The Internet Journal of Pain, Symptom Control and Palliative Care
Volume 10 Number 1

Ozone: A Versatile Agent; An Overview Of Its Varied Applications In Current Medical Practice

V Himanshu, Y Nirmal, J Mirinda

Citation

V Himanshu, Y Nirmal, J Mirinda. *Ozone: A Versatile Agent; An Overview Of Its Varied Applications In Current Medical Practice*. The Internet Journal of Pain, Symptom Control and Palliative Care. 2013 Volume 10 Number 1.

Abstract

Ozone therapy is one of the most powerful among all therapies known today. Specific therapeutic applications of ozone include the treatment of vascular disease such as stroke, obstructive arteriopathy, venous insufficiency, inflammatory bowel disease such as Crohn's disease, ulcerative colitis, cancer, ulcers, infected wounds, gangrenes, burns, acute and chronic viral disease and spinal disc problems.

Ozone has beneficial effects on every part of the body. The effects include inactivation of bacteria, viruses and fungi, dissolution of malignant tumors, enhancement of circulation, activation of the immune system, stimulation of oxygen metabolism and formation of peroxides.

Ozone with all these miraculous properties and accompanied by its lack of toxicity is undoubtedly an important tool in medicine. We in this article will highlight, the history and synthesis of ozone, the proposed mechanism of action and routes of administration of ozone and current applications of ozone in medical practice.

INTRODUCTION

Ozone is triatomic oxygen. As a gas it is blue, both liquid ozone (-112 C) and solid ozone (-193 C) are of deep blue color. It is this blue ozone in the atmosphere that causes the sky to be blue.

Ozone is gradually gaining popularity in various medical fields especially in pain management. Among the various diseases presented with pain the following have been treated with ozone therapy with good results, examples include rheumatoid arthritis, polymyositis/fibromyositis, ankylosing spondylitis, osteo-arthritis, synovitis, gout, chrondrocalcinosis, pyrophosphate arthropathy, calcific peri-arthritis, calcific tendinitis, calcinosis and inter-vertebral disc prolapse1.

There are different methods of ozone administration like inhalation of ozone/oxygen or ozone/air mixture; insufflations through rectum/vagina; treating with ozonated water (drinking, dressing wound/ulcers etc.); auto-transfusion of ozonated blood, application of ozonated oil and so on depending on type and site of disease2.

OZONE : PAST AND THE PRESENT

Dr. Kellogg in his book on diphtheria, mentioned the use of ozone as a disinfectant as early as 1881. In October of 1893, the world's first water treatment plant using ozone was installed in Ousbaden, Holland. In 1885, the Florida Medical Association published "Ozone" by Dr. Charles J. Kenworth, MD, detailing the use of ozone for therapeutic purposes.

In 1929 a book called "Ozone and Its Therapeutic Action" was published in the US listing 114 diseases and how to treat them with ozone. In 1961 Hans Wolff introduced the techniques of major and minor autohemotherapy23. In 1979 Dr. George Freibott began treating his first AIDS patient with ozone and in 1980 Dr. Horst Kief reported success treating AIDS with ozone.

Today after 125 years of usage ozone therapy is a recognized modality in many nations: Germany, France, Italy, Russia, Romania, Czech Republic, Poland, Hungary, Bulgaria, Israel, Cuba, Japan, Mexico, and in five US states. Its widest use is in Germany.

TECHNIQUE FOR GENERATION OF OZONE

The first ozone generators were developed by Werner von Siemens in Germany in 1857. In September 1896, the electrical genius Nikola Tesla patented his first ozone generator, and in 1900, he formed the Tesla Ozone Company. Tesla sold ozone machines to doctors for medical use, the same thing we are doing 100 years later, with a

design based on one of his from the 1920s.

Oxygen is the only gas that picks up and holds electrical energy thereby becoming tremendously active. The list of substances that are inert to ozone is very short and includes glass, teflon, kynar, silicone and gold. Therefore, any ozone generator and auxilliary equipment must be composed of these substances only. The various ways to produce medical grade ozone are listed below :

1. Ultraviolet light: Ultraviolet light in the 180-190 nanometer wavelength produce only 1-3 ug/ ml, sufficient only for air purification and cleaning of water in small quantities. This concentration of ozone is not fit for medical use.

2. Corona discharge : Corona discharge generates high concentrations of ozone, up to 140 ug/ml. this is the most cost effective way to produce large quantities of ozone but reliability is always a problem.

3. Cold plasma : best for medical use as it produces a clean flow of 50 ug/ml with good long term reliability.

OZONE CONCENTRATION (PERCENT CONCENTRATION)

The quantity of ozone in comparison with the quantity of oxygen in the gas stream is called percent concentration. A litre of oxygen weighs 1.4 grams.
It is measured in micrograms (ug) of ozone per millilitre (or cc) of the mixture.
0.5% x 1.4 gm = 7 ug/cc LOWER LIMIT.
2.0% x 1.4 gm = 28ug/cc (commonly used concentration for pain procedures).
5.0% x 1.4 gm = 70ug/cc UPPER LIMIT
5% or 70 ug/cc is considered to be the upper limit of concentration for internal use of medical ozone.

USE OF OZONE IN VARIOUS DISEASE CONDITIONS

1. EFFECTS OF OZONE ON THE AIRWAYS: Airway Hyperreactivity And Inflammation

Upon ozone inhalation, an increase in airway hyperreactivity is noticed accompanied by airway inflammation. Ozone acts similar to smoking, it attaches to Toll-like receptor 4 which activates NADPH-oxidase to produce reactive oxygen species (ROS). ROS inturn causes release of substances which enter nuclei to activate the COX2 gene. COX2 then produces PGE2, which stimulates cytokines like TNF and IL-6. These induce airway inflammation during the early stage of exposure. These reactions also occur in airway epithelial cells, endothelial cells, and macrophages4,5,6.

2. OZONE THERAPY IN PERIPHERAL OBSTRUCTIVE ARTERIAL DISEASES (POAD) :

Ozone therapy firstly lead to the activation of glycolysis with an increase in adenosine triphosphate (ATP) and 2,3-diphoshoglycerate (2,3-DPG). Consequently the sigmoidal oxygen-binding curve of Hb shifts to the right and increases the release of oxygen in the ischemic tissues. Ozone by various mechanism, increases vascular endothelial growth factor (VEGF) which stimulates neoangiogenesis. Increase in biosynthesis of erythropoietin occurs which augments oxygen delivery. An increase in glycolytic enzymes enhances glucose metabolism and biosynthesis of nitric oxide and carbonmonoxide, which also stimulate blood flow and oxygen delivery into hypoxic tissues. Thus, these biological responses may induce the excellent therapeutic effects of ozone-induced mild oxidative stress in POAD7,8.

According to the Fontaine-Leriche classification, patients at either stage II (intermittent claudication and transitory pain) or stage III (continuous pain, cyanosis and initial ulcers) achieve the best results. Stage IV includes incipient necrosis of toes and unbearable pain leads to surgical amputation that can be reduced or delayed with ozonated-AHT in about 50% of cases. In patients at stage III and IV, the topical therapy is most important when performed with ozonated water and olive oil because it helps to accelerate healing of ulcers

In comparison to pentoxyfilline and prostanoids (the gold standard of orthodox treatment), ozonated AHT has proved more effective and without side effects in ischemic vascular disease9,10.

3. OZONE THERAPY IN AGE-RELATED MACULAR DEGENERATION (ARMD) :

"Dry" (atrophic) form of ARMD are suitable for treatment with ozonated AHT. Usually 15-18 treatments, at an initial ozone concentration of 20 mg/ml of gas per ml blood, slowly upgraded to 60 mg/ml (twice weekly), followed by two monthly session as a maintenance therapy, allows to maintain the improvement. The disease does not progress during ozone therapy11.

4. OZONE THERAPY IN NEURODEGENERATIVE DISEASES :

Increased/severe oxidative stress activates nuclear transcriptional factor kappa B (NF□B), resulting in an inflammatory response and tissue injury via the production of COX2, PGE2, and cytokines. This is associated with neuronal cell death in chronic neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis12.

Ozone therapy induces moderate oxidative stress and activates another nuclear transcriptional factor, nuclear factor- erythroid 2- related factor 2 (Nrf2). Nrf2 then induces the transcription of antioxidant response elements (ARE) resulting in the production of numerous antioxidant enzymes such as superoxide dismutase, glutathione-s-transferase, catalase, heme-oxygenase-1, NADPH-quinone-oxidoreductase, phase II enzymes of drug metabolism and heat shock proteins (HSP). Both free antioxidants and anti-oxidative enzymes not only protect cells from oxidation and inflammation but they may also be able to reverse the chronic oxidative stress13,14.

5. OZONE THERAPY IN DIABETIC FOOT MANAGEMENT :

Diabetes is a disorder of metabolism and of the circulation. Chronic metabolic irregularities linked to poor circulatory perfusion and nerve damage can affect a number of organ systems, including skin tissues. The conditions include infected wounds, skin ulcers and gangrene. These wounds, in the context of diabetes, are notoriously difficult to resolve. Healing resistance is thus a well-recognized element of frustration in their clinical care15.

In case of diabetic ulcer conditions, multiple factors play into healing resistance. Among them are circulatory impairments, neurological deficits, tissue injury, and immunological compromise. A central factor is the proliferation of infectious microorganisms that, by the variety of their families, their toxin-producing capacities, and their resistance to antibiotics, offer daunting obstacles to standard treatment regimens16.

How Ozone helps :

Ozone has powerful bactericidal, fungicidal and virostatic properties widely used in disinfecting infected wounds. Ozone attacks PUFA in the bacterial cell membrane and increases the porosity leading to cell damage, cell rupture and death. It acts indirectly by activating macrophages and T cells and leads to phagocytosis and antibody production, effectively killing the bacteria. Ozone induces synthesis of interferon and blocks viral replication. Ozone in a higher concentration attacks fungi. Ozone improves blood circulation and tissue oxygenation. Ozone increases and activates body's own antioxidants and radical scavengers. Ozone induces production of PDGF(platelet derived growth factor), TGF-beta which helps in healing and repairs. This property is useful in treatment of chronic ulcers, bed sores, non-healing wounds, burns, etc17,18,19.

MODES OF ADMINISTRATION OF OZONE

1. DIRECT INTRAVENOUS ADMINISTRATION :

A volume of upto 420ml of O2-O3 (concentration 70ug/ml) has been injected daily slowly for several hours for two weeks. This practice is best avoided for the fear of gas embolism. After the advent of ozone autohemotherapy this practice is abandoned20.

2. DIRECT INTRAARTERIAL ADMINISTRATION :

Slow injection of 20ml of O2-O3 mixture (30ug/ml) have been injected into femoral artery in advanced cases of limb ischemia. It has now been replaced by ozone autohemotherapy20.

3. OZONE AUTOHEMOTHERAPY :

In the minor technique, 5-10ml of venous blood is drawn and immediaqtely mixed with equal volume of ozone and is injected intramuscularly. This is used in the treatment of asthma, cancer and herpetic infections with varied success21.

In the major ozone autohemotherapy, 60-100ml of blood collected in CPD ozonated (10-30ug/ml) and is rapidly infused. This can be done daily oe 2-3times a week.Preferably, avoid bubbling ozone through the blood as this promotes hemolysis. Instead, continuous rotation for 5-10min should be done to ensure continuous interaction. Ozone upto concentration of 80ug/ml has been used and a time gap of 10min before reinfusion minimises chances of hemolysis. Reinfusion into the donor can be done in 20-30min. Upto 70 consecutive sessions of majot autohemotherapy have been done in a patient safely22,23,24.

4. PER RECTAL OZONE :

A mixture of 02-03 with a concentration no higher than

40ug/ml is insufflated into the rectal canal as high as possible with a Teflon cannula(rubber is destroyed by ozone). One should start with daily application of 150ml gas at a concentration of 10ug/ml, and can go as high as 40ug/ml and 750ml. Satisfactory results have been obtained in patients of AIDS with cryptosporoidosis, ulcerative colitis, crohn's disease, acute and chronic hepatitis25.

The ozone insufflation via rectum is the most unreliable administration route because we never know the percentage of the really effective ozone dose insufflated into the rectum. Shortcomings include :

(i) Many patients may refuse the administration of ozone via rectum.

(ii) Part of the ozone dose may be unwillingly eliminated immediately after the gas introduction.

(iii) The fecal content and the abundant mucoproteins certainly neutralize part of the ozone dose.

(iv) Ozone may not be absorbed by the rectal mucosa. This is because ozone immediately reacts with a variety of biomolecules present in the luminal content and only some part of the generated compounds are absorbed and may exert therapeutic activity26.

PROLOTHERAPY OR REGENERATIVE INJECTION THERAPY (RIT)

Prolotherapy or Regenerative Injection Therapy (RIT) includes the injection of mild inflammation producing substances thereby causing the release of cytokines which inturn start a fibroblastic reaction that is similar to the natural healing process. This results in creation of new, stronger, flexible, and less pain sensitive joint. Patients with pain originating from a joint, ligament or tendon with strong immune system and willingness to receive follow-up visits.

CONSTITUENTS OF PROLOTHERAPY:

1. Osmotic agents :

10%-25% Dextrose, glycerin.

2. Agents that attach to the cell wall and stimulates growth:

Diluted phenol, Sarapin, guaiacol, quinine, urea, ozone or tannic acid.

3. Chemotactic agents:

Sodium morrhuate, a fatty acid derived from cod liver oil.

MECHANISM OF ACTION OF PROLOTHERAPY :

Injection of a proliferant causes low level inflammation. This results in :

Phase I (early phase – upto 3days) where granulocyte activity appear and release of inflammatory cellular contents occur. Here a soupy mixture without structure is present.

Phase II (intermediate phase – next 10days) : macrophages predominate here and cause release of chemotactic factors which attract fibroblasts and act as growth factors. A matrix forms at this stage.

Phase III : collagen starts to form, giving strength to the tissue. There is a gradual dehydration of the matrix with more orderly collagen fibers. This eventually leads to new, stronger connective tissue. The whole process may take several months.

All through these stages, the "body decides" which ligaments to strengthen depending upon the physical needs in each individual . This is why it is important to advise patients to stretch and stay active during therapy.

Since prolotherapy treats the root causes, it is extremely useful for a osteoarthritis knee.

ADMINISTRATION OF PROLO-THERAPY KNEE JOINT:

It is a very simple injection technique that involves a medial approach into the knee capsule. The commonly practiced method is 3ml of 25% dextrose with 3ml of 2% lignocaine and then 10 cc's of the ozone gas is injected. The general dosage of ozone used is 20-30 ug/ml.

Table 1

COMPARISON OF PROLOTHERAPY WITH INTRA-ARTICULAR STEROID INJECTION

PROLO-OZONE THERAPY	INTRARTICULAR STEROID THERAPY
1. Better relief of pain and muscle stiffness	1. Comparatively lesser pain relief.
2. 8 -10 or even more injections/year can be done.	2. Not > 4 steroid injection/year are recommended.
3. Surgery has been averted in many patients as basic degenerative pathology is reversed.	3. Patients eventually need surgery if pain not controlled by injections.
4. very safe. No ozone related side effects documented.	4. Side effects of steroids including osteoporosis may be found in some cases.
5. Can be used in diabetics and patients with metabolic abnormalities.	5. Preferably avoided as hyperglycemia, pituitary suppression etc are known to occur.

How safe is prolotherapy ?

The Florida Academy of Pain Medicine produced a position paper after reviewing 78 specific articles and nine text books, as well as 51 relevant articles and chapters from other text books.

They concluded that "RIT is a safe and effective treatment modality that is very useful in a significant number

of pain syndromes arising from ligament and tendon diathesis, as well as other clearly delineated pain problems."

INTERVERTEBRAL DISC PROLAPSE & OZONE NUCLEOLYSIS

Ozone nucleolysis may be done27 :

1. Must have failed conservative treatment for >4 wks.
2. Must have positive CT/MRI scan.
3. Should not have red flag signals.
4. Should not have sequestrated disc. (degenerated disc without any prolapse and nerve root irritation, contained disc or disc bulge with root irritation, extruded disc).

HOW DOES OZONE THERAPY WORK 28 :

Ozone readily dissolves in the water of the nucleus pulposus and reacts with glycoproteins composed of carbohydrates and polypeptide chains, namely proteoglycans and collagen types II and IV. Formation of reactive oxygen species, is likely followed by generation of hydroxyl radicals according to the Fenton's reaction:

PUFA+O3+H2O−−−−−−−−−−aldehyde 1+aldehyde 2+H2O2

Transient formation of hydroxyl radical occurs, which is the most reactive radical attacking and breaking down any biomolecule within its reach: the rapid reabsorption of hydrolytic products and free water lead to a progressive shrinkage of the nucleus and frequently to a progressive disappearance of the herniated material. The inflammatory process induced by the hernia disappears thereafter28,29,30.

It is almost equivalent to Surgical Discectomy and so the procedure is called Ozone Discectomy Or Ozonucleolysis Or popularly Ozone Therapy For Disc Prolapse.

HOW IS OZONE NUCLEOLYSIS DONE :

Procedure is done usually under local anaesthesia with intravenous sedation under Carm guidance.

1. The patient in prone position.
2. C-arm first in AP view (fig 1) is done to view the diseased disc.
3. C-arm is tilted cranially/caudally (fig 2) to square the end plates.
4. C-arm is rotated obliquely (fig 2) away from vertebral column such that facet joint come at the center of the end plates.
5. The needle entry point is just lateral to the superior pars/articular pillar exactly at the center of the disc (Fig 3 for L5-S1 discectomy, fig 4 for L4-L5 discectomy).
6. A 22 G spinal needle is introduced into the diseased disc. The position of needle tip may be confirmed by complete AP & lateral view and 3-10 cc of oxygen-ozone mixture (at a concentration of 25-40 microgram/ml, fig 5,6) is injected into the disc.
7. An even simpler and popular approach for treating the low back pain is the administration of gas into the paravertebral muscles corresponding either to trigger points or to the metamers of the herniated disk. It is an easy approach consisting in one or up to four injections of 5-10 ml of the gas mixture per site performed very slowly. The ozone concentration must not exceed 20-25 g/ml, because it is painful.
8. Ozone molecule has a half-life of 20 minutes only. For injection, ozone is always freshly prepared from an ozone generator for immediate administration. While needle with the syringe is taken out, some amount of oxygen-ozone mixture is also injected into the paraspinal muscle and para-radicular soft tissue to reduce nerve root inflammation and increased oxygenation of the para-spinal muscles31,32,33.
9. The therapeutic benefit is almost 80% for the direct procedure and about 73% for the chemical acupuncture34

Figure 1

C-arm first in AP view

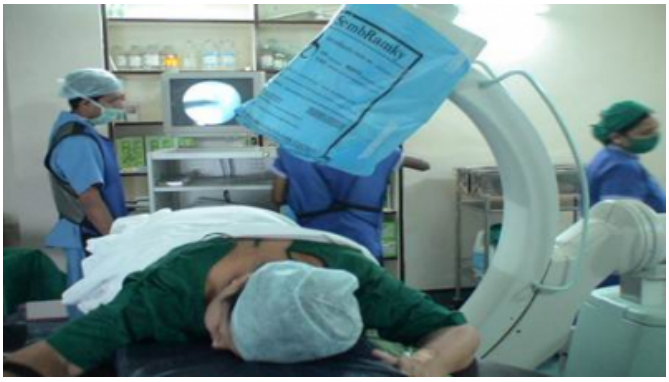

Figure 2

C-arm is tilted cranially/caudally

Figure 3

The needle entry point is just lateral to the superior pars/articular pillar exactly at the center of the disc for L5-S1 discectomy

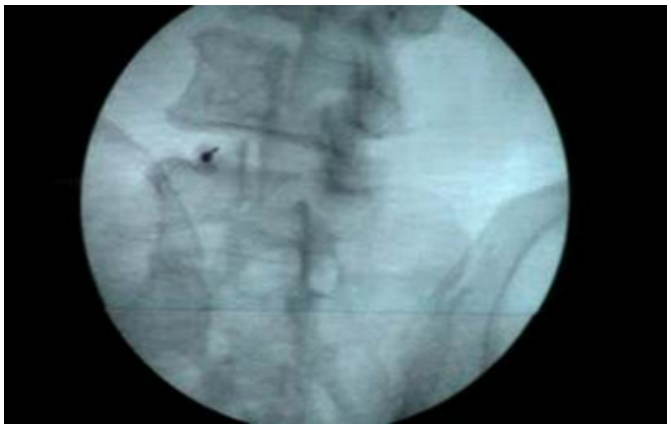

Figure 4

The needle entry point is just lateral to the superior pars/articular pillar exactly at the center of the disc for L4-L5 discectomy

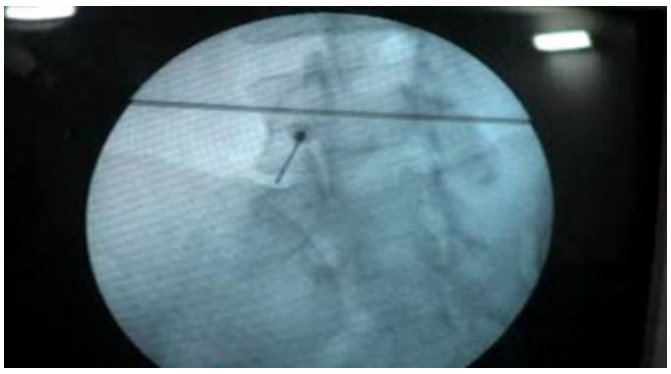

Figure 5

A 22 G spinal needle is introduced into the diseased disc. The position of needle tip may be confirmed by complete AP & lateral view and 3-10 cc of oxygen-ozone mixture (at a concentration of 25-40 microgram/ml is injected into the disc.

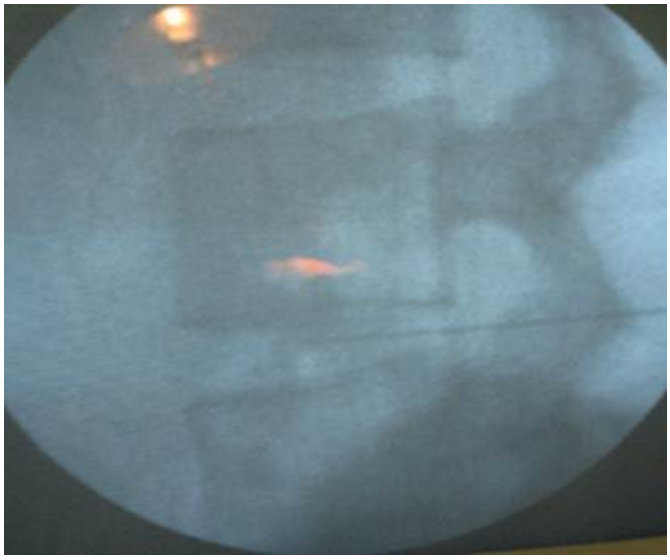

Figure 6

A 22 G spinal needle is introduced into the diseased disc. The position of needle tip may be confirmed by complete AP & lateral view and 3-10 cc of oxygen-ozone mixture (at a concentration of 25-40 microgram/ml is injected into the disc.

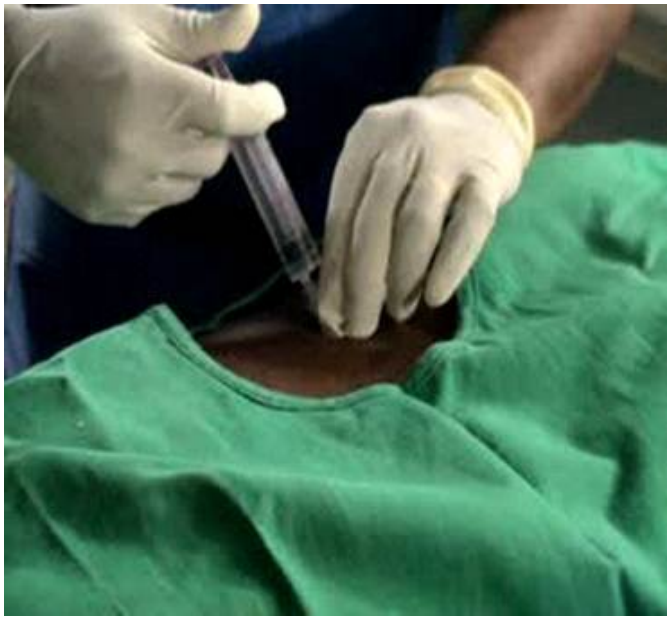

Table 2

OZONE NUCLEOLYSIS Vs SURGICAL DISCECTOMY

OZONE NUCLEOLYSIS	SURGICAL DISCECTOMY
No general anaesthesia needed	General anaesthesia required.
Duration of procedure short (20-30min).	Requires at least 60 mins.
Done as a day care procedure	Requires at least 2-3 day hospital stay.
Success rate of about 80-90%.	Success rate of 49% to 95%.
Percutaneous procedure (less invasive).	Comparatively much more invasive.
Very few side effects and complications.	Comparatively more side effects.
Shorter hospital stay and cheaper.	Costlier as longer hospital stay.

ABSOLUTE CONTRA INDICATIONS :

Favism (Deficiency of G6PD) & Pregnancy (radiation exposure to fetus).

RELATIVE CONTRA INDICATIONS :

Intraforaminal herniation, hyperthyroidism, severe hypertension, multiple hypersensitivities, cervical disc – discoartrosis, foraminal stenosis and calcified disc herniation35.

CONCLUSION

Prolo-ozone therapy of knee joint is a very simple injection technique that has made osteo-arthritis of the knees of mild to moderate severity one of the most rewarding conditions to treat. Pain physicians can get excellent results and can save patients from having extensive surgical procedures done. Prolotherapy is an cheap, extremely safe and OPD based treatment modality.

Ozone nucleolysis is also steadily gaining popularity in different countries including India due to low cost, no anaesthesia required, less hospital stay, fewer post-procedural discomfort & morbidity and increased safety profile.

In the future, newer modification in techniques and administration of ozone, more and more publication of scientific materials in the medical journals will make ozone application acceptable to the medical community.

Sooner or later, the ozone therapy will eventually be accepted by orthodox medicine. But for this to happen, research and publication of various randomized and well controlled clinical trials in diseases have to be done and validity, efficacy and lack of toxicity of ozone therapy has to be definitely demonstrated.

References

1. Lippman M: Health effects of ozone, a critical review. J Am Air Pollut Control Assoc 1989, 39:672-695.
2. Bocci V, Zanardi I, Michaeli V, Travagli V: Mechanisms of action and chemical-biological interactions between ozone and body compartments: a critical appraisal of the different administration routes.Current Drug Therapy 2009, 4:159-173.
3. Wolff HH: Die Behandlung peripherer Durchbutungsstorungen mit Ozon. Erfahr Hk 1974, 23:181-184.
4. Bhalla DK, Gupta SK: Lung injury, inflammation, and inflammatory stimuli in rats exposed to ozone. J Toxicol Environ Health 2000, 59:211-228.
5. Crapo JD: Morphologic changes in pulmonary oxygen toxicity. Ann Rev Physiol 1986, 48:721-731.
6. Aris RM, Christian D, Hearne PQ, Kerr K, Finkbeiner WE, Balmes JR: Ozone-induced airway inflammation in human subjects as determined by airway lavage and biopsy. Am Rev Respir Dis 1993, 148:1363-1372.
7. Bocci V, Travagli V, Zanardi I: May oxygen-ozone therapy improves cardiovascular disorders ? Cardiovascular & Haematological Disorders-Drug Targets 2009, 9:78-85.
8. Bocci V, Zanardi I, Travagli V: Ozone: a new medical drug in vascular diseases. Am J Cardiovas Drugs 2011, 11:73-82.
9. Travagli V, Zanardi I, Bernini P, Nepi S, Tenori L, Bocci V: Effects of ozone blood treatment on the metabolite profile of human blood. Intern J Toxicol 2010, 29:165-174.
10. Di Paolo N, Bocci V, Salvo DP, Palasciano G, Biagioli M, Meini S, Galli F, Ciari I, Maccari F, Cappelletti F, Di Paolo M, Gaggiotti E: Extracorporeal blood oxygenation and ozonation (EBOO): a controlled trial in patients with peripheral artery disease. Int J Artif Organs 2005, 28:1039-1050.
11. Masaru S, Velio Bocci. Mechanisms of Action Involved in Ozone Therapy: Is healing induced via a mild oxidative stress. Medical Gas Research 2011, 1:29 doi:10.1186/2045-9912-1-29.
12. Johnson JA, Johnson DA, Kraft AD, Calkins MJ, Jakel RJ, Vargas MR, Chen PC: The Nrf2-ARE pathway: An indicator and modulator of oxidative stress in neurodegeneration. Ann N Y Acad Sci 2008, 1147:61-69.
13. Jazwa A, Cuadrado A: Targeting heme oxygenase-1 for neuroprotection and neuroinflammation in neurodegenerative diseases. Curr Drug Targets 2010, 11:1517-1531.
14. Singh S, Vrishni S, Singh BK, Rahman I, Kakkar P: Nrf2-ARE stress response mechanism: a control point in oxidative stress-mediated dysfunctions and chronic inflammatory disease. Free Radic Res 2010, 44:1267-1288.
15. Mart?nez-Sanchez G, Al-Dalain SM, Menendez S, Re L, Giuliani A, Candelario-Jalil E, Alvarez H, Fernández-Montequín JI, León OS: Therapeutic efficacy of ozone in patients with diabetic foot. Eur J Pharmacol 2005, 523:151-161.
16. Bocci V, Zanardi I, Huijberts MSP, Travagli V: Diabetes and chronic oxidative stress. A perspective based on the possible usefulness of ozone therapy. Diabe Metabo Syndr: Clinical Research and Reviews 2011, 5:45-49.
17. Bocci V, Paulesu L: Studies on the biological effects of ozone 1. Induction of interferon gamma on human leukocytes. Haematologica 1990, 75:510-515.
18. Bocci V, Luzzi E, Corradeschi F, Paulesu L, Di Stefano A: Studies on the biological effects of ozone 4. An attempt to define conditions for optimal induction of cytokines. Lymphokine Cytokine Res 1993, 12:121-126.
19. Bocci V, Valacchi G, Corradeschi F, Fanetti G: Studies on the biological effects of ozone 8. Effects on the total antioxidant status and on interleukin-8 production. Mediators Inflamm 1998, 7:313-317.
20. Bocci V, Bianchi L, Larini A: The ozone enigma in medicine. The biochemical relationship between ozone and body fluids may account for its biological, therapeutic and toxic effects. Riv Ital Ossigeno-Ozonoterapia 2003,

2:113-120.
21. Travagli V, Zanardi I, Silvietti A, Bocci V: A physicochemical investigation on the effects of ozone on blood. Int J Biol Macromol 2007, 41:504-511.
22. Bocci V: Scientific and medical aspects of ozone therapy, State of the art. Arch Med Res 2006, 37:425-435.
23. Bocci V: The case for oxygen-ozonetherapy. Br J Biomed Sci 2007, 64:44-47.
24. Bocci V, Borrelli E, Travagli V, Zanardi I: The ozone paradox: Ozone is a strong oxidant as well as a medical drug. Medicinal Res Rev 2009, 29:646-682.
25. Bocci V, Zanardi I, Travagli V: Oxygen/ozone as a medical gas mixture. A critical evaluation of the various methods clarifies positive and negative aspects. Medical Gas Research 2011, 1:6.
26. Bocci V, Borrelli E, Corradeschi F, Valacchi G: Systemic effects after colorectal insufflation of oxygen-ozone in rabbits. Int J Med Biol Environ 2000, 28:109-113.
27. Andreula CF, Simonetti L, De Santis F, Agati R, Ricci R, Leonardi M: Minimally invasive oxygen-ozone therapy for lumbar disk herniation. Am J Neuroradiol 2003, 24:996-1000.
28. Bocci V, Pogni R, Corradeschi F, Busu E, Cervelli C, Bocchi L, Basosi R: Oxygen-ozone in orthopaedics: EPR detection of hydroxyl free radicals in ozone-treated "nucleus pulposus" material. Riv Neuroradiol 2001, 14:55-59.
29. Muto M, Andreula C, Leonardi M Treatment of herniated lumbar disc by intradiscal and intraforaminal oxygen-ozone (O2-O3) injection. J Neuroradiol. 2004 Jun;31(3):183-9.
30. Lehnert T, Mundackatharappel S, Schwarz W, Bisdas S, Wetter A, Herzog C, Balzer JO, Mack MG, Vogl TJ. Nucleolysis in the herniated disk. Radiologe. 2006 May 13.
31. Buric J, Molino Lova R. Ozone chemonucleolysis in non-contained lumbar disc herniations: a pilot study with 12 months follow-up. Acta Neurochir Suppl. 2005;92:93-7.
32. Andreula CF, Simonetti L, De Santis Fet al: Minimally invasive oxygen ozone therapy for lumber disc herniation. American Journal of Neuroradiology 2003; 24: 996-1000.
33. Gautam Das, S. Ray, S. Iswarari, M. Roy, P. Ghosh; Ozone Nucleolysis for Management of Pain and Disability in Prolapsed Lumber Intervertebral Disc: A Prospective Cohort Study; Interventional Neuroradiology 15: 330-334, 2009.
34. Vijay S. Kumar: Total clinical and radiological resolution of acute, massive lumber disc prolapse by ozonucleolysis. Rivista Italiana di Ossigeno-ozonoterapia 4: 2005.
35. Vad VB, Bhat AL, Lutz GE, Cammisa F. Transforaminal epidural steroid injections in lumbosacral radiculopathy; A prospective randomized study. Spine.

Author Information

V Himanshu, Dr, Assistant Professor
Dept of Anaesthesiology and Consultant Critical care and Pain , SRMS IMS
Bareilly. India

Y Nirmal, Dr, Associate Professor
Dept of Internal Medicine, Chief Coordinator, Critical Care, SRMS IMS
Bareilly. India

J Mirinda, Dr, Post graduate student
Dept of Pulmonary Medicine, (Ex Resident ICU), SRMS IMS
Bareilly. India