



RESEARCH PAPER

# Pitfalls of Intralesional Ozone Injection in Diabetic Foot Ulcers: A Case Study



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## KEYWORDS:

Wound healing;  
Adjunctive treatments;  
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Adverse event

**Abstract** Although the history of ozone therapy dates back to the 19th century, its use has shown a rapid growth of interest in recent decades. Intralesional ozone injection is seldom performed and its safety has not yet been reliably assessed for the treatment of diabetic foot wounds. Herein, we describe a diabetic patient who developed severe foot necrosis and infection after receiving intralesional ozone injections for a non-healing wound.

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## Introduction

Although the history of ozone therapy dates back to the 19th century, its use has shown a rapid growth of interest in recent decades. Some of the current ozone application methods include autohemotherapy, intramuscular, intra-articular, and paravertebral injections, rectal or vaginal insufflations, and topical ozone. Intralesional ozone injection is seldom performed and its safety has not yet been reliably assessed for the treatment of chronic wounds. Ozone therapy is generally regarded as “very safe with virtually no adverse events,”<sup>1</sup> yet it may be toxic if not used in therapeutic doses.<sup>2</sup> Herein, we describe a patient who

developed severe foot infection and necrosis after receiving intralesional ozone injections for a non-healing ulcer.

## Case Report

A 67-year-old female patient with type-2 DM for 22 years presented with wet gangrene of the left foot. The patient had her second and third toe amputated nine years ago and had remained ulcer-free since. Four weeks ago, she developed an ulcer with surrounding erythema and swelling on the fourth toe of her left foot. After an unsuccessful course of topical antibiotherapy for almost two weeks, she sought wound care at an ozone therapy center where a physical medicine and rehabilitation specialist administered ozone treatments. Her medical records at the ozone therapy center revealed an ulcer with 1 × 2 cm size on the fourth toe at her admission. Although she received topical ozone

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therapy and major autohemotherapy for seven days, the results were far from satisfactory. Thereafter, the physician decided to perform an intralesional injection of ozone. The procedure was very painful. Following the second daily injection, the pain grew worse and the patient noticed redness around the wound, which spread to the plantar surface of the foot the following day. Within two days, the forefoot developed a large necrotic, edematous wound. The patient was advised by her ozone therapist to admit to a specialized wound care center.

Upon physical examination, she had skin necrosis ( $7 \times 10$  cm) on the plantar surface of the foot. Admission inflammatory markers were elevated: WBC:  $12,900/\mu\text{l}$ , C-reactive protein (CRP):  $94.5$  mg/L, erythrocyte sedimentation rate (ESR):  $67$  mm/h. Her glycemic control was poor: Hemoglobin A1c:  $11\%$  and fasting blood glucose:  $299$  mg/dl. The patient was hospitalized and evaluated by an experienced diabetic foot team. The necrosis was debrided (Fig. 1). A comprehensive treatment scheme comprising surgical debridement of necrotic tissues, culture-driven intravenous antibiotic regimen, aggressive glycemic control and daily wound dressings were commenced. She also received hyperbaric oxygen therapy during this time. Following eight weeks of treatment, the wound base grew good granulation tissue and the patient was referred to the plastic surgery department for reconstructive surgery (Fig. 2). The wound was covered with a split thickness skin graft harvested from the anterior thigh region of the same lower limb following intensive surgical debridement, and the fourth toe was amputated. The limb was immobilized and the first dressing change was carried out on the second postoperative day. Serial daily wound dressing changes were performed over ten days, but the skin grafting was unsuccessful. As a second surgical intervention, great toe amputation and wound repair with fillet flap was planned. Therefore, instead of amputating the whole toe, the phalanges of the great toe were removed, and its skin flap was used to cover the plantar defect area. Complete



**Figure 2** She was transferred to plastic surgery department for reconstructive surgery.

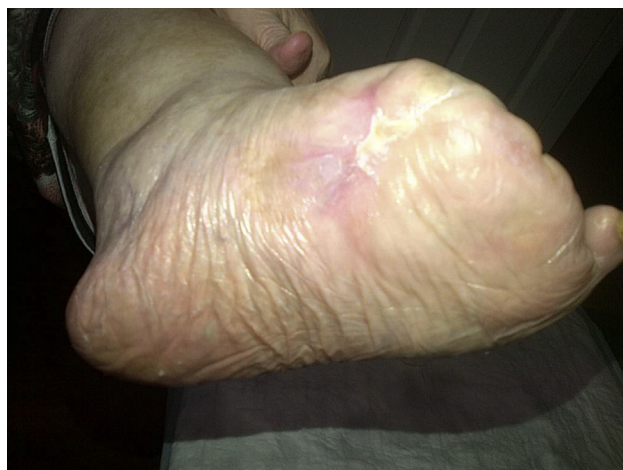
healing was achieved after this surgery. The patient's picture, which was taken at the two-month follow-up meeting, is presented in Fig. 3.

## Discussion

Topical ozone therapy is rarely used to treat chronic wounds. Martinez-Sanchez et al conducted a randomized controlled clinical trial on 101 patients assigned to two groups. While the study group ( $n = 52$ ) received ozone therapy (local and rectal insufflation of the gas) the control group ( $n = 49$ ) received topical and systemic antibiotics.<sup>3</sup> After 20 days of treatment, although the healing rate was significantly higher in the ozone group ( $2.66 \pm 0.05$  cm<sup>2</sup>/days vs.  $1.21 \pm 0.01$  cm<sup>2</sup>/days [ $P = 0.005$ ]), the number of patients with complete healing was similar in both groups (39 [78%] vs. 34 [69%],  $P = \text{N.S.}$ ). In a study conducted by Wainstein et al, 61



**Figure 1** Foot ulcer at admission.



**Figure 3** Complete healing of the wound.

patients with diabetic foot ulcers were randomly assigned to ozone ( $n = 32$ ) and placebo ( $n = 29$ ) groups.<sup>4</sup> Only 34 (56%) of these patients completed the study. The intention-to-treat analyzes failed to demonstrate a significant benefit of ozone therapy over standard therapy (41% vs. 33%,  $P = 0.34$ ). Because intralesional ozone injection has not yet been used in any of the studies involving diabetic patients with foot ulcers, its safety has not yet been assessed. However, serious complications associated with ozone injections for lumbar disc herniation have been previously reported. These complications include vitreoretinal hemorrhages,<sup>5</sup> ventral and dorsal root injury,<sup>6</sup> vertebral stroke,<sup>7</sup> pyogenic discitis and ventral epidural abscess,<sup>8</sup> and fulminant septicemia and death.<sup>9</sup> One of the major concerns regarding intralesional ozone injections is that it may drive the superficial infection, as in our case, into the deeper tissue. Additionally, skin irritation has been reported following topical ozone application and respiratory irritation due to the spreading of the ozone from the generator.<sup>10</sup>

Current certification programs for the use of ozone therapy are open for all physicians, regardless of their specialty, and require a short period of theoretical and practical training. Given this short period of training, it would be bold to pretend that this course could deliver a comprehensive understanding of all the aspects of diseases for which ozone therapy is currently used. The use of this treatment modality for an indication out of one's own expertise may not only cause severe complications, as described in the current case, but may also be the subject of medico-legal issues. Adjunctive treatment modalities should only be used after comprehensive wound management strategies fail to succeed.<sup>11,12</sup> Scientific evidence supporting the use of intralesional ozone injection in the treatment of chronic wounds is missing. Furthermore, ozone therapy is not recommended for deep, heavily infected or necrotic wounds.<sup>10</sup> Medical ozone treatments are generally offered at non-academic health institutions including ozone therapy centers and private physicians' offices. Physicians in private practice may not report negative results or complications. Thus, it is likely that the rate of ozone treatment complication is underestimated.

A wound-care center with a multidisciplinary team should, ideally, consist of a diabetologist, surgeon, podiatrist, orthotist, educator, and plaster technician, in close collaboration with an orthopedic, podiatric, and/or vascular surgeon and dermatologist.<sup>13</sup> Many centers that adopt such multidisciplinary teams, report reduced rates of amputation.<sup>14,15</sup> We must increase the number of these centers throughout the world in order to provide the best and most comprehensive means of wound-care management.

This case report highlights three main issues. First, the role of ozone therapy is still poorly defined in the management of foot ulcers and should be used with caution for selected patients. Second, adjunctive therapies should only be applied when conventional treatments fail to heal the wound. Third, specific and comprehensive training courses are essential for those who wish to apply ozone therapy to diabetic foot ulcers.

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