Gaseous and Aqueous Ozone Therapy for Treatment of Mucositis Secondary to Chemotherapy/Radiotherapy: A Case Report

By JAMES E. SHENBERG, DDS, AND CHARLES BLUM

As the field of dentistry enters the 21st century, advances in care of the teeth and oral cavity include applications that use ozone as a therapeutic agent (1,2). Studies have examined ozone's effect on dental caries (3) and primary root caries (4,5), orthodontic applications (6), and as an antimicrobial, antiviral, and antifungal agent in the oral cavity (7). This case report will present a novel, low-risk, effective therapeutic option incorporating gaseous and aqueous ozone for treating mucositis secondary to chemotherapy and radiotherapy.

Mucositis, a painful inflammation and ulceration of the mucous membranes lining the digestive tract, is one of the most common adverse reactions to radiation therapy for head and neck cancers and chemotherapy (8). The exact pathophysiology of its development is unknown, but it is thought to be divided into direct and indirect mucositis. Chemotherapy and/or radiation therapy interfere with the normal turnover of epithelial cells, leading to mucosal injury; subsequently, mucositis can also occur from indirect invasion of gram-negative bacteria and fungal species because most of the cancer drugs cause changes in blood counts (9).

Frequently, mucositis adversely affects quality of life, particularly with pain and interference with oral function. In patients who are immunocompromised or debilitated, this complication can become life-threatening (9). Mucositis may limit the patient's ability to tolerate chemotherapy or radiation therapy, and nutritional status is compromised. Because mucositis may drastically affect cancer treatment as well as a patient's quality of life, patients with oral mucositis are at a higher risk of unplanned breaks in radiation therapy and hospitalization (10).

The incidence and severity of mucositis varies among patients and among treatments. Mucositis occurs in an estimated 40% of patients treated with standard chemotherapy, and it not only increases with the number of treatment cycles, it also increases depending on the number of previous episodes. Similarly, patients who undergo bone marrow transplantation and receive high doses of chemotherapy have a 76% chance of developing mucositis. Patients receiving radiation, particularly for head and neck cancers, have a 30% to 60% chance of developing mucositis (8).

Oral and gastrointestinal mucositis can affect up to 100% of patients undergoing high-dose chemotherapy and hematopoietic stem cell transplantation, 80% of patients with malignancies of the head and neck receiving radiotherapy, and a wide range of patients receiving chemotherapy (11). Since infection may have an important role in the pathophysiology of oral mucositis, several antimicrobial agents have been investigated for their efficacy in preventing and treating this condition Newer drugs, such as the topical antimicrobial peptide iseganan HCl, initially showed promise in reducing mucositis and its related oral pain, but the results of a phase 3 trial were disappointing, and the line of inquiry was abandoned (12).

A comprehensive review of 89 usable studies relating to the treatment of chemotherapy- and radiotherapy-induced mucositis assessed data on 7523 randomized patients. Interventions evaluated were acyclovir, allopurinol mouthrinse, aloe vera, antibiotic pastille or paste, benzydamine, beta carotene, calcium phosphate, camomile, chlorhexidine, etoposide, folinic acid,

glutamine, granulocyte/macrophage colony-stimulating factor (GM-CSF), histamine gel, honey, hydrolytic enzymes, ice chips, iseganan, keratinocyte GF, misonidazole, pilocarpine, pentoxifylline, povidone, prednisone, propantheline anticholinergic, prostaglandin, sucralfate, systemic antibiotic clarithromycin, traumeel, and zinc sulphate. Treatment with Chinese medicine (herbs) was also evaluated. Of the 33 interventions included in trials, 12 showed some evidence of a benefit (albeit sometimes weak) for either preventing or reducing the severity of mucositis (13).

Another study of cancer-related mucositis concluded there is weak and unreliable evidence for the common therapeutic interventions such as allopurinol mouthwash, granulocyte macrophage-colony stimulating factor, immunoglobulin, or human placental extract to improve or eradicate mucositis. The authors stated, "There is no evidence that patient-controlled analgesia (PCA) is better than continuous infusion method for controlling pain; however, less opiate was used per hour, and duration of pain was shorter, for PCA" (14).

Currently, no single intervention completely prevents or treats oral mucositis (15-20). Treatment of established mucositis remains a challenge and focuses on a palliative management approach. Topical anesthetics, mixtures (also called cocktails), and mucosal coating agents have been used, despite the lack of experimental evidence supporting their efficacy (21). Physical approaches like cryotherapy, low-energy helium-neon laser (22), or modern radiotherapy techniques that exclude the oral cavity from radiation fields are effective in preventing mucositis. Nevertheless, a consensus protocol of prophylaxis and treatment of oral mucositis has not yet been obtained (23). While the evidence base for ozone therapy for secondary effects of chemotherapy or radiotherapy is currently being investigated, studies that used gaseous and aqueous ozone application alone have not been adequately represented in the literature (24).

Case Study

Patient Presentation: A 69-year-old woman was treated for adenosquamous carcinoma of the left parotid gland and developed mucositis while receiving the Anderson regimen for the head and neck. The patient had no prior history of mucositis, and at three weeks after beginning chemotherapy and radiotherapy, she developed mucositis, which progressed from her mouth to her lips and tongue. Ozone therapy (HealOzone therapy [25,26] and TherOzone protocols [20,21]) were applied to the ulcerations generally two to four times per week during chemotherapy and radiotherapy interventions.

Methods: The treatment protocol involved application of ozone in both aqueous and gaseous forms. Ozone in a gaseous form was provided at 40 to 60 seconds per lesion; the aqueous solution of ozone bubbles and water is 2 to 4 ppm. The gaseous ozone concentration is 2100 ppm, with a flow rate of ozone/air mix at 5m/s; the patient gargled with the aqueous solution for 1 to 2 minutes. She received treatment with both forms of ozone daily until the breakout resolved.

Results: Following the initial three weeks of chemotherapy and radiotherapy until completion, without gaseous and aqueous ozone therapy, the patient's visual analogue scales were a 6/10 and she need continuous pain medication. She was able to consume only soft foods or liquids, and her pain levels rose to a 7 to 8/10. With ozone therapy her pain levels reduced to a 2 to 3/10 without medication and she could eat solid food. Initially the patient was treated daily for 2 to 3 days, at which time the mucositis subsided for approximately 2 to 3 days, when ozone treatment was resumed.

The profound reduction or elimination of pain medication during the regular treatment phase, along with her ability to eat solid food, was significant. When intervals between therapies increased, her symptoms worsened; and when she received more regular care, her symptoms subsided. Because it was difficult for her to travel to the office for treatment, the effect of treatment versus no treatment was clearly defined.

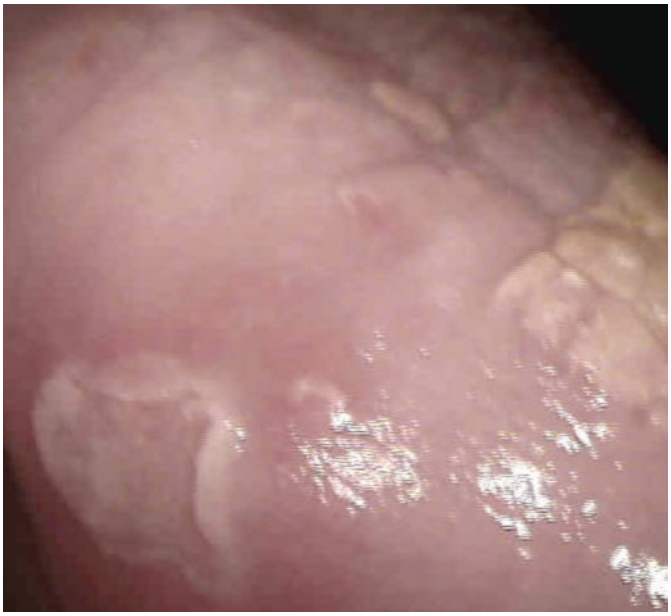
Figure 1 illustrates a typical patient presentation before ozone therapy. Figure 2 shows a patient after three days and three treatments, and Figure 3 after seven days and four total treatments.

Discussion

Her dentist found it most effective to apply both gaseous and aqueous ozone to mucositis ulcerations daily. Ozone purportedly acts discriminately as a result of its concentration of 4494 mg/m3, which affects bacteria, viruses, and infected human cells only because, unlike healthy human cells, infected cells have no layer of oxidation-resistant enzymes. There is increasing interest in ozone in oral health care, and there is growing evidence that it can be a useful therapeutic agent (1,29-31).

Patients with mucositis may need help depending on lesion's size and presentation and the delivery method used. For gaseous ozone, the small diameter of the cup may call for overlap of the treatment site. Lesions that are farther down the throat will require gargling with the aqueous ozonated water. Generally 40 to 60 seconds per site is sufficient for the general treatment protocol. However, in severe cases or if the patient is capable, an application twice a day seems to facilitate a more rapid recovery.

Figure 1. First day, patient presentation before gaseous and aqueous ozone treatments.



Since studies have found a relationship between mucositis and possible secondary infections associated with chemotherapy and radiotherapy, ozone application in gaseous or aqueous form can be a low-risk, high-benefit alternative to antibiotics, antifungals, and antiviral medications. Gaseous and aqueous ozone is effective in destroying bacteria, fungi, viruses, molds, and yeasts (24-31). Purportedly, in mucositis, such sources of an infection must be destroyed before the infected area can heal. Apparently ozone attacks only inflamed cells that have lost their enzyme layer, allowing a localized attack on the infected cells. Studies have found that ozone application promotes faster growth of healthy tissue than do other wound disinfectants (32,33). Ozone also helps relieve pain associated with mucositis, which allows the patient to return to more normal nutrition and activities of daily living.

Mucositis-type ulcerations in the oral cavity, such as an aphthous ulceration, have also been successfully treated with gaseous ozone (34). In another study with aqueous ozone, Cardoso et al found that "in gastric ulcer models induced by stress, there was a significant reduction in the incidence of ulcers types I, II, and III" (35).

Figure 2. Three days after initial presentation and three treatments.

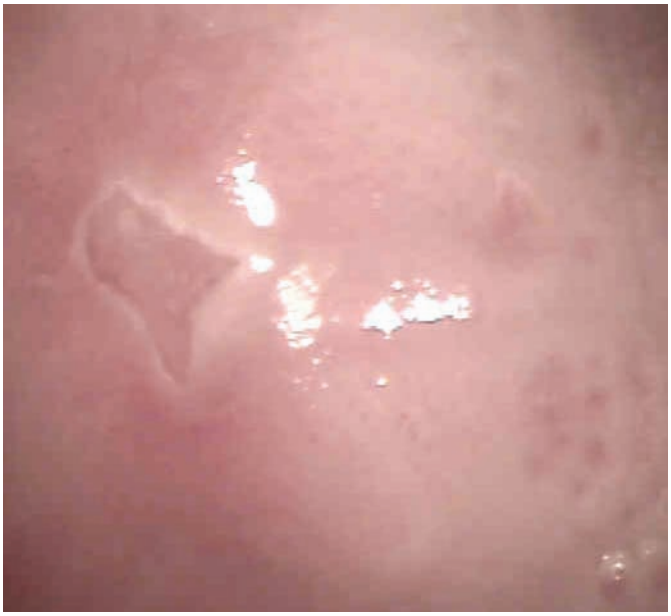
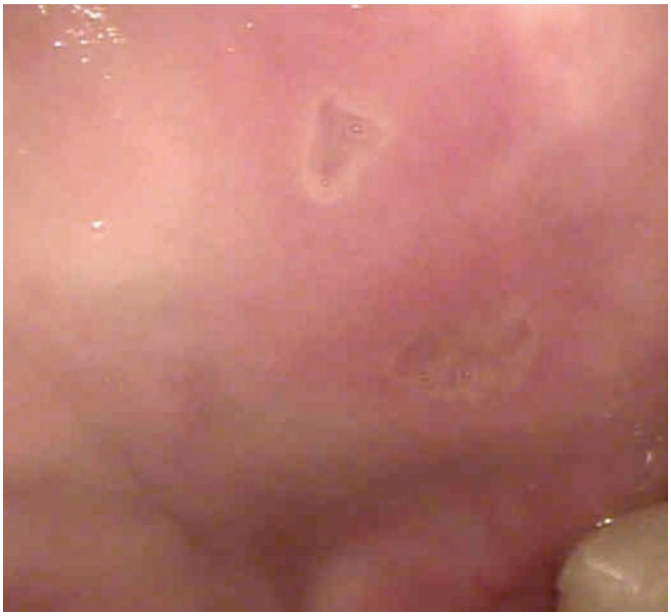


Figure 3. Seven days after initial presentation and four total treatments.



Therapeutic ozone may have some contraindication or cautions when used in a clinical setting. Ozone is toxic at certain levels, particularly to the eyes, mucous membranes, and respiratory tract. So far aqueous ozone has not shown

any significant levels of toxicity. Therefore, health care practitioners must exercise some degree of caution when applying gaseous ozone in particular, and to some degree aqueous ozone, in patients with mucositis.

Some types of gaseous ozone devices may release concentrated ozone into the oral cavity, which may have negative secondary effects on the respiratory tract and adjacent mucous membranes. One device transmits ozone by a suction device that deploys ozone only when there is negative pressure. If suction is compromised, ozone deployment is immediately stopped. Such devices localize ozone delivery to just the target area, protecting adjacent tissues within the respiratory tract from exposure to gaseous ozone.

Some aqueous ozone systems produce solutions up to 4.0 ppm, which can be sustained for 30 minutes (because of the instability of the ozone molecule) in room-temperature water. There is slight outgassing from the aqueous solution, but the levels of ozone are so low that no toxic effect has been observed. The ozone in aqueous solution is not toxic for rinsing the mouth or other body cavities, nor is there any negative gastrointestinal effect from ingestion.

While no studies support the contention that repeated high levels of aqueous ozone may affect normal, ambient bacterial flora, high levels of aqueous ozone should not be used for long-term repeated use without specific indications. Therefore, when used without specific safeguards, ozone may be toxic and unsafe and could affect the normal (helpful) bacteria/flora in the oral cavity and the gastrointestinal system.

As new therapeutic modalities are used to treat a serious condition such as mucositis, it is essential to evaluate the risk of an intervention, particularly in someone compromised by cancer, chemotherapy, and radiation therapy. Since the multitude of therapeutic interventions for mucositis are questionable and offer some risk, ozone therapy may offer a viable alternative to current therapeutic options.

Conclusion

Since mucositis is a common side effect of chemotherapy and radiotherapy, finding a low-risk, effective method of treatment is important. Mucositis has a significant effect on quality of life and nutritional health, particularly in patients with cancer, whose immune systems are compromised by chemotherapy and radiotherapy. This case report presents a patient receiving chemotherapy and radiotherapy whose mucositis responded positively to gaseous and aqueous ozone therapy, enabling her to eat normally, eliminate pain medication, and improve her quality of life during oncological therapeutic interventions. It is difficult to extrapolate for large patient cohorts from a single case study, so further research into the therapeutic use of gaseous and aqueous ozone is indicated. This research should help determine whether a similar response to mucositis with ozone interventions can be generalized to a larger population of patients who present with mucositis secondary to chemotherapy and radiotherapy. ■

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