OZONE THERAPY – AN UPDATE

HEALTH TECHNOLOGY ASSESSMENT SECTION
MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH MALAYSIA

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Please contact: htamalaysia@moh.gov.my, if you would like further information.

Health Technology Assessment Section (MaHTAS),
Medical Development Division
Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Government Office Complex
62590 Putrajaya

Tel: 603 88831246

Fax: 603 8883 1230

Available at the following website: http://www.moh.gov.my

Prepared by:

Dr. Hanin Farhana Kamaruzaman
Assistant Director
Health Technology Assessment Section (MaHTAS)
Ministry of Health Malaysia

Matron Sin Lian Thye
Nursing Supervisor
Health Technology Assessment Section (MaHTAS)
Ministry of Health Malaysia

Reviewed by:

Datin Dr. Rugayah Bakri
Deputy Director
Health Technology Assessment Section (MaHTAS)
Ministry of Health Malaysia

DISCLOSURE

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EXECUTIVE SUMMARY

Introduction

Ozone is a controversial gas because although it is very useful in the stratosphere by absorbing dangerous B and C ultraviolet radiations, it is toxic for other systems, especially the pulmonary tract in the troposphere. Ozone therapy has been used for various medical conditions including chronic limb ischaemia, infections, low back pain due to disc problems, age-related macular degeneration and others. However, as stated in Ozone Therapy health technology assessment (HTA) report conducted by Health Technology Assessment Section (MaHTAS), Ministry of Health Malaysia in 2005, the data on the usage of ozone therapy as therapeutic options for various health conditions lacks sufficient safety and therapeutic advantage over available conventional therapeutic modalities. This technology review was requested by Executive Officer of Policy and International Relation Division, Ministry of Health Malaysia following a request from Royal Embassy of Saudi Arabia, Kuala Lumpur to update the HTA report that was published in 2005.

Objective /aim

The objective of this technology review was to assess the safety and efficacy or effectiveness of ozone therapy in the treatment of medical conditions.

Results and conclusions

There were few low level evidences retrieved on the efficacy or effectiveness of ozone therapy in the treatment of certain medical conditions. However, the evidences obtained were limited to some medical problems only such as treatment of back pain and were not sufficient to conclude that ozone therapy is effective in treating other medical conditions such as HIV infections and cancers.

Although ozone therapy is claimed to be minimally invasive and complications related to this treatment are rare, there are a lot of other considerations to take into account before deciding that ozone therapy is safe. Life-threatening event and permanent disability have been reported with regards to the procedures in administrating oxygen-ozone therapy.

Methods

Electronic databases were searched, which included PubMed, Ovid Medline(R), EBM Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Cochrane database of systematic reviews, EBM Reviews - HTA Databases, Horizon Scanning database, FDA website, and Google for published reports. The articles included in the search strategy were those which were published within year 2005 to first week of May 2011. Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) and evidence was graded according to US/Canadian Preventive Services Task Force (Harris 2001).

OZONE THERAPY – AN UPDATE

1. INTRODUCTION

Ozone is a controversial gas because although it is very useful in the stratosphere by absorbing dangerous B and C ultraviolet radiations, it is toxic for the pulmonary tract in the troposphere. Ozone normally present as a gas made of three atoms of oxygen with a cyclic structure. It is being continually created from and destroyed into molecular oxygen (O_2) and these chemical reactions are catalyzed by very high frequency ultraviolet light from the sunlight.

Ozone therapy has been used for various medical conditions including chronic limb ischaemia, infections, low back pain due to disc problems, age-related macular degeneration and others. However, as reported in Ozone Therapy health technology assessment (HTA) report conducted by Health Technology Assessment Section (MaHTAS), Ministry of Health Malaysia in 2005, the data on the usage of ozone therapy as therapeutic options for various health conditions lacks sufficient safety and therapeutic advantage over available conventional therapeutic modalities. [1]

This technology review was requested by Executive Officer of Policy and International Relation Division, Ministry of Health Malaysia following a request from Royal Embassy of Saudi Arabia, Kuala Lumpur to update the HTA report that was published in 2005.

2. OBJECTIVE /AIM

The objective of this technology review was to update on the safety and efficacy or effectiveness of ozone therapy in treatment of medical conditions such as infectious diseases, ischemia, ophthalmology diseases, otolaryngology diseases, obstetric and gynecology conditions, orthopedic disorders, cancer and skin disorders.

3. TECHNICAL FEATURES

Ozone is an inactivated, trivalent (O_3) form of oxygen. Ozone breaks down into two atoms of regular oxygen by giving up an atom of singlet oxygen over a period of 20 to 30 minutes.[2] As any other gas, ozone dissolves physically in pure water according to Henry's law in relation to the temperature, pressure and ozone concentration. Only in this situation ozone does not react and remains active for a couple of days in a tightly closed glass bottle as the ozonated water, which is useful as a disinfectant.

Ozone is 1.6-fold denser and 10-fold more soluble in water compared to oxygen.[1] It is an unstable gas that cannot be stored and should be used at once because it has a half-life of 40 minutes at 20°C. Ozone concentration is measured in u/ml or gms/L of oxygen, 5% or 70 u/ml is usually the maximum concentration used in clinical medical applications. High concentrations will damage red cells and inhibit growth of healthy cells. [2]

Medical ozone, used to disinfect and treat disease, has been around for over 150 years. The medical generator of ozone produces it from pure oxygen passing through a high voltage gradient. [1] Consequently, the generator collected a gas mixture comprising of no less than 95% oxygen and no more than 5% ozone. Air must be excluded because toxic nitrogen dioxide (N_2O_2) will be formed. The ozone generators are made of high quality, ozone-resistant materials such as stainless steel, neutral gas and Teflon.

The mechanism of action for ozone therapy remains hypothetical but possible explanations of its effect is characterized by the formation of reactive oxygen species (ROS) during the ozonation process which function as physiological enhancers of various biological processes. Other postulated mechanisms include the generation of peroxides and lipid oxidation products (LOP) by ozonolysis with unsaturated fatty acids in cell membranes and increased expression of intracellular enzymes with antioxidant activity. [1]

Administration of ozone therapy that are used in medical practice are similar as those that has been discussed in the previous HTA report and no new technique of ozone therapy administration has been introduced to date. The route of administrations are:

i. Direct intra-arterial and/or intravenous injection

An oxygen-ozone mixture is slowly injected into an artery or vein with a hypodermic syringe. This method is use primarily for arterial circulatory disorder.

ii. Rectal insufflations

A mixture of ozone and oxygen is introduced through the rectum and absorbed into the body through the intestine. It is considered as one of the safest method and has been used in various health problems such as ulcerative colitis, cancer, HIV-related problems and others.

iii. Intramuscular injection

Oxygen-ozone mixture in a small amount is injected via intramuscular route to the patient (usually in the buttocks). This method is commonly used to treat allergies and inflammatory diseases.

iv. Major and minor autohemotherapy

Autohemotherapy involves removing an amount (usually 10 mls for minor and 50 mls for major) of the patient's blood from a vein with a hypodermic syringe. The blood is then mixed with oxygen-ozone and return back to the patient intravenously. These methods have been used to treat arthritis, cancer heart disease and HIV infection.

v. Ozonated water

The ozone gas is bubbled through water and the water is used externally to bathe wounds, burns and slow healing skin infections. It is also used as disinfectant by dentists who perform dental surgery.

vi. Intra-articular injection

In this method, ozone gas is bubbled through water and the mixture is injected directly between the joints. It is used primarily to treat arthritis, rheumatism and other joint diseases.

vii. Ozone bagging

This non-invasive method uses a specially made plastic bag that is placed around the area to be treated. An oxygen-ozone mixture is pumped into the bag and mixture is absorbed into the body through skin. Ozone bagging is primarily recommended for treating leg ulcers, gangrene, fungal infections, burns and slow healing wounds.

viii. Ozonated oil

Used primarily to treat skin problems, ozone gas is added to olive oil and applied as a balm or salve for long-term, low-dose exposure. [1]

4. METHODOLOGY

4.1. Searching

Electronic databases were searched, which included PubMed, Ovid Medline(R), EBM Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Cochrane database of systematic reviews, EBM Reviews - HTA Databases, Horizon Scanning database (National Horizon Scanning, Australia and New Zealand Horizon Scanning), FDA website, and Google for published reports. The articles included in the search strategy were limited to those which were published within year 2005 to first week of May 2011. All studies that use ozone therapy as treatment of medical conditions were included and not limited to the researches that only compare ozone therapy with standard treatment. The search strategy used the terms which were either used singly or in various combinations; ozone, ozone therapy, medical ozone, oxygen-ozone therapy, therapeutic ozone, back pain, diabetic foot, chronic ulcer, dental, hepatitis, kidney disease, cancer, respiratory problems, obstetric and gynecology problem and cardiovascular disease.

4.2. Selection

All published articles related to safety and efficacy or effectiveness of ozone therapy in treating medical conditions were included. Studies conducted in animals were excluded. Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) and evidence was graded according to US/Canadian Preventive Services Task Force (Appendix 1).

5. RESULTS AND DISCUSSION

Six articles reported on the efficacy or effectiveness of ozone therapy in treating specific medical conditions. However, these articles were of low level of evidence due to the short duration of follow up and small number of patients involved.

Two case reports discussing the issue of safety in ozone therapy were included in this review.

5.1. EFFICACY OR EFFECTIVENESS

Scientific databases have been searched for any latest articles regarding the efficacy or effectiveness of ozone therapy in treating medical conditions that has been discussed in the HTA report 2005 such as HIV infections, ophthalmologic diseases, otorhinolaryngology diseases, conditions related to obstetrics and gynaecology problems, ischemia, treatment of cancer and skin problems. However, there was no retrievable new scientific evidence on the above mentioned conditions. There were only few evidences discussing on treatment of ozone therapy on specific disease which will be discussed further in this report.

5.1.1 Ozone therapy in treating low back pain

Medical oxygen-ozone therapy has become an option of treatment for low back pain secondary to lumbar disc herniation that has failed to respond to conservative management. The choice was due to its ease of execution and minimally invasive procedure. However, there were limited scientific evidences retrieved on the efficacy or effectiveness of ozone therapy for treatment of low back pain.

Gallucci *et al* conducted a clinical trial comparing the effectiveness of intraforaminal and intradiscal injections of a mixture of a steroid, local anaesthetic and oxygen-ozone (O_2-O_3) versus intraforaminal and intradiscal injections of a steroid and an anaesthetic in the management of radicular pain related to acute lumbar disc herniation. The trial involved 159 patients with lumbar disc herniation and radicular pain. They are divided into two groups. Seventy seven patients in group A underwent intradiscal and intraforaminal injections of a steroid and an anaesthetic, and another 82 patients in group B underwent the same treatment with the addition of oxygen-ozone mixture. An Oswestry Low Back Pain Disability Questionnaire was administered before treatment and at intervals of 2 weeks, 3 months and 6 months post-intervention. Results from the trial showed that the treatment was successful in 36 patients (47%) in group A and in 61 (74%) patients in group B (p-value <0.01). It was concluded that intraforaminal and intradiscal injections of a steroid, an anaesthetic and oxygen-ozone mixture are more effective at 6 months post-treatment compared to injections of only a steroid and anaesthetic in the same site within the same period.[3, level II-2]

Paoloni *et al* conducted a multicenter randomized, simulated-therapy controlled trial to assess the benefit of intramuscular paravertebral injections of an oxygen-ozone mixture. Total of 60 patients suffering from acute low back pain caused by lumbar disc herniation were included in the study and they were divided into two groups. The first group consisted of 36 patients of whom 15 received intramuscular infiltrations of oxygen-ozone mixture (20ml with an ozone concentration of 20 µg/ml) thrice per week for five consecutive weeks. The injections were administered in the paraspinal lumbar muscles bilaterally. The second group was a control group, consisted of 24 patients, and they received simulated treatment that lasted as long as the oxygen-ozone treatment. The frequency and site of injections were similar in both groups. Local and radiating pain were assessed using a 10-cm horizontal visual analog scale (VAS) while disability related to the low back pain (LBP) were assessed using Backill questionnaire score. Both outcomes measures were assessed at the scheduled visits during the treatment period (15 and 30 days after treatment started) and after treatment ended (2 weeks, 3 months and 6 months intervals). The study demonstrated that 61% of patients from the group that received oxygen-ozone therapy had become pain-free after 6 months of treatment received compared to 33% in the simulated therapy group. A significant improvement was also observed in LBP-related disability in the oxygen-ozone group patients compared to the simulated therapy group. The study concluded that in treating acute low back pain with lumbar disc herniation, oxygen-ozone intramuscular lumbar paravertebral injections which were minimally invasive, seemed to safely and effectively relieve pain as well as reduce the disability related to low back pain.[4, level II-2]

5.1.2 Ozone therapy in treating diabetic foot

Martínez-Sánchez *et al* conducted a clinical trial in Institute of Angiology and Vascular Surgery, Cuba to investigate the therapeutic efficacy of ozone in the treatment of patients with Type II Diabetes Mellitus and diabetic feet, and to compare ozone with antibiotics therapy. One hundred and one patients were randomized to two different groups of treatment. A total of 49 patients in the first group were treated with systemic antibiotics according to the microbe present using the conventional method of treatment and topical antibiotics applied to the diabetic foot wound for 20 days. The second group with total of 51 patients were treated daily with ozone for 20 sessions by rectal insufflations (ozone dose of 10 mg at concentration of 50 mg/L) and local ozone treatment whereby the lesion was covered with a plastic bag and sealed to the leg, which was then put under vacuum in order to eliminate the air inside. The bag was then refilled with ozone at a concentration of 60 mg/L and left for treatment for an hour. After that, the bag was removed and the lesion was covered with ozonized sunflower oil. The efficacy of the treatments was evaluated by comparing the glycaemic index, the area and perimeter of the lesions and biochemical markers of oxidative stress in both groups after 20 days of treatment. From the study, the glucose levels were improved in 84% of the patients treated with ozone and 40% of the patients treated with antibiotics, with significant differences in both groups (p-value <0.05). For the wound lesion comparison, the reduction in lesion area with time was significantly greater in the ozone group (2.66 +/- 0.03 cm^2/days) than in the antibiotics group (1.21 +/- 0.01 cm^2/days). Apart from that, the duration of hospitalization decreased in patients treated with ozone compared with the antibiotic

therapy group (mean length of hospitalization = 13 days in ozone group versus 18 days in antibiotics group). Otherwise, there was equal significant improvement in biochemical markers of oxidative stress for both groups after 20 days of treatment without one being superior to another. [5, level II-2]

5.1.3 Ozone therapy in treatment of chronic hepatitis

Gu X B *et al* conducted a randomized clinical trial in a hospital of infectious disease in China to observe effects of medical ozone therapy on patients with chronic severe hepatitis in terms of plasma renin activity (PRA), angiotensin II (AII), aldosterone (ALD), renal blood flow and renal function of these patients. Eighty five patients with chronic severe hepatitis were randomly divided into ozone therapy group (43 patients) and control group (42 patients). The patients in the ozone therapy were treated with basic treatments plus autohemotherapy ozone system. 100 mm venous blood was drawn from each patient and was mixed with 100 ml (35 µg/ml) medical ozone which was then returned the blood to the patient intravenously, once every other day for 20 days. On the other hand, the patients in the control group were given only basic therapy. From the study, there was marked significant improvement in liver function of the patients treated with ozone therapy as well as increased in prothrombin activity and level of serum albumin in this group when compared with the control group. In ozone therapy group, not only the PRA, AII and ALD level decreased significantly after 20 days of treatment compared with those before treatment, but they were also significantly lower than those of control group after 20 days of treatment. Renal damage was found in 5% of patients (2 patients) in ozone therapy group while in the control group, 21% of patients (9 patients) had renal damage. [6, level II-3]

5.1.4 Ozone therapy in treatment of asthma

Rosales *et al* conducted a clinical trial in Cuba to determine the relationship and behaviour of serum immunoglobulin E (IgE) level, peripheral blood mononuclear cell (PBMC) human leukocyte antigen DR (HLA-DR) expression and erythrocyte glutathione antioxidant pathway in asthma patients treated with different dosage and method of systemic ozone therapy. One hundred and thirteen asthmatic patients aged 15 to 50 years old were enrolled in the study. They were divided into three groups. Two groups were treated by ozone major autohemotherapy (MAHT) and the other one by ozone rectal insufflations (RI). All received three cycles of treatment which comprised 15 sessions per cycle, and time between cycles was 5 or 6 months in all groups. The first group with 35 patients were treated with MAHT using an ozone dose of 4 mg. The second group of 41 patients were treated with MAHT using an ozone dose of 8 mg while the third group with 37 patients were treated rectal insufflations of ozone dose of 10 mg. Serum IgE, HLA-DR expressions in PBMC and biomarkers for antioxidant pathway were measured before and at the end of each cycle. Lung function test and symptoms test were recorded at the beginning and after the third cycle, which was about one year after initiation of ozone treatment. The study demonstrated that IgE and HLA-DR level decreased with the three types of treatments, while increments in reduced glutathione, glutathione peroxidise, glutathione reductase and glutathione S-transferase were achieved with all treatments. Lung function and symptoms test were markedly improved in all the groups. However,

when comparing between the three types of ozone therapy, the best response was obtained in the order: MAHT at 8 mg better than MAHT at 4 mg better than RI at 10 mg. It was concluded that ozone therapy can be seen as a new therapeutic or adjuvant approach for atopic asthma due to its immunomodulation and oxidative stress regulation properties.[7, level II-2]

5.1.5 Ozone therapy in treating dental problems

Azarpazhooh and Limeback from Faculty of Dentistry, University of Toronto, Canda conducted a systematic review on scientific literatures which evaluated the clinical application of ozone in treating dental and root caries. The reviewers retrieved a total of 45 relevant articles on treatment of dental problems using ozone therapy such as usage of ozonated water for irrigation, efficacy of ozone gas in oral and maxillofacial surgery, usage of ozone restorative dentistry and its effect on dental materials. In conclusion, the review demonstrated that while laboratory studies suggest a promising potential of ozone in dentistry, the clinical evidence for application of ozone in dentistry is not extensive, thus there was still a need for the highest level of evidence to justify the routine use of ozone as a treatment modality in dentistry.[8, level I]

5.2. SAFETY

Ozone has been approved by US FDA to be used for food treatment and storage, however, the ozone generators must be assessed for the approval. In January 2010, US FDA seized 77 ozone generators from Applied Ozone Systems of Auburn, California and prohibited the usage of these generators. The agency's inspection revealed significant deviations from the FDA's current good manufacturing practice (GMP) requirements for medical devices, and confirmed that the company has not obtained FDA marketing approval or clearance for the devices to be used as medical ozone generators. [9]

As for usage of ozone therapy in treating medical conditions, few complications have been reported. Ginanneschi *et al* described a case report on a 59 year old lady who presented with chronic low back pain. She was found to have normal neurological examination prior to ozone treatment. The patient was assessed and later judged not to be a candidate for a conventional surgical approach, however, she was then subjected for ozone therapy a month later. She received a percutaneal intradiscal (L5) injection of oxygen-ozone mixture with an ozone concentration of 10 µg/ml. A few minutes after the procedure, she experienced paraesthesia along the anterolateral compartment of the left leg and hyperaesthesia over the dorsum of the left foot, progressed to sciatic pain over the left lower limb. On clinical examination, the left patellar reflex disappeared. Nerve conduction study was performed a month after the procedure showed that there was significant reduction in the amplitude of the sensory evoked response of the left peroneal superficial nerve compared with the contralateral nerve. According to clinical, physical and electrophysiologic findings, she was diagnosed with ventral and dorsal root injury secondary to the ozone therapy intradiscal procedure. [10, level III]

In another article, Gazzeri *et al* reported a rare but fatal complication secondary to oxygen-ozone therapy for the treatment of herniated lumbar disc. A 57 year old man with chronic lumbar pain was initially diagnosed with L4-L5 and L5-S1 lumbar discs herniation based on CT scan findings. He was suffering from excruciating lower and bilateral sciatic radicular pain associated with gait disturbance. He was then treated in another institution with six cycles of lumbar paravertebral injections of oxygen-ozone gas mixture, which resulted in occasional or no relief of the existing symptoms. Fifteen days after the last cycle of ozone therapy, he presented to the author's hospital for further consultation from specialist. Upon admission, apart from the existing low back pain, the patient also complained of decreased sensation over the left S1 distribution and some tenderness in the lumbosacral area. Three days after admission, the patient developed septic shock and requiring tracheal intubation due to respiratory failure. Urgent abdominal and pelvic CT scan revealed abscess collection along the paravertebral muscles with intact spinal canal. Blood cultures isolated *Eschericia coli*. The patient succumbed a few hours after the event with the diagnosis of septic shock secondary to fulminating *E.coli* infection. The most likely route of infection in this patient's condition was related to a lack of sterility during the injection of oxygen-ozone therapy that he received. [11, level III]

6. CONCLUSION

6.1. EFFICACY / EFFECTIVENESS

There were few low level of evidence retrieved on the efficacy or effectiveness of ozone therapy in treatment of certain medical conditions. However, the evidences obtained were limited to some medical problems only and were not sufficient to conclude that ozone therapy is effective in treating other medical conditions.

6.2. SAFETY

Although ozone therapy is claimed to be minimally invasive and complications related to this treatment are rare, there are a lot of other considerations to take into account before deciding that ozone therapy is safe. Life-threatening event and permanent disability such as peripheral nerve root injury has been reported with regards to the procedures in administrating oxygen-ozone therapy. The equipments in preparing the ozone therapy itself, such as ozone generators and the operators must be strictly regulated and monitored.

7. REFERENCES

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8. APPENDIX

8.1 Appendix 1

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)