

Intravesical Ozone Therapy for Progressive Radiation-Induced Hematuria

BERNARDINO CLAVO, M.D.,^{1–4} DOMINGA GUTIÉRREZ, R.N.,¹ DIONISIO MARTÍN, M.D.,⁵
GERARDO SUÁREZ, R.N.,^{1,3} MARÍA A. HERNÁNDEZ, M.D.,^{1,3} and FRANCISCO ROBAINA, Ph.D.^{2,3}

ABSTRACT

Background: Progressive radiation-induced cystitis can become a serious clinical problem the therapeutic solution of which is limited and almost invariably aggressive. Ozone therapy is a nonconventional therapy that has been reported to offer benefits in late-onset wound healing and ischemic disorders. This report describes a patient with progressive radiation-induced hematuria from standard conservative treatment that was further treated with ozone therapy.

Method: Ozone therapy was achieved by intravesical instillation of ozonized bi-distilled water over a period of 30 minutes, three sessions per week during the first weeks. Later, ozone therapy sessions were decreased and involved ozonized water or direct intravesicular instillation of ozone at 20–25 $\mu\text{g/mL}$.

Results: Hematuria was successfully controlled by intravesical application of ozone therapy.

Conclusions: The successes achieved with this technique suggest that intravesicular instillation of ozonized bi-distilled water or ozone merits further investigation with a view to its application to counter this radiation-induced side-effect.

INTRODUCTION

Cystitis and hematuria are potential adverse effects of radiation of the pelvic organs, principally in treatment of prostate or bladder cancer, because of the high doses delivered. Control of symptoms and conservative management of these conditions are sufficient for most patients. However, in more advanced cases the treatment options are limited: intramuscular or intravesical treatment with superoxide dismutase (orgotein)¹ and/or instillation of sodium hyaluronate² and blood transfusions when considered necessary. A more aggressive approach is the administration of intravesical formalin.³ Even hypogastric artery embolization or cystectomy may be indicated when symptom treatment is insufficient. Among the conservative options is the use of hyperbaric breathing chambers. This technique has been used to treat

wounds that have difficulty healing and also the side-effects of radiation. The technique has been used in palliative treatment of radiation-induced cystitis⁴ but the benefits are short-term and the equipment/facilities are not universally available.⁵ Ozone therapy, on the other hand, is a nonconventional treatment that, when administered in any of several different ways via local or topical application, has been shown to offer benefits in the healing of late-onset wounds. Also, beneficial effects have been observed, after systemic treatment, in tissue blood flow and oxygenation, especially in poorly oxygenated tissues.^{6,7} Although this technique does not produce hyperoxia, several effects have been reported that are comparable to those observed with hyperbaric chambers.⁸ This university hospital has used the technique for the treatment of several disorders. Beneficial effects of ozone therapy in patients with late-onset scarring and those with side-

¹Department of Radiation Oncology and Research Unit and ²Chronic Pain Unit of the Dr. Negrin University Hospital, Las Palmas, Spain.

³Canary Islands Institute for Cancer Research (ICIC), Las Palmas, Spain.

⁴Grupo de Investigación Clínica en Oncología Radioterápica (GICOR), Spain.

⁵Department of Urology of the Insular Hospital, Spain.

effects induced by chemo radiotherapy have been observed. The current report describes a patient treated with intravesical ozone therapy because of persistent hematuria secondary to radiation-induced cystitis.

CASE PRESENTATION AND MANAGEMENT

A 70-year-old man was diagnosed 6 years ago as having an adenocarcinoma of the prostate (stage pT3N0M0), which was treated by radical prostatectomy. Thirty-two months later he showed prostate specific antigen (PSA) increase and tumor relapse, which was histologically confirmed. He underwent radiotherapy (70 Gy) and hormone blockade with goserelin and flutamide. Eighteen (18) months later he presented with radiation-induced rectitis and soft rectorrhagia, which were controlled with local application of corticoids. Eighteen months later the patient presented with dysuria and microscopic hematuria. Cystoscopy showed an overall hyperemic bladder mucosa without evidence of relapse or of new tumor, and which suggested radiation-induced cystitis. Circumference enlargement of rectum and bladder observed on computed tomography suggested radiation cystitis as well, but again without evidence of relapse or of new tumor. Bone scan did not show any anomalous uptake. With initial hemoglobin of 9.1 g/dL, intravesical washing with saline and treatment with intramuscular orgotein, erythropoietin, and iron was initiated. Two weeks later the patient presented with macroscopic hematuria with hemoglobin of 7.1 g/dL. He re-

ceived blood transfusion and an intravesical instillation of sodium hyaluronate. Macroscopic hematuria continued to worsen and the hemoglobin concentration decreased further. Ten days later the sodium hyaluronate treatment was discontinued. With written informed authorization from the patient, an intravesical instillation of ozonated water was performed. The O₃/O₂ gas mixture was prepared using medical grade oxygen with an OZON 2000 device (Zotzmann + Stahl GmbH, Plüderhausen, Germany). Ozone was bubbled for 10 minutes through sterile bi-distilled water such that the ozone concentration in the water reached about 20–25 µg/mL. Instillation was over a period of about 30 minutes in each ozone-therapy session. After the first week of ozone therapy administered on 3 alternating days, macroscopic evidence of hematuria disappeared. By week 2 of ozone therapy the hemoglobin concentration began to increase by approximately 0.5 g/dL per week. By week 3, in which the patient had two more instillation sessions, a second cystoscopy was performed and showed significant improvement. Since then, therapy continued with one intravesical instillation session per week using ozonized bi-distilled water and, subsequently, by direct instillation of ozone at 20–25 µg/mL. After 8 additional weeks, the analysis of the patient's urine showed only about 10 red cells per microscopy field and the ozone therapy was concluded. The only side-effect reported by the patient was soft bladder pruritus after the initial sessions. Follow-up for the next 6 months showed no evidence of macroscopic hematuria.

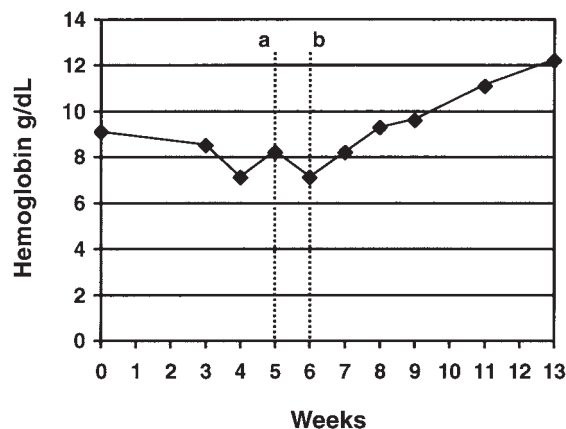


FIG. 1. Clinical history, treatment, and hemoglobin levels. Week 2: first clinical evaluation, microscopic hematuria, commencement of treatment with erythropoietin, iron, and orgotein; first cystoscopy. Week 4: macroscopic hematuria; patient received blood transfusion plus treatment with intravesical instillations using sodium hyaluronate. Week 5 (vertical line "a"): macroscopic hematuria was increased and plasma hemoglobin concentration started to fall *de novo*. Sodium hyaluronate was discontinued and intravesical instillations with ozone-enriched bi-distilled water were started. Week 6 (vertical line "b"): macroscopic hematuria completely cleared. Week 8: Second cystoscopy showed significant improvement.

DISCUSSION

Progressive radiation-induced cystitis can become a debilitating clinical problem, and therapeutic options for its resolution are limited or aggressive or both. Ozone-therapy can offer renewed health or, at least, palliation of some radiation-induced side-effects. As yet, the optimal frequency and duration of intravesical instillation for radiation-associated cystitis and hematuria have not been determined. Approximately three sessions per week for the first 2–3 weeks appear adequate, followed by a progressively wider spacing of the sessions. In the present case, the direct temporal relationship between the application of the ozone therapy and the clinical improvement seems unambiguous. Clinical application of ozone therapy has little or no side-effects but appropriate care needs to be taken to avoid direct inhalation of ozone by the patient and the clinical staff. Standard sterile-care procedures are recommended.

Based on the available literature data on ozone therapy, it can be hypothesized that the mechanism of action includes a local effect on the pro-oxidant/antioxidant balance. Ozone can locally produce a slight and transient oxidative stress that can stimulate antioxidants by upregulation of their synthesis and that leads to a protection against free-radical damage of tissue. This has been demonstrated by blood auto-

transfusion for heart disorders in humans⁹ and by rectal insufflation in rats for hepatic^{10,11} and renal¹² disorders. A complementary effect enhancing the local repair mechanisms could be the known effects that ozone therapy has on hematology parameters^{6,8} as well as on tissue oxygenation, as demonstrated using the polarographic probe technique.⁷

There appear to be no reports on the application of intravesical ozone therapy except a very brief comment in a monograph describing certain differences between hyperbaric oxygen chambers and ozone therapy.¹³ The present report of the successful use of ozone therapy for the treatment of radiation-induced cystitis and/or hematuria suggests a novel use for such a therapy and the possible use for treatment of other radiation-induced side-effects that may well be forthcoming in future research.

ACKNOWLEDGMENTS

Editorial assistance was provided by Dr. Peter R. Turner of t-SciMed (Reus, Spain).

REFERENCES

1. Sanchiz F, Milla A, Artola N, et al. Prevention of radioinduced cystitis by orgotein: A randomized study. *Anticancer Res* 1996;16:2025–2028.
2. Nordling J, Jorgensen S, Kallestrup E. Cystistat for the treatment of interstitial cystitis: A 3-year follow-up study. *Urology* 2001;57:123.
3. Ferrie BG, Rundle JS, Kirk D, Paterson PJ, Scott R. Intravesical formalin in intractable haematuria. *J Urol* 1985;91:33–35.
4. Bevers RF, Bakker DJ, Kurth KH. Hyperbaric oxygen treatment for haemorrhagic radiation cystitis. *Lancet* 1995;346:803–805.
5. Del Pizzo JJ, Chew BH, Jacobs SC, Sklar GN. Treatment of radiation induced hemorrhagic cystitis with hyperbaric oxygen: Long-term followup. *J Urol* 1998;160:731–733.
6. Giunta R, Coppola A, Luongo C, et al. Ozonized autohemotransfusion improves hemorheological parameters and oxygen delivery to tissues in patients with peripheral occlusive arterial disease. *Ann Hematol* 2001;80:745–748.
7. Clavo B, Perez JL, Lopez L, et al. Effect of ozone therapy on muscle oxygenation. *J Altern Complement Med* 2003;9:251–256.
8. Verrazzo G, Coppola L, Luongo C, et al. Hyperbaric oxygen, oxygen-ozone therapy, and rheologic parameters of blood in patients with peripheral occlusive arterial disease. *Undersea Hyperb Med* 1995;22:17–22.
9. Hernandez F, Menendez S, Wong R. Decrease of blood cholesterol and stimulation of antioxidative response in cardiopathy patients treated with endovenous ozone therapy. *Free Radic Biol Med* 1995;19:115–119.
10. Leon OS, Menendez S, Merino N, et al. Ozone oxidative preconditioning: A protection against cellular damage by free radicals. *Mediators Inflamm* 1998;7:289–294.
11. Peralta C, Leon OS, Xaus C, et al. Protective effect of ozone treatment on the injury associated with hepatic ischemia-reperfusion: Antioxidant–prooxidant balance. *Free Radic Res* 1999;31:191–196.
12. Barber E, Menendez S, Leon OS, et al. Prevention of renal injury after induction of ozone tolerance in rats submitted to warm ischaemia. *Mediators Inflamm* 1999;8:37–41.
13. Bocci V. Hyperbaric oxygen therapy (HOT) versus ozonotherapy. In: Bocci V, ed. *Oxygen-Ozone Therapy: A Critical Evaluation*. Dordrecht, The Netherlands: Kluwer Academic Publishers, 2002:359–362.

Address reprint requests to:

Bernardino Clavo, M.D.

Department of Radiation Oncology

Research Unit

Chronic Pain Unit

Dr. Negrín, University Hospital

C/ Barranco la Ballena s/n

35020 Las Palmas (Canary Islands)

Spain

E-mail: bernardinoclavo@terra.es

Copyright of Journal of Alternative & Complementary Medicine is the property of Mary Ann Liebert, Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.