Original Article

Ozone disc nucleolysis in cervical intervertebral disc herniation: A nonrandomized prospective analysis in 246 patients

ABSTRACT

Background: Inherent complications associated with surgery and limited success of percutaneous minimally invasive procedures make researches wanting for an ideal treatment for cervical disc herniation.

Objective: We prospectively study the role of ozone disc nucleolysis in cervical intervertebral disc herniation.

Patients and Methods: From January 2008 to December 2020, we prospectively study 246 consecutive patients of cervical disc herniation treated by a single session of intradiscal injection of ozone–oxygen mixture (ozone disc nucleolysis). There were 55% of females and 45% of males. Age ranged from 28 to 68 years with a mean of 47. The outcome was measured on visual analog scale (VAS) scale and neck disability index (NDI) along with Mcnab method.

Results: The mean baseline VAS score was 7.87 which became 3.09 at 1 month, 1.42 at 3 months, 1.40 at 6 months, and 1.35 at 1 year. The mean NDI was 36.27 at baseline which improved to 9.24 at 1 month, 6.25 at 3 months, 6.20 at 6 months, and 6.22 at 1 year. This was found to be significant with $P < 0.05$. Modified McNab criterion showed excellent recovery in 138 (56.10%), good recovery in 50 (20.32%), and fair recovery in 22 (8.94%), resulting in a successful rate of 85.36%. Mediocre recovery was seen in the remaining 36 patients amounting to a 14.64% failure rate.

Conclusion: This study showed that ozone disc nucleolysis significantly reduces the pain related to cervical disc herniation along with a significant reduction in disability.

Keywords: Cervical disc herniation, cervical radiculopathy, ozone disc nucleolysis

INTRODUCTION

Neck pain with or without radiation to arm leads to disability and loss of man-hours.[1] Cervical disc herniation is a common cause of neck pain in adults. Its prevalence increases with age and is most often seen in the third to fifth decades of life. Occurrence is more frequent in females which accounts for approximately 60% of caseload.[2] Cervical disc herniation presents most commonly as a degenerative spine.[3] However, modern-day repetitive stress and traumatic injuries are emerging causes of it. Majority of patients recover by conservative management which includes rest, medications, and physical therapies. Close to 10%–25% of cases may require surgical interventions.[4] Inherent complications associated with cervical spine surgery in best of the hands makes minimally invasive procedures

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most sought after treatment modalities.[5] Etiopathogenesis not only involves mechanical compression, but it is due to amalgamation of bio-chemico-mechanical factors.[2,6,7] Most of the routinely available minimally invasive such as percutaneous lumbar discectomy, laser discectomy, percutaneous plasma disc decompression, intradiscal electrothermal therapy, and percutaneous intradiscal radiofrequency thermocoagulation are based on mechanical decompression.[6] Ozone disc nucleolysis is the only modality which not only does decompression but neutralizes the biochemical processes responsible for radiculopathy. We report a nonrandomized prospective study on consecutive patients affected by cervical disc herniation and treated by ozone disc nucleolysis.

PATIENTS AND METHODS

From January 2008 to December 2020, a total of 246 consecutive patients with cervical disc herniation were treated by a single session of intradiscal injection of ozone–oxygen mixture (ozone disc nucleolysis). There were 55% of females and 45% of males. Age ranged from 28 to 68 years with a mean of 47.

Inclusion criterion

1. Cervical radicular pain concurring with magnetic resonance imaging (MRI) evidence of intervertebral disc herniation
2. Visual analogue scale (VAS) score ≥6
3. Numbness along the dermatomal distribution corresponding to disc herniation as seen on MRI
4. Functional disability due to neck pain with or without radiating pain
5. Patient willingness.

Exclusion criterion

1. Clinical and/or MRI evidence of cervical myelopathy

Table 1: Neck Disability Index

SECTION 1: Pain Intensity A. I have no pain at the moment. B. The pain is mild at the moment. C. The pain comes & goes & is moderate. D. The pain is moderate & does not vary much. E. The pain is severe but comes & goes. F. The pain is severe & does not vary much.	SECTION 6: Concentration A. I can concentrate fully when I want to with no difficulty. B. I can concentrate fully when I want to with slight difficulty. C. I have a fair degree of difficulty in concentrating when I want to. D. I have a lot of difficulty in concentrating when I want to. E. I have a great deal of difficulty in concentrating when I want to. F. I cannot concentrate at all.
SECTION 2: Personal Care (Washing, Dressing etc.) A. I can look after myself without causing extra pain. B. I can look after myself normally but it causes extra pain. C. It is painful to look after myself and I am slow & careful. D. I need some help but manage most of my personal care. E. I need help every day in most aspects of self-care. F. I do not get dressed; I wash with difficulty and stay in bed.	SECTION 7: Work A. I can do as much work as I want to. B. I can only do my usual work but no more. C. I can don most of my usual work but no more. D. I cannot do my usual work. E. I can hardly do any work at all. F. I cannot do any work at all
SECTION 3: Lifting A. I can lift heavy weights without extra pain. B. I can lift heavy weights, but it causes extra pain. C. Pain prevents me from lifing heavy weights off the floor, but I can if they are conveniently positioned, for example on a table. D. Pain prevents me from lifting heavy weights, but I can manage light to medium weights if they are conveniently positioned. E. I can only lift very light weights. (4 pts) F. I cannot lift or carry anything at all.	SECTION 8: Driving A. I can drive my car without neck pain. B. I can drive my car as long as I want with slight pain in my neck. C. I can drive my car as long as I want with moderate pain in my neck. D. I cannot drive my car as long as I want because of moderate pain in my neck. E. I can hardly drive my car at all because of severe pain in my neck. F. I cannot drive my car at all.
SECTION 4: Reading A. I can read as much as I want to with no pain in my neck. B. I can read as much as I want with slight pain in my neck. C. I can read as much as I want with moderate pain in my neck. D. I cannot read as much as I want because of moderate pain in my neck. E. I cannot read as much as I want because of severe pain in my neck. F. I can not read at all because of neck pain.	SECTION 9: Sleeping A. I have no trouble sleeping. B. My sleep is slightly disturbed (less than 1 hour sleepless). C. My sleep is mildly disturbed (1-2 hours sleepless). D. My sleep is moderately disturbed (2-3 hours sleepless). E. My sleep is greatly disturbed (3-5 hours sleepless). F. My sleep is completely disturbed (5-7 hours sleepless).
SECTION 5: Headache A. I have no headaches at all. B. I have slight headaches that come infrequently. C. I have moderate headaches that come in-frequently. D. I have moderate headaches that come frequently. E. I have severe headaches that come frequently. F. I have headaches almost all the time.	SECTION 10: Recreation A. I am able to engage in all recreational activities with no pain in my neck at all. B. A am able to engage in all recreational activities with some pain in my neck. C. I am able to engage in most, but not all, recreational activities because of pain in my neck. D. I am able to engage in only a few of my usual recreational activities because of pain in my neck. E. I can hardly do any recreational activities because of pain in my neck. F. I cannot do any recreational activities at all.

2. Positive red flags for axial skeletal trauma, infection, or malignancy
3. Patient refusal.

On selecting with the above criterion, all patients had undergone clinical examination and MRI evaluation. Baseline VAS score and neck disability index (NDI) were noted. VAS score involves a numerical scale of severity of pain from 0 to 10 where 0 is no pain and 10 is agonizing pain. NDI score is a modified version of the Oswestry Disability Index and includes 0–5 scoring for each of 10 activities of daily living.[8] The minimum score was zero and the maximum score was 50. Patient score was depicted out of 50 [Table 1].

Clinical profile: There were 324 cervical disc herniations treated in 246 patients. Affected disc distributions were C5 – 6:178, C6 – 7:83, C4 – 5:55, and C3 – 4:08, as seen on pretreatment MRI. Two hundred forty patients had neck pain with radiculopathy. Three patients had only radiculopathy and three patients presented with only severe neck pain. One hundred fifty-six patients had paresthesia. At least one disc level corresponded to the dermatomal distribution of the pain and paresthesia in each patient. Seventy patients had undergone treatment at two levels and four patients had three levels. The rest of the patients had solitary disc herniation.

Patients were admitted for 1 day. Written informed consent was obtained. The procedure was carried out in cath lab (Artis Zee, Siemens, Erlangen, Germany) with high-resolution plat panel c-arm. Procedure was performed with the patient in the supine position. The patient's neck is extended with a thin pillow under the interscapular region. Caudal angulation is given to the image receptor to bring the disc in a tangential plane with adjacent endplates parallel to each other. This way all discs between C2 and D1 could be treated. The approach is right anterolateral. The operator displaces carotid sheath laterally, and trachea- esophagus medially between the thumb and index finger of one hand. The needle is then inserted by

Table 2: Modified MacNab criterion

OUTCOME	DESCRIPTION
Successful treatment	
Excellent	Disappearance of symptoms Complete recovery in working and sports activities
Good	Occasional episodes of neck pain or arm pain No limitations of occupational activities
fair	Improvement of symptoms bur limitation of heavy activities
Failure of treatment	
mediocre	Insufficient improvement of symptoms Periodic administration of drugs Limitation of physical activities
No results	No improvement
bad	Worsening of clinical situation

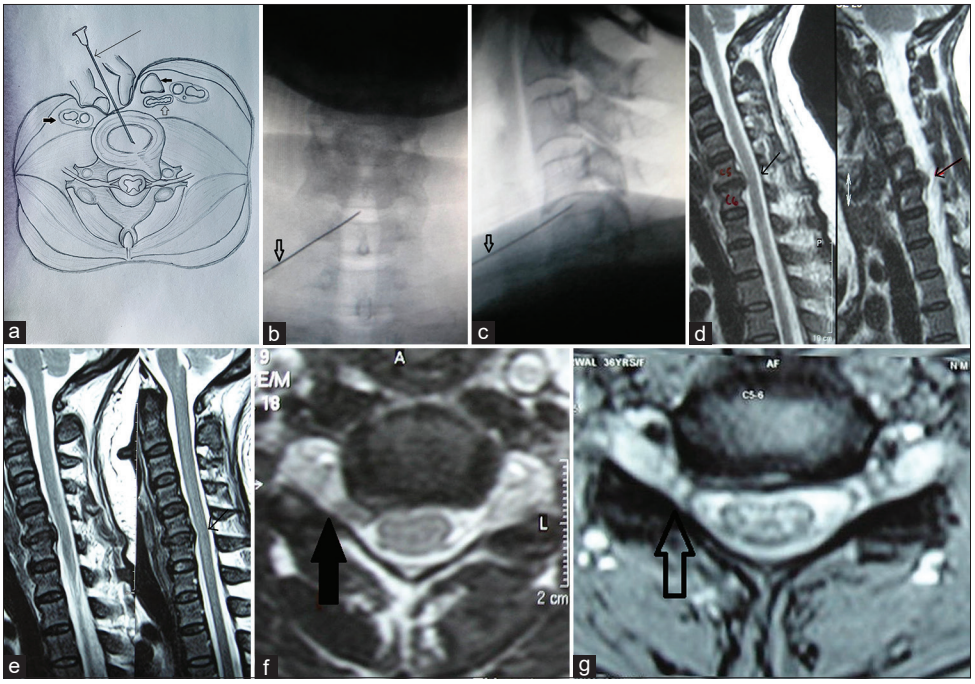

Figure 1: (a) cross sectional drawing showing needle path (slender arrow),trachea (Solid black arrow), Esophagus (Empty black arrow), Right carotid sheath (white bordered black arrow), (b) Fluoroscopic image anteroposterior view showing needle in centre of the disc (empty arrow), (c) Fluoroscopic image lateral view showing needle in centre of the disc (empty arrow), (d) MRI sagittal image showing pre treatment disc herniation (slender arrow), (e) MRI sagittal image showing post treatment disc resorption with healing of annulus (slender arrow), (f) MRI axial image showing pre treatment disc herniation (Solid arrow), (g) MRI axial image showing post treatment disc resorption (Solid arrow)

other hand though the soft tissue window between carotid sheath and trachea-esophagus [Figure 1a]. Local anesthesia is not required in this location. 22G spinal needle (Top Spinal Needle. Meditop corporation, Malaysia) with a length of 3.5 inches was used. The needle tip is directed toward the center of the disc [Figure 1b and c]. The position of the needle is checked with anteroposterior and lateral views [Figure 1b and c]. Ozone was generated from medical-grade oxygen (Medical Ozonator, India). 30% ozone–oxygen mixture is aspirated into 3cc Luer Lok syringe through 0.22 μ filter (Millipore Merck, Burlington, United States) and one-two milliliter injected intradiscally under fluoroscopic guidance. Some of the ozone–oxygen mixture gets dispersed into surrounding soft tissues. Steroid injection of triamcinolone 2 mL injected intramuscularly in the deltoid muscle of on the painful side.

At the end of treatment, patients were advised to rest in the supine position for 2 h and then mobilized gradually over the next several hours. On discharge, patients were given supplementary medications and are instructed to gradually resume their activities daily living. All the patients were advised to avoid heavy activities for 2 to 4 weeks along with passive physiotherapy such as intereferential therapy, transcutaneous electrical nerve stimulation, ultrasound, and

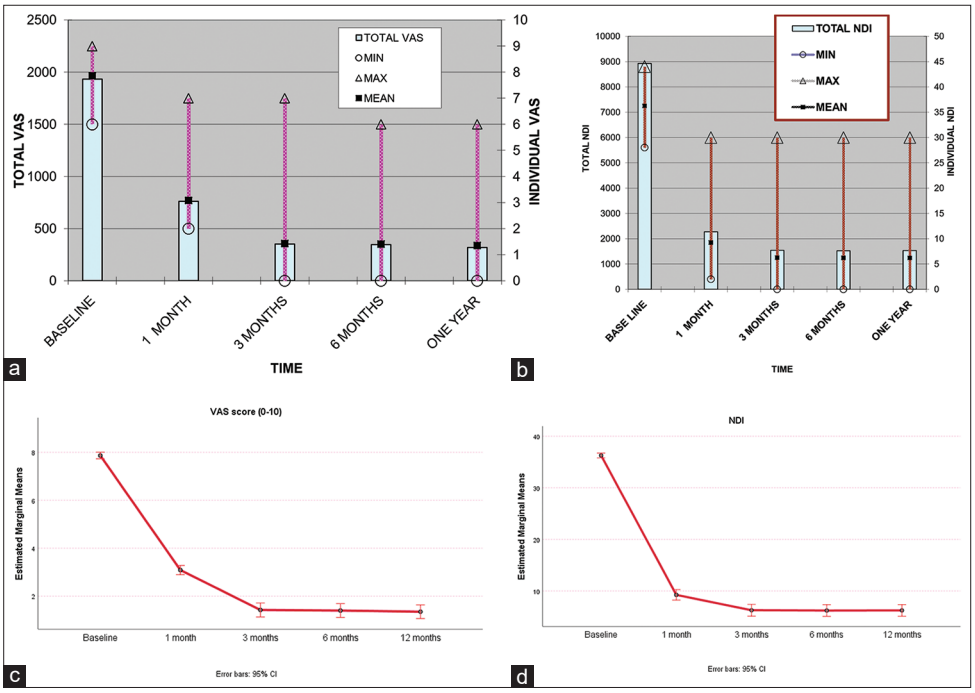

Figure 2: (a) Outcome as per VAS scale over time. Baseline is pre treatment score and 1 month, 3 months, 6 months and one year are post treatment scores, (b) Outcome as per Neck Disability Index score over time. Baseline is pre treatment score and 1 month, 3 months, 6 months and one year are post treatment scores, (c) Mean (95% C.I.) for VAS, (d) Mean (95% C.I.) for NDI I)

Table 3: VAS and NDI scores

	Mean	95% C.I. for mean		Change from baseline			*P*#
				Mean	95% C.I. for difference		
VAS score*							
Baseline	7.87	7.73	8.00	-	-	-	-
1 month	3.09	2.90	3.28	4.78	4.54	5.01	<0.0001
3 months	1.42	1.13	1.72	6.44	6.12	6.77	<0.0001
6 months	1.40	1.11	1.69	6.47	6.15	6.79	<0.0001
12 months	1.35	1.07	1.63	6.52	6.20	6.83	<0.0001
NDI*							
Baseline	36.27	35.80	36.74	-	-	-	-
1 month	9.24	8.23	10.24	27.03	26.08	27.99	<0.0001
3 months	6.25	5.10	7.40	30.02	28.92	31.11	<0.0001
6 months	6.20	5.06	7.33	30.07	28.99	31.15	<0.0001
12 months	6.22	5.08	7.36	30.05	28.96	31.13	<0.0001

*$P<0.0001$ (Repeat measures ANOVA); #paired *t*-test (comparison versus baseline)

acupuncture as deemed appropriate. We would prefer active muscle strengthening exercises after relief from pain. The outcome was assessed by VAS scale and NDI score at 1, 3, and 6 months and 1 year. The outcome was also assessed by the modified McNab criterion [Table 2].

Data analysis

Statically analysis was done by one-way analysis of variance (ANOVA) test. The results were considered statistically significant if $P < 0.05$. Repeated-measures ANOVA was used for the analysis of baseline and follow-up data of VAS and NDI scores. Pairwise comparisons of baseline data for VAS and NDI scores with follow-up data were compared using paired *t*-test.

RESULTS

The mean baseline VAS score was 7.87, which became 3.09 at 1 month, 1.42 at 3 months, 1.40 at 6 months, and 1.35 at 1 year. This was significant with $P < 0.05$. Similarly, the mean NDI was 36.27 at baseline which improved to 9.24 at 1 month, 6.25 at 3 months, 6.20 at 6 months, and 6.22 at 1 year [Figure 2 and Table 3]. This was found to be significant with $P < 0.05$. Modified McNab criterion for outcome showed excellent recovery in 138 (56.10%), good recovery in 50 (20.32%), and fair recovery in 22 (8.94%). Excellent, good, and fair recovery considered successful treatment is seen in 210 out of 246 patients (85.36%). Mediocre or no recovery was seen in the remaining 36 patients amounting to a 14.64% failure rate. There were no bad results seen. We could do 6-month postprocedure MRI in 12 patients, of which eight patients showed a reduction in disc herniation as compared to pretreatment MRI, as shown in [Figure 1d-g].

DISCUSSION

Ozone disc nucleolysis with its multimodal capabilities is emerging as the most comprehensive and least invasive treatment modality for cervical disc herniations. Disc herniation may be contained such as disc bulge and disc protrusion or noncontained like disc extrusion and disc sequestration. The appropriate treatment of cervical disc herniation is a challenge as mechanical and biochemical factors are involved in the pathophysiology of this disease. Mechanical compression leads to a range of microvascular changes. Mild compression produces venous congestive nerve root edema, and severe compression results in arterial ischemia initiating root cry which sets off sharp shooting pain along the dermatome.[2,7] When disc ruptures, the immune-privileged nucleus displaces through 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 unfavorable effect of inflammation of nerve roots and dorsal root ganglia. There is another favorable effect that helps in the resorption of extruded nucleus pulposus. However, this natural resorption is painful and slow phenomenon. Inflammatory markers such as interleukin-6 (IL-6), IL-12, IFN γ, and presence of CD68 macrophages have greater presence in 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. 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 nerve downhill.[9] Tumor necrosis factor α and phospholipase A2 are present in significant amount in herniated nucleus pulposus. These are responsible for partial demyelination that increases nerve root sensitivity making them more susceptible to mechanical pressure.[7] The mechanical compression due to herniated disc then able to trigger hyperexcitability leading to neuropathic paresthesia and pain. Thus, symptoms arising from disc herniation are due to amalgamation of bio-chemico-mechanical factors.[2,7,9] Ozone disc nucleolysis involves the injection of oxygen–ozone mixture. This mixture exploits the biochemical properties of ozone. Medicinal ozone is generated from medical-grade oxygen by corona discharge. It is to be used judiciously as a pharmaceutical agent in prescribed doses. In general, the accepted therapeutic dose is 10–40 μg of ozone per ml of oxygen. At 10% ozone acts as immunomodulatory. At 25–30, it helps in dehydration of the disc nucleus. Outside this therapeutic window, ozone momentarily activates cellular reactions at 1% and will be cytotoxic above 40%. Most of the trials prove the concentration of Ozone at 25%–30% will be optimum for therapeutic effects in disc herniation.[10-12] Ozone acts differently at different concentrations in different tissues. Mechanisms of action of intradiscal ozone injection involve fragmentation of glycosaminoglycans which are abundantly present in nucleus pulposus with subsequent release of water molecules This leads to a small decrease in volume of nucleus with a significantly greater decrease in pressure resulting in recoil of nucleus and restoration of the intervertebral disc. This is applicable to contained discs 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. In uncontained discs, the immune-privileged nucleus is exposed to the host immune system with antibody-mediated inflammatory reactions leading to resorption and remission of the extruded nucleus by phagocytosis and lysis. Reactions that occur inside the disc space differ from that occur outside. Moreover, in epidural space, ozone acts as anti-inflammatory agent modulating and hastening switch from M1 to M2 macrophages converting an inflammatory phase to a reparative phase.[9] Ozone is also implicated in the regeneration of myelin sheaths.[13] We know the pathogenesis of the symptoms involves mechanical compression along with biochemical reactions. Our treatment strategy should fight on these two fronts simultaneously to give the patient lasting relief. All the minimally invasive treatment options and surgical decompression can relieve only mechanical compression. Only ozone–oxygen mixture has the ability to neutralize the inflammatory processes responsible for chemical radiculopathy along with decompression by shrinkage of the herniated disc.

Patient selection is key to successful ozone disc nucleolysis, as seen this study. Neck pain and or radiculopathy corresponding to disc herniation without cervical cord compression are ideal candidates to be offered this treatment. The reasons for failure were large disc protrusions, calcified disc, and spinal canal stenosis due to nondiscal elements. We have seen younger patients were responding better to this treatment. Acute disc herniation had a better outcome than chronic degenerative disc disease. Various studies have reported the technique and effectiveness of ozone therapy for cervical disc herniation.[14-17] The results are consistent and long lasting with the adaptation of lifestyle modifications. The results are comparable to the other minimally invasive procedures. It is only treatment modality which acts by mechanical decompression along with neutralizing the inflammatory processes implemented in radiculopathy.

Only right anterolateral approach is available for cervical discs as the left anterolateral is avoided to prevent injury to the esophagus. Complications related to ozone disc nucleolysis are very rare. The reported incidence is approximately 0.1%.[6,18,19] The most common are paresthesia, headache, syncope, and visual disturbances. These are transient events and almost complete recover in few hours. Air embolism, vitreoretinal hemorrhage, and pneumoencephaly are very rare.[20,21] There is one case each of cardiopulmonary arrest and vertebrobasilar stroke developing after ozone–oxygen mixture injection has been reported.[22,23] Recently, massive emphysema and pneumomediastinum have been reported.[24] However, we believe that these later complications are due to increased epidural pressure as a result of inadvertent injection of large quantity of ozone–oxygen mixture. Standardization of the quantity of ozone injection will minimize these complications to almost nil. We recommend a maximum of 3 ml in intradiscal space of the cervical disc. In our institutional experience, we did not encounter any permanent disability in the last 15 years.

CONCLUSION

This study showed that ozone disc nucleolysis significantly reduces the pain related to cervical disc herniation. There is a significant reduction in disability during activities of daily living. It is cost-effective with a short recovery time leading to curtailing loss of man-hours. Ozone disc nucleolysis is minimally invasive, least risky, and optimally effective treatment option. We strongly recommend it for cervical disc herniation with radiculopathy with or without neck pain not responding to conservative management. However, randomized control trial with a large study population is recommended to further validate our results.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Safiri S, Kolahi AA, Hoy D, Buchbinder R, Mansournia MA, Bettampadi D, *et al.* Global, regional, and national burden of neck pain in the general population, 1990-2017: Systematic analysis of the Global Burden of Disease Study 2017. BMJ 2020;368:m791.
2. Sharrak S, Al Khalili Y. Cervical disc herniation. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK546618. [Last updated on 2021 Sep 03].
3. Boden SD, McCowin PR, Davis DO, Dina TS, Mark AS, Wiesel S. Abnormal magnetic-resonance scans of the cervical spine in asymptomatic subjects. A prospective investigation. J Bone Joint Surg Am 1990;72:1178-84.
4. Caridi JM, Pumberger M, Hughes AP. Cervical radiculopathy: A review. HSS J 2011;7:265-72.

5. Cheung JP, Luk KD. Complications of anterior and posterior cervical spine surgery. Asian Spine J 2016;10:385-400.
6. Steppan J, Meaders T, Muto M, Murphy KJ. A metaanalysis of the effectiveness and safety of ozone treatments for herniated lumbar discs. J Vasc Interv Radiol 2010;21:534-48.
7. Buric J, Rigobello L, Hooper D. Five and ten year follow-up on intradiscal ozone injection for disc herniation. Int J Spine Surg 2014;8:10.14444/1017.
8. Vernon H, Mior S. The neck disability index: A study of reliability and validity. J Manipulative Physiol Ther 1991;14:409-15.
9. Erario ML, Croce E, Moviglia Brandolino MT, Moviglia G, Grangeat AM. Ozone as modulator of resorption and inflammatory response in extruded nucleus pulposus herniation. Revising Concepts. Int J Mol Sci 2021;22:9946.
10. Viebahn-Haensler R, León Fernández OS. Ozone in medicine. The low-dose ozone concept and its basic biochemical mechanisms of action in chronic inflammatory diseases. Int J Mol Sci 2021;22:7890.
11. Costanzo M, Cisterna B, Vella A, Cestari T, Covi V, Tabaracci G, *et al*. Low ozone concentrations stimulate cytoskeletal organization, mitochondrial activity and nuclear transcription. Eur J Histochem 2015;59:2515.
12. Madrid Declaration on Ozone Therapy. International Meeting of Ozone Therapy Schools. AEPROMO. Madrid, España: Spanish Association of Medical Professionals in Ozone Therapy (AEPROMO); 2010.
13. Ozturk O, Tezcan AH, Adali Y, Yıldırım CH, Aksoy O, Yagmurdur H, *et al*. Effect of ozone and methylprednisolone treatment following crush type sciatic nerve injury. Acta Cir Bras 2016;31:730-5.
14. Rashid U, Rauf F, Hameedullah A, Atif M, Leonardi M. Ozonucleolysis in cervical radiculopathy. Neurol Res Surg 2018;1:1-3.
15. Alexandre A, Corò L, Azuelos A, Buric J, Salgado H, Murga M, *et al*. Intradiscal injection of oxygen-ozone gas mixture for the treatment of cervical disc herniations. Acta Neurochir Suppl 2005;92:79-82.
16. Beyaz SG, Sayhan H. Six-Month results of cervical intradiscal oxygen-ozone mixture therapy on patients with neck pain: Preliminary findings. Pain Physician 2018;21:E449-56.
17. Xiao Y, Tian JL, Li J, Zhang JS. CT-guided ozone injection for the treatment of cervical disc herniation. Riv Ital Ossigeno Ozonoterapia 2006;5:109-15.
18. Magalhaes FN, Dotta L, Sasse A, Teixera MJ, Fonoff ET. Ozone therapy as a treatment for low back pain secondary to herniated disc: A systematic review and meta-analysis of randomized controlled trials. Pain Physician 2012;15:E115-29.
19. Muto M, Ambrosanio G, Guarnieri G, Capobianco E, Piccolo G, Annunziata G, *et al*. Low back pain and sciatica: Treatment with intradiscal-intraforaminal O (2)-O (3) injection. Our experience. Radiol Med 2008;113:695-706.
20. Dall'Olio M, Princiotta C, Cirillo L, Budai C, de Santis F, Bartolini S, *et al*. Oxygen-ozone therapy for herniated lumbar disc in patients with subacute partial motor weakness due to nerve root compression. Interv Neuroradiol 2014;20:547-54.
21. Ezeldin M, Leonardi M, Princiotta C, Dall'olio M, Tharwat M, Zaki ML, *et al*. Percutaneous ozone nucleolysis for lumbar disc herniation. Neuroradiology 2018;60:1231-41.
22. Beyaz SG, Altaş C, Sayhan H. Cardiopulmonary arrest and pneumoencephaly developing after epidural oxygen-ozone mixture therapy. Anesth Essays Res 2018;12:285-7.
23. Corea F, Amici S, Murgia N, Tambasco N. A case of vertebrobasilar stroke during oxygen-ozone therapy. J Stroke Cerebrovasc Dis 2004;13:259-61.
24. İlhan B, Doğan H. Novel complication of ozone therapy: Massive emphysema and pneumomediastinum. Am J Emerg Med 2021;41:190-2.