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CASE REPORT

Neurological Crisis Following Intravenous Ozone Therapy; a Case Report

Chloe Y Y Wong[1], Komal Saxena[1], John Meneer[1], Koshy George[2], Gerben Keijzers[1,3,4]*

1. Department of Emergency Medicine, Gold Coast University Hospital, Southport, Queensland, Australia
2. Department of Neurology, Gold Coast University Hospital, Southport, Queensland, Australia
3. Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Queensland, Australia
4. School of Medicine and Dentistry, Griffith University, Gold Coast, Queensland, Australia

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Abstract: Ozone therapy, often marketed as an immune-boosting alternative treatment, lacks robust evidence of efficacy and poses significant safety risks. Despite claims of therapeutic benefits, Regulatory agencies, such as the U.S. Food and Drug Administration (FDA), warn against its use due to its toxic properties and lack of proven benefits at tolerable exposure levels. This case report highlights severe neurological complications, including ischemic infarcts and persistent cognitive deficits, following intravenous ozone (O3) therapy in a previously healthy patient. A 36-year-old woman presented to the emergency department with chest pain, syncope, and generalized seizure shortly after receiving intravenous ozone therapy. Diagnostic imaging revealed multiple ischemic infarcts in the thalamus and cerebellum, consistent with an embolic event. The patient required intensive care unit (ICU) admission, and despite improved neurological function experienced lasting cognitive impairments necessitating long-term rehabilitation.

Keywords: Embolism, Air; Complementary Therapies; Emergency Service, Hospital; Neurology; Ozone

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1. Introduction

The growing use of alternative therapies, including intravenous ozone therapy, poses significant challenges to healthcare systems, including emergency medicine. Despite claims of therapeutic benefits, ozone (O3) therapy lacks robust evidence supporting its efficacy and raises safety concerns (1). Regulatory agencies, such as the U.S. Food and Drug Administration (FDA), warn against its use due to its toxic properties and lack of proven benefits at tolerable exposure levels (2). Complications of ozone therapy include a range of neurological adverse events such as ischemic infarctions and altered mental status, and have been associated with ozone-induced encephalopathy (OIE). Haggiag et al. reported cases of OIE following intramuscular ozone injections, where patients exhibited focal neurological signs and posterior circulation ischemic lesions (3). Embolic events, particularly in patients with predisposing factors like patent foramen ovale (PFO), have also been highlighted (4).

Respiratory complications result from environmental exposure, including oxidative damage to lung tissue, as ozone is a potent oxidizing agent. High concentrations can disrupt cellular integrity, leading to pulmonary inflammation and impaired gas exchange. A systematic review highlighted that exposure to ozone levels at or below current U.S. Environmental Protection Agency standards can result in significant respiratory effects, including decreased lung function and increased respiratory symptoms (5). Cardiovascular risks, though less common, involve arrythmias and vascular injury, exacerbating pre-existing conditions. Short-term exposure to ozone has been associated with an increased risk of acute myocardial infarction and higher rate of hospital admissions for other cardiovascular diseases (6, 7).

Severe neurological sequelae following intravenous ozone therapy underscore the need for timely diagnostic evaluation and evidence-based management. Emergency clinicians play a critical role in recognizing and reporting unsafe practices, contributing to improved guidelines, patient safety, and public health policies addressing the risks of alternative treatments. This report highlights the importance of clinician vigilance in identifying adverse effects of alternative therapies.

2. Case presentation

A 36-year-old female presented to the emergency department (ED) with sudden-onset severe chest pain, syncope, and a witnessed generalized tonic-clonic seizure lasting three minutes. These symptoms developed minutes after an elective private outpatient intravenous (IV) ozone therapy ses-

***Corresponding Author:** Chloe YY Wong, Department of Emergency Medicine, Gold Coast University Hospital, 1 Hospital Boulevard, Southport, Queensland, Australia. Email: Yianyee.Wong@health.qld.gov.au, Tel: +61424008598 / +61756875274, ORCID: https://orcid.org/0009-0003-0535-8458.

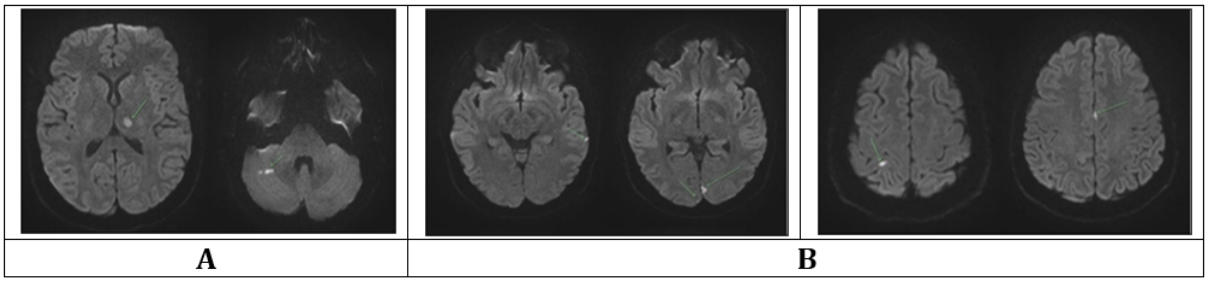

Figure 1: Area of abnormal restricted diffusion, largest in the left hypothalamus and right cerebellum (A); Smaller areas of abnormal restricted diffusion seen in the left temporal lobe, bilateral occipital lobes, right parietal lobe, and frontal lobe (B).

sion involving autotransfusion of 150 mL of ozone-infused venous blood with 500 IU of heparin, with the indication 'to boost her immunity'. She had no significant medical history, with no prior history of seizures or recreational drug use.

On arrival, the patient was agitated, confused, and had a Glasgow Coma Scale (GCS) score of 9 (E4, V1, M4). Vital signs included a blood pressure of 96/79 mmHg, a heart rate of 113 bpm, and a respiratory rate of 25-30 breaths/min. No gross neurological deficits were observed on examination. A 2mg bolus of intravenous (IV) Midazolam was administered to facilitate imaging due to agitation. A non-contrast brain computed tomography (CT) scan and CT angiogram performed 40 minutes after ED arrival showed no acute intracranial pathology, but a magnetic resonance imaging (MRI) 8 hours later following neurology consult revealed multiple ischemic infarcts in the left thalamus and right cerebellum, consistent with an embolic event (Figure 1a and 1b). Bloodwork showed an elevated activated partial thromboplastin time (aPTT) of 148, attributed to the heparin. Her ECG demonstrated sinus tachycardia with a QTc of 420 ms.

The primary suspected diagnosis was cerebral air embolism, with differentials including ozone-induced encephalopathy, acute embolic stroke, and seizure with postictal state. However, the usual stroke pathways (which would consider thrombolysis or clot retrieval) in the ED were not activated considering the likely cause of her presentation at the time. Challenges to diagnosis that followed included the time to subsequent MRI following a normal CT head angiogram due to competing departmental patient load. Following consults with neurology and toxicology, the patient was managed medically with levetiracetam 60mg/kg for seizure prophylaxis, and aspirin 100mg once daily was initiated for thromboembolic prophylaxis. A persistent low GCS of 9 and agitation led to intubation and ICU admission. An echocardiogram revealed a small patent foramen ovale (PFO), suggesting a right to left shunt as the potential route of embolism to the brain. Electroencephalogram (EEG) was normal with no epileptiform discharged or seizures recorded. Hyperbaric oxygen therapy was considered and discussed with the toxicology consulting team but deemed of low utility as a treatment option due to lack of supporting evidence.

She was extubated on day 3, and by day 4, her GCS improved to 15 with normal cranial nerve and limb examinations. However, she continued to exhibit significant cognitive deficits in speech, memory, and comprehension during the first 6 months, requiring rehabilitations through speech and occupational therapy. She was medically restricted from driving for 6 months. At nine months post-presentation, she continues to struggle with her attention span, concentration during cognitive tasks, and frequent migraines.

3. Discussion

Ozone therapy has been used in medical practice since the late 19th century to ameliorate wound infections and reemerged in the mid-20th century as potential treatment for infections and autoimmune diseases (1, 8). Despite its historical use, medical ozone remains controversial due to its toxic properties (2). The U.S. Food and Drug administration (FDA) does not endorse ozone therapy, citing its toxicity and lack of proven therapeutic benefit. Specifically, the FDA warns that ozone must be present in high concentrations to act as a germicide, far beyond what is safe for human exposure (2).

Haggiag et al. reported neurological complications following paraspinal intramuscular ozone therapy, coining the term "ozone-induced encephalopathy" (OIE). These patients exhibited altered mental status, focal neurological signs, and ischemic lesions in the posterior cerebral circulation. Our case resembles these presentations but differs as she did not display any focal neurology and received the ozone therapy intravenously. Two of the three patients reported, like our patient, had pre-existing PFO (3). Our patient has long-term and ongoing cognitive deficits at nine months post presentation contrasting with most cases in literature, documenting recovery with minimal long-term sequelae, which are rarely reported.

Proposed treatments such as hyperbaric oxygen (HBO) for cases of OIE are not well understood. For cerebral air embolism due to other causes such as decompression illness, HBO therapy is most effective when initiated as soon as possible after diagnosis. The recommended timeframe for starting HBO therapy is within 4-6 hours of symptom onset, as early intervention can reduce the size of air emboli and minimize hypoxic brain injury. However, the benefits of HBO therapy may still provide benefits if started within 24 hours (9). While creating guidelines for rare pathologies like OIE or cerebral air embolism may not be feasible, modifying existing

stroke pathways to address rare presentations could improve timely management.

Clinicians have a duty to escalate adverse outcomes from unregulated therapy to appropriate authorities. Familiarity with local pathways for reporting malpractice or unsafe practices is central in upholding patient safety. This case was reported to the Ombudsman, which is the pathway of escalation within Queensland, Australia.

Our multidisciplinary approach to this case provides valuable insights into the challenges of rare but severe complications associated with intravenous ozone therapy. The strengths include a comprehensive diagnostic approach, considering the evidence regarding less commonly utilized treatments like hyperbaric oxygen and the emphasis on reporting unregulated practices. Our reflections and learning points are summarized in the next section. Limitations include delays in diagnosis due to pathway challenges in approaching rare presenting neurological emergencies such as this, the lack of ability to generalize findings in different healthcare settings given the variability of resources and the incomplete long-term follow-up of this patient beyond 9 months to assess full recovery or persistent sequelae.

4. Learning points

• Serious risks of ozone therapy: Significant and lasting neurological deficits can result from IV ozone therapy, though such cases are rarely reported.

• Importance of reporting: Adverse events from unregulated practices lacking robust evidence to support their safety should be reported to relevant authorities to ensure patient safety.

• Understanding alternative therapies: Awareness of common alternative treatments can help clinicians anticipate potential complications and presentations and foster open communication with patients regarding the risks associated with unregulated therapies. We recognize that the growing popularity of alternative therapies, like IV ozone therapy, reflects broader cultural beliefs and societal attitudes about wellness and preventative care.

• Adaptability of protocols: Stroke pathways in the ED may benefit from flexibility to address rare presentations or aetiologies of stroke based on current evidence for the timing of hyperbaric therapy in cerebral embolism

5. Declarations

5.1. Acknowledgments

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5.2. Ethical considerations

The patient provided written informed consent for the publication of this case, including all relevant details and images. The patient has reviewed and approved the final manuscript. This report complies with ethical standards set by the Institutional Ethics Committee of Gold Coast University Hospital and adheres to the principles outlined in the Declaration of Helsinki.

5.3. Funding

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5.4. Conflict(s) of Interest

None of the authors have a conflict of interest.

5.5. Authors Contribution

C.Y.Y.W conceptualized the case narrative and lessons learnt from the case, drafted, edited, and revised the manuscript. K.S contributed to the data collection and drafting of the manuscript. J.M and K.G provided case insight, suggestions for revision and intellectual oversight. G.K. supervised the overall project, provided suggestions for revision and intellectual oversight, and contributed to final manuscript approval. All authors reviewed and approved the final manuscript.

5.6. Using artificial intelligence chatbots

AI-assisted chatbots were utilized solely to aid in rephrasing sentences and editing the manuscript to meet word count requirements. The authors ensured that all intellectual content, including the analysis, interpretation, and conclusions, was independently generated. The final manuscript was critically reviewed and revised by the authors to maintain accuracy, originality, and adherence to ethical standards.

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