked with anteroposterior and lateral views.

Three to five ml of gas are injected at 30 micrograms/ml concentration. The injected dose depends on the disc morphology: fissuration will allow gas mixture diffusion either along anterior or posterior longitudinal ligament or anterior epidural space.

RESULTS

Neck pain: among the 1268 patients, neck pain was abolished entirely in 1080 cases (85.1%); VAS reduction of 4 or more points was obtained in 156 cases (12.3 %), while the result was poor in 32 patients (2,52 %).

Radiated radicular pain was abolished entirely in 79.65% (1010 patients); among the 1268 patients, a VAS reduction of 4 or more points was obtained in 11.67 % (148 patients). The result was poor in 8,67 % (110 patients).

Dizziness and tinnitus were relevant symptoms in 317 out of our 1268 patients (25% of the entire series). A good improvement in these symptoms has been achieved with this treatment. The benefit was evident during outpatient therapies; in 58% of cases (184 patients): the observed benefit is generally long-lasting. The recurrence of the disorder at the end of the treatment was observed in 27% of cases.

Sensory dysfunction was abolished in 77,99% (989 patients) and improved in 15.8% (201 patients). Dysfunction remained unchanged in 78 cases.

Motor dysfunction such as M4 or M3 was present in 64.9% of our 1268 patients, i.e. 824 cases. An M3-level motor deficit was present in 228 patients (17.98%). M4 motor deficit was observed in 596, that is 47%. The motor defect pre-existed in our cure with a mean pre-existence time of 14 days. We observed complete regression of motor deficit in 97% of M4 patients (578 cases); recuperation was partial in the remaining 3%. Among M3 patients, recuperation was complete in 90% (205 patients).

Multiple-level disc pathology was present in 491 (38.7% of cases). The treatment was performed simultaneously in all pathological discs. The results obtained do not differ from those obtained for single-level pathology.

Patients underwent CT/MRI control 8 months after treatment. In 38,72% (491 cases), we observed a significant reduction in the volume of the hernia. The correlation with clinical signs was not statistically significant.

DISCUSSION

Mechanical compression of a nervous structure leads to a range of microvascular changes. Mild compression produces venous congestive nerve root oedema, severe compression results in arterial ischemia, and the root sets off sharp shooting pain along the dermatome (14, 15).

Experimental models suggest that material from the nucleus pulposus may act as a chemical or immunologic irritant to the nerve and that these mechanisms may produce an inflammatory response (2). When the disc ruptures, the immune-privileged nucleus displaces through a tear in the annulus fibrosus leading to direct exposure of the nucleus to our immune system, which, in turn, triggers the release of inflammatory mediators. These inflammatory mediators recruit monocytes from the immune system resulting in the chemotaxis of macrophages and angiogenesis. Subsequent lymphocyte activation with the secretion of interferon-gamma (IFN γ) and macrophage recruitment lead to one unfavourable effect of inflammation of nerve roots and dorsal root ganglia. Another favourable effect helps in the resorption of extruded nucleus pulposus. However, this natural resorption is a painful and slow phenomenon. Inflammatory markers such as interleukin-6 (IL-6), IL-12, IFN γ, and CD68 macrophages are more present in an extruded disc. There are two different types of macrophages seen in autoimmune-mediated inflammatory reactions.

M1 macrophages produce pro-inflammatory cytokines, and M2 macrophages produce anti-inflammatory cytokines. There is always a sequence in that activation of M1 is followed by M2. However, when and how activation of M1 switches to activation of M2 macrophages is unpredictable; the M1-mediated pro-inflammatory phase may last longer, leading to prolonged and painful illness. These inflammatory cascades of reactions are responsible for inflammatory radiculopathy with radiating pain along the course of the nerve (16). Tumor necrosis factor α and phospholipase A2 are significant in herniated nucleus pulposus. These are responsible for partial demyelination that increases nerve root sensitivity making them more susceptible to mechanical pressure (15). The mechanical compression due to herniated disc can trigger hyperexcitability leading to neuropathic paresthesia and pain.

Until now, studies have hypothesised that injection of such a powerful oxidant, such as ozone, induces overexpression of antioxidant enzymes, which neutralise excessive reactive oxygen species (ROS) formation (8). After intradiscal injection, ozone can accelerate the degradation of proteoglycans in the degenerated nucleus pulposus, leading to its reabsorption and dehydration with the consequent reduction of herniated material responsible for nerve root compression (6, 8).

In our opinion, the most important aspect is the biochemical modification of the medium in the epidural space. In epidural space, ozone acts as an anti-inflammatory agent modulating and hastening the switch from M1 to M2 macrophages, converting an inflammatory phase to a reparative one (16). Studies on pain, which often is disproportionate to the morphological evidence of discal-radicular conflict, have demonstrated that it is provoked by acid metabolites from the degenerative processes inside the disc and ischemia of the nerve root and the ganglion. In the 90s, attention was brought to A2 phospholipase. Saal et al. demonstrated that A2 phospholipase is the cause of radicular pain, independent of the immunological response or a direct inflammatory process (2). A2 phospholipase is responsible for the arachidonic acid liberation and hence prostaglandins. High levels of A2 phospholipase have been demonstrated in herniated discs. Ozone injected in the disc and in the epidural space of the conjugation foramen and along the posterior longitudinal ligament acts as a powerful stimulus to the activation of antioxidant defence, favouring the normalisation of redox balance with neutralisation of acidosis, increased synthesis of ATP, Ca2+ reuptake and resolution of oedema (1, 2, 8).

Thus, symptoms arising from disc herniation are due to the amalgamation of bio-chemico-mechanical factors (14-16). The complete biochemical reaction to an intradiscal injection of oxygen-ozone gas mixture for treating cervical disc herniations is not yet understood, but there is strong clinical evidence that the effect is dramatic and long-lasting. The benefit is rapidly obtained on pain and nerve dysfunction, with progressive reduction of tingling. EMG controls have confirmed the recuperation of nerve function. We presume that this is achieved by amelioration of nerve ischemia. The oxygen-ozone gas mixture at 10% ozone concentrations acts as immunomodulatory. At 25–30% concentration, it helps to dehydrate the disc nucleus. Outside this therapeutic window, ozone will be cytotoxic above 45%. Most trials prove

that the ozone concentration at 25%–30% will be optimum for therapeutic effects in disc herniation (15, 17, 18, 19). Ozone acts differently at different concentrations in different tissues. Mechanisms of intradiscal ozone injection involve fragmentation of glycosaminoglycans which are abundantly present in the nucleus pulposus, with subsequent release of water molecules; this leads to a small decrease in volume of the nucleus with a significantly greater decrease in pressure resulting in the recoil of the nucleus and restoration of the intervertebral disc. This is probably the case in contained disc herniations, where the nucleus pulpous is protected by the Fas-ligand which prevents infiltration of immunocytes. Proteoglycans present in the annulus also limit the inflammatory reaction. Here, dehydration of the nucleus and cytokine-mediated repair of the annulus is more dominant reactions.

About tinnitus, Alcantara et al. (20) described how chiropractic treatment could reduce tinnitus, vertigo and hearing loss in a patient with cervical subluxation and temporomandibular disorder. Symptoms eventually ceased after nine sessions. Kessinger et al. (10) documented clinical changes after chiropractic sessions in a geriatric patient with tinnitus, vertigo, hearing loss and cervical alterations from C3 to C7. The patient's symptoms were alleviated throughout the sessions, and structural/functional improvements were also evident through radiographic examination.

The observation that we are here reporting of clinical improvement of these symptoms by oxygen-ozone treatment is interesting because it brings back to the idea that these are functional alterations which may have anatomopathological bases but are possibly reduced or eliminated working on metabolism.

The possibility of treating patients by an easy method which is rapidly effective for solving clinical problems is at hand. This treatment is useful in patients who did not respond to physical and conventional pain therapy as a last step in conservative treatment before deciding on open surgery. Most of these patients will not need more surgery anymore since ozone may act directly on the cause eliminating clinical symptoms. This technique is simple, has no risks, and offers the patient a solution without the discomfort of surgery and its possible risks.

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