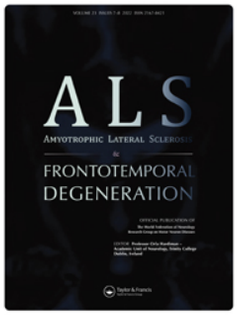

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iafd20

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To cite this article: Yuyao Sun, Paul Barkhaus, Benjamin Barnes, Morgan Beauchamp, Michael Benatar, Tulio Bertorini, Mark Bromberg, Gregory T. Carter, Jesse Crayle, Merit Cudkowicz, Mazen Dimachkie, Eva L. Feldman, Timothy Fullam, Terry Heiman-Patterson, Sartaj Jhooty, Isaac Lund, Christopher Mcdermott, Gary Pattee, Kaitlyn Pierce, Dylan Ratner, Paul Wicks & Richard Bedlack (2022): ALSUntangled #68: ozone therapy, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, DOI: 10.1080/21678421.2022.2145904

To link to this article: https://doi.org/10.1080/21678421.2022.2145904

Published online: 18 Nov 2022.

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2022; 0: 1–5

REPORT

ALSUntangled #68: ozone therapy

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Abstract

ALSUntangled reviews alternative and off-label treatments for people living with amyotrophic lateral sclerosis (PALS). Here we review ozone therapy. Ozone therapy has possible mechanisms for slowing ALS progression based on its anti-oxidant, anti-inflammatory, and mitochondrial effects. A non-peer-reviewed report suggests that ozone treatment may slow progression in a mTDP-43 mouse model of ALS. One verified "ALS reversal" occurred on a cocktail of alternative treatments including ozone. There are no ALS trials using ozone to treat PALS. There can be potentially serious side effects associated with ozone therapy, depending on the dose. Based on the above information, we support an investigation of ozone therapy in ALS cell or animal models but cannot yet recommend it as a treatment in PALS.

Keywords: *ALS, ozone therapy, oxidative stress, neurodegeneration, alternative therapy*

Introduction

ALSUntangled reviews alternative and off-label treatments on behalf of people living with amyotrophic lateral sclerosis (PALS). Here we review ozone therapy, for which we have had 556 requests (1).

Overview

Ozone is a gaseous molecule with a pungent smell. It is generated when diatomic oxygen (O_2) is exposed to an electrical field or ultraviolet light, which causes a portion of the diatomic oxygen molecules to split into individual oxygen atoms.

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(Received 10 October 2022; accepted 6 November 2022)

ISSN 2167-8421 print/ISSN 2167-9223 online
DOI: 10.1080/21678421.2022.2145904

These free oxygen atoms combine with diatomic oxygen molecules to form ozone (O_3). Ozone is an unstable molecule due to the weak bonds holding the third oxygen atom, rendering it a powerful oxidizing agent which is used to disinfect and sanitize water and hard surfaces (2).

There are currently no FDA-approved medical indications for ozone therapy. In fact, the FDA has advised against the medical use of ozone (3) and reportedly even shut down clinic advertisements touting ozone as a medical treatment (4). Nonetheless, different experimental and/or off-label methods have been and still are being employed to administer ozone to the human body, including local ozone injection as well as systemic administration *via* infusion of ozonized saline solution, rectal ozone insufflation, or using an ozone sauna, wherein a body part is bagged and exposed to ozone gas. Ozone autohemotherapy involves collecting venous blood from a patient, blending it with an oxygen/ozone mixture and then reinfusing it via the same vein (5). This review focuses on systemic ozone application (e.g. infusion, rectal insufflation, sauna, or autohemotherapy). Ozone therapy is different from hyperbaric oxygen therapy, which was reviewed separately in a previous ALSUntangled paper (6). Ozone is currently being offered as an ALS treatment on multiple websites (e.g. 7,8).

Mechanisms

Oxidative stress, neuroinflammation, and mitochondrial dysfunction are believed to play roles in ALS pathophysiology. There is some evidence that ozone therapy might modify these processes.

Antioxidant effects

Oxidative stress is an imbalance between production of damaging reactive oxygen species and their elimination by antioxidants. Oxidative stress can lead to protein misfolding and insoluble inclusions, which are associated with ALS (9,10). As a potent oxidizer, ozone can transiently worsen oxidative stress (11). However, this worsening in turn can activate the nuclear factor-related erythroid factor 2 (Nrf2) pathway, ultimately leading to the transcription of antioxidant response elements (AREs, 11,12). In small study of patients with multiple sclerosis, ozone therapy (20 ug/ml delivered rectally three times per week) was associated with increased markers of antioxidant activity and decreased markers of oxidative damage to lipids and proteins (12).

Anti-inflammatory effects

Neuroinflammation, characterized by microglial and astrocyte activation, as well as T lymphocyte infiltration, is associated with the progression of ALS (13). In rats, inhaled ozone can promote neuroinflammation (14). However, ozone delivered *via* injection to rats reportedly reduces pro-inflammatory cytokines by blocking the action of nuclear factor-kB (NF-kB) and promoting the Nrf2 pathway (15). In small numbers of patients with multiple sclerosis, ozone delivered rectally was associated with increased Nrf2 phosphorylation and decreased pro-inflammatory cytokine expression (12); ozone delivered via autohemotherapy was associated with increased expression of anti-inflammatory Treg cells (16).

Mitochondrial effects

Mitochondria produce the energy required for most of the cellular processes. Mitochondrial dysfunction is proposed to play a role in ALS progression (17). In animal models, ozone was shown to reduce mitochondrial damage in rat models of ischemia-reperfusion heart injury (18) and noise-induced hearing loss (19). It is not clear how similar the mitochondrial dysfunction seen in these animal models is to that seen in PALS.

Since ozone therapy is associated with reduced markers of oxidative stress and inflammation in small studies of humans with multiple sclerosis (12,16), ALSUntangled assigns a TOE "Mechanism" grade of A (Table 1).

Pre-clinical models

Ozone therapy has been studied in mSOD1 and mTDP43 mouse models of ALS. In mSOD1 mice, intraperitoneal injections of ozone for five consecutive days starting at symptom onset were associated with reduced markers of neuroinflammation and increased motor neuron counts in

Table 1. Table of evidence for ozone therapy.

	Grade	Explanation
Mechanism	A	Peer-reviewed publications show that ozone treatment is associated with decreased markers of oxidative stress and inflammation in patients with multiple sclerosis.
Pre-clinical	D	Non-peer- reviewed reports suggest that ozone therapy was associated with improved motor performance and prolonged survival in a mTDP43 mouse model of ALS.
Cases	C	One unpublished case report with validated diagnosis and improvements (however, ozone therapy was part of many treatments used)
Trials	U	Ozone therapy has not been studied in ALS trials
Risks	D	More than 0% but less than 5% of exposed patients experienced death or hospitalizations

some but not all areas of the brain (20). However, these injections had no effect on motor performance or survival (21). In 42-d-old mTDP43 mice, aerosolized ozone treatment for 4 h a day for 15 d was associated with improved motor performance and lengthened survival compared to animals treated with filtered air (22). Ozone therapy was also associated with several metabolic changes related to glucose regulation and insulin resistance in this mouse model (21,22). These mTDP43 studies were flawed by very small sample sizes and, as of this writing; they have not been published in peer-reviewed journals. Therefore, ALSUntangled assigns a TOE "Pre-Clinical Models" grade of D (Table 1).

Data in PALS

Cases

In the online community PatientsLikeMe, three members report receiving ozone therapy as a treatment for ALS. Two PALS completed treatment evaluations and both rated effectiveness as "slight" (23). We did not have records to verify the diagnoses nor the perceived benefits of ozone in these patients. Google search identified the website of Mr. Kim Cherry, who reports that his ALS reversed on a regimen of ozone treatments, in addition to hyperbaric oxygen therapy, various vitamins and supplements, detox, special diets, and attitude changes (24). His ALS diagnosis and his improvements have been independently verified by our group (25,26). Mr. Cherry's disease onset was mid-2010 and slowly progressed to his nadir in January 2012, at which time his ALSFRS-R score was 31. His ALSFRS-R score in August 2015 had improved to 47 (6). Associations like this do not prove causality.

Based upon these cases, we assign a TOE "Cases" grade of C (Table 1).

Trials

Ozone therapy has not been evaluated in an ALS clinical trial. As such, ALSUntangled assigns a TOE "Trials" grade of U (Table 1). Of potential interest, ozone therapy has been trialed in several other neurological conditions (reviewed in reference 11), including ischemic stroke (27), fibromyalgia (28), and multiple sclerosis (12,16,29). None of these trials produced results compelling enough to warrant FDA approval.

Dosing, risks, and costs

There is an online protocol for using ozone as an ALS treatment (30). However, it is not clear to us that this protocol has ever been studied so we do not know what benefits and/or side effects it might produce. Ozone therapy should never be administered by inhalation because of the risk of life-threatening pulmonary edema (3,31). The dose-effect relationship of ozone therapy delivered in other ways (autohemotherapy, ozonized saline solution, insufflation, etc.) is hormetic (32). This means that low doses can be anti-oxidant and anti-inflammatory, but higher doses can be toxic. According to the Madrid Declaration of ozone therapy (31), an online document written by scientists, dentists, pharmacists, and physicians with interests and experience in administering ozone, the potential therapeutic dosage for systemic treatment ranges between 5.0 and 6.0 mg per treatment, and concentrations of 10–50 μg/Nml are safe. Non-serious adverse events may occur at these doses, related to the administration technique. For example, side effects of autohemotherapy can include itching on lips and tongue, nausea, bad taste in the mouth, and dyspnea. Rectal insufflation can cause bloating and constipation. Higher doses of ozone may cause serious side effects, including stroke, myocardial infarction, and death (31). Given all this, if ozone therapy is at all useful in the treatment of ALS, the therapeutic dosing range is likely quite narrow. Because of the small risk of serious side effects including death, we assign a TOE "Risks" grade of D.

The cost of ozone therapy is variable. Clinics administering ozone intravenously charge anywhere from $100 to over $1000 per session (33). In our opinion, it is unlikely that insurance would cover this. In terms of devices currently on the market that can generate ozone by design or as a byproduct, FDA has regarded them as adulterated and/or misbranded if used or intended for use in any medical condition for which there is no proof of safety and effectiveness (3).

Conclusion

Ozone therapy has possible mechanisms for treating ALS. A preclinical study in very small numbers of mTDP43 mice (which has yet to be peer-reviewed) suggested benefits on motor function and survival (21,22); however, these benefits were not seen in mSOD1 mice (20). One verified "ALS reversal" occurred on a cocktail of alternative therapies including ozone (24); an association such as this does not prove causality. There have been no trials of ozone therapy in PALS. There may be potentially serious side effects associated with ozone therapy, depending on the dose (31). Based on all this, we support further investigation of ozone therapy in ALS cell or animal models, but we cannot yet recommend it as an ALS treatment.

Declaration of interest

Richard Bedlack has research support from ALSA, Orion, MediciNova, and the Healey Center, and consulting support from AB Science, Alexion, ALSA, Amylyx, Biogen, Black Swan, Brainstorm Cell, Corcept, Cytokinetics, GenieUs, Guidepoint, ITF Pharma, Mallinkrodt, New Biotic, Orphazyme, PTC Therapeutics, Shinkei, and Woolsey Pharma.

Funding

ALSUntangled is sponsored by the Amyotrophic Lateral Sclerosis Association (ALS) Association.

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References

1. Future Reviews [Internet]. ALS untangledTM. [cited 2022 Sep 17]. Available at: https://www.alsuntangled.com/future-reviews/
2. Ozone [Internet]. Wikipedia. [cited 2022 Oct 8]. Available at: https://en.wikipedia.org/wiki/Ozone
3. CFR - Code of federal regulations title 21 [Internet]. [cited 2022 Mar 5]. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=801.415
4. Court prohibits Dallas wellness center touting ozone therapy as covid-19 treatment [Internet]. FDA.gov [cited 2022 October 10]. Available at: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/press-releases/court-prohibits-dallas-wellness-center-touting-ozone-therapy-covid-19-treatment
5. Ozone Therapy [Internet]. Wikipedia. [cited 2022 Oct 8]. Available at: https://en.wikipedia.org/wiki/Ozone_therapy
6. . ALSUntangled Group. ALSUntangled No. 35: hyperbaric oxygen therapy. Amyotroph Lateral Scler Front Degener. 2016;17:622–4.
7. Dementia, ALS and Alzheimers-Better Brains with Ozone [Internet]. SecondNatureCare. [Cited 2022 October 10]. Available at: https://www.secondnaturecare.com/blog/dementia-als-and-alzheimers-better-brains-with-ozone
8. ALS Therapy [Internet]. Dr. Grodski. [Cited 2022 October 10]. Available at: https://drgrodski.com/conditions/als_therapy_vancouver/
9. Zuo X, Zhou J, Li Y, Wu K, Chen Z, Luo Z, et al. TDP-43 aggregation induced by oxidative stress causes global mitochondrial imbalance in ALS. Nat Struct Mol Biol. 2021;28:132–42.
10. Arias-Salvatierra D, Silbergeld EK, Acosta-Saavedra LC, Calderon-Aranda ES. Role of nitric oxide produced by iNOS through NF-κB pathway in migration of cerebellar granule neurons induced by Lipopolysaccharide. Cell Signal. 2011;23:425–35.
11. Masan J, Sramka M, Rabarova D. The possibilities of using the effects of ozone therapy in neurology. Neuroendocrinology 2021;42:13–21.
12. Delgado-Roche L, Riera-Romo M, Mesta F, Hernández-Matos Y, Barrios JM, Martínez-Sánchez G, et al. Medical ozone promotes Nrf2 phosphorylation reducing oxidative stress and pro-inflammatory cytokines in multiple sclerosis patients. Eur J Pharmacol. 2017;811:148–54.
13. Liu J, Wang F. Role of neuroinflammation in amyotrophic lateral sclerosis: cellular mechanisms and therapeutic implications. Front Immunol. 2017;8:1005.
14. González-Guevara E, Martínez-Lazcano JC, Custodio V, Hernández-Cerón M, Rubio C, Paz C. Exposure to ozone induces a systemic inflammatory response: possible source of the neurological alterations induced by this gas. Inhal Toxicol. 2014;26:485–91.
15. Vaillant JD, Fraga A, Díaz MT, Mallok A, Viebahn-Hänsler R, Fahmy Z, et al. Ozone oxidative postconditioning ameliorates joint damage and decreases pro-inflammatory cytokine levels and oxidative stress in PG/PS-induced arthritis in rats. Eur J Pharmacol. 2013;714:318–24.
16. Tahmasebi S, Qasim MT, Krivenkova MV, Zekiy AO, Thangavelu L, Aravindhan S, et al. The effects of oxygen-ozone therapy on regulatory T-cell responses in multiple sclerosis. Cell Biol Int. 2021;45:1498–509.
17. Dafinca R, Barbagallo P, Talbot K. The role of mitochondrial dysfunction and ER stress in TDP-43 and C9ORF72 ALS. Front Cell Neurosci. 2021; 15:653688. Available at: 10.3389/fncel.2021.653688
18. Meng W, Xu Y, Li D, Zhu E, Deng L, Liu Z, et al. Ozone protects rat heart against ischemia-reperfusion injury: a role for oxidative preconditioning in attenuating mitochondrial injury. Biomed Pharmacother. 2017;88:1090–7.
19. Nasezadeh P, Shahi F, Fridoni M, Seydi E, Izadi M, Salimi A. Moderate O3/O2 therapy enhances enzymatic and non-enzymatic antioxidant in brain and cochlear that protects noise-induced hearing loss. Free Radic Res. 2017;51:828–37.
20. Bette M, Cors E, Kresse C, Schutz B. Therapeutic treatment of superoxide dismutase 1 (G93A) amyotrophic lateral sclerosis model mice with medical ozone decelerates trigeminal motor neuron degeneration, attenuates microglial proliferation, and preserves monocyte levels in mesenteric lymph nodes. Ijms. 2022;23:3403.
21. Rodriguez A, Ferrer-Donato A, Cabrera-Pinto M, Sesena S, Fernandez P, Aranda A, et al. Effect of ozone exposure on amyotrophic lateral sclerosis pathology using a mouse model of TDP-43 proteinopathy. bioRxiv 2021;02.12.430915.
22. Rodriguez-Sanchez S, Valiente N, Sesena S, Cabrera-Pinto M, Rodriguez A, Aranda A, et al. Could ozone become a complimentary therapeutic approach to improve metabolic and endocrine response of ALS patients? Scientific Reports 2022; in review.
23. PatientsLikeMe [Internet]. PatientsLikeMe. [cited 2022 Aug 1]. Available at: https://www.patientslikeme.com/treatment_evaluations/browse?id=ozone-therapy
24. ALS WINNERS - THE ROAD TO RECOVERY [Internet]. ALS winners - the road to recovery. [cited 2022 Mar 12]. Available at: https://www.alswinners.com/
25. ALS Reversals [Internet]. ALS reversals. [cited 2022 Mar 6]. Available at: https://alsreversals.com/
26. Harrison D, Mehta P, van Es MA, Stommel E, Drory VE, Nefussy B, et al. "ALS reversals": demographics, disease characteristics, treatments, and co-morbidities. Amyotroph Lateral Scler Frontotemporal Degener. 2018;19:495–9.
27. Qiu J, Chen HS. Efficacy and safety of ozone therapy administered by autologous blood transfusion for acute ischemic stroke: study protocol for a multi-center open-label large-sample parallel randomized controlled trial. Asia Pac Clin Transl Nerv Syst Dis. 2016;1:0–37.

28. Tirelli U, Cirrito C, Pavanello M, Piasentin C, Lleshi A, Taibi R. Ozone therapy in 65 patients with fibromyalgia: an effective therapy. Eur Rev Med Pharmacol Sci. 2019;23:1786–8.
29. Molinari F, Simonetti V, Franzini M, Pandolfi S, Vaiano F, Valdenassi L, et al. Ozone autohemotherapy induces long-term cerebral metabolic changes in multiple sclerosis patients. Int J Immunopathol Pharmacol. 2014;27:379–89.
30. Degenerative diseases protocol [Internet]. AEPromo.org. [Cited 2022 October 10]. Available at: https://www.aepromo.org/asociados/files/protocolos/jun2016/en/23-Degenerative-diseases-protocol.pdf
31. Madrid declaration on ozone therapy [Internet]. [cited 2022 Sep 15]. Available at: https://edisciplinas.usp.br/pluginfile.php/5803895/mod_folder/content/0/2020%20Declaración-de-Madrid_EN-7.pdf
32. Bocci VA, Zanardi I, Travagli V. Ozone acting on human blood yields a hormetic dose-response relationship. J Transl Med. 2011;9:66.
33. How much does ozone therapy cost? [Internet]. Vitalforceal. [cited 2022 October 10]. Available at: https://vitalforceal.com/uncategorized/how-much-does-iv-ozone-therapy-cost/