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CLINICAL STUDY

Adjuvant Hyperbaric Oxygen Therapy in the Treatment of Hemodialysis Patients with Chronic Osteomyelitis

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Background. Hemodialysis dependence is an independent risk factor for hematogenous complication, including distant metastatic infection and osteomyelitis. Chronic osteomyelitis is a serious disease that fails to respond to aggressive medical and surgical treatment. Hyperbaric oxygen therapy has been proved to enhance bone and soft tissue healing in many studies. This article presents the preliminary result of hyperbaric oxygen therapy in hemodialysis-dependent patients with chronic osteomyelitis. *Materials and methods.* Ten hemodialysis dependent patients who were diagnosed with chronic diffuse osteomyelitis were treated prospectively with adjunctive hyperbaric oxygen therapy, in addition to aggressive surgical debridement and antibiotic treatment. *Results.* The hyperbaric oxygen therapy averaged 20 daily sessions. Successful treatment was achieved in eight patients (80%). The mean length of treatment was 21 days. The preliminary results are comparable with other series. *Conclusion*. Hyperbaric oxygen is effective as an adjunct to aggressive medical and surgical treatment in chronic refractory osteomyelitis among hemodialysis-dependent patients.

Keywords chronic osteomyelitis, hemodialysis, hyperbaric oxygen therapy

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INTRODUCTION

Hemodialysis dependence is an independent risk factor for hematogenous complication, including distant metastatic infection and osteomyelitis.[1] Osteomyelitis represents an inflammatory process with a bacterial infection involving bone. The disease involves ischemia as well as infection, and it may be acute, subacute, or chronic. The term “refractory osteomyelitis” refers to a failure to heal despite adequate surgical and antibiotic therapy. Osteomyelitis also may be classified by the Cierny-Mader[2] classification as medullary, superficial, localized, and diffuse.

Chromic osteomyelitis has been a difficult problem for patients and the physicians. Appropriate antibiotic therapy is necessary to arrest osteomyelitis, along with adequate surgical therapy. Traditional treatments have included operative procedures and antibiotics. Adjunctive therapy for treating chronic osteomyelitis may be achieved by placing beads, sponsor-coated implants, to deliver local antibiotic therapy and using hyperbaric oxygen therapy.

Hyperbaric oxygen can produce a variety of effects. It increases the killing ability of leukocytes, inhibiting toxin formation by certain anaerobic bacteria. It reduces tissue edema, maintaining tissue oxygenation in the absence of hemoglobin. In addition, it stimulates fibroblast growth, increases collagen formation, and promotes more rapid growth of capillaries. There actions of hyperbaric oxygen are useful in chronic refractory osteomyelitis.[3]

In this article, we present the preliminary result of hyperbaric oxygen therapy in hemodialysis patients with chronic refractory osteomyelitis.

MATERIALS AND METHODS

From January 2002 to December 2005, ten hemodialysis-dependent patients with a diagnosis of chronic diffuse osteomyelitis by Cierny-Mader classification were included in the study. All patients met the treatment criteria: the infection persisted for longer than one month, at least one surgical debridement had been performed, at least two weeks of parenteral antibiotics had been administered, and the patients had been followed for at least one year after surgery. These patients were treated with adjunctive hyperbaric oxygen therapy besides surgical debridement and antibiotic treatment. The patients' medical records were retrospectively studied.

Hyperbaric oxygen therapy protocol was utilized as follows. Patients received hyperbaric oxygen therapy at a pressure of 2.5 atm absolute and lasted for 90 minutes. The patients were all treated daily for twenty treatments.

Patients' laboratory data were reviewed for analysis before and after treatment. Comparison using student's unpaired *t*-test was considered significant at $p < 0.05$. Data was expressed as mean ± SEM.

RESULTS

Ten hemodialysis patients who met the criteria of chronic diffuse osteomyelitis by Cierny-Mader classification were included in this study (see Table 1). There were six male and four female patients. Mean age was 46 years old. The affected bone lesions were located at the tibia bone in seven cases and in the humerus bone for three cases. Patients' wound culture results showed nine cases of *Staphylococcus aureus* and one case of *Pseudomonas aeruginosa*. All patients received surgical debridement and parenteral antibiotics. Eight cases succeeded in the arrest of the disease. Two cases failed in the arrest of the disease and received amputation.

By comparison with laboratory data between pre-treatment and post-treatment groups, only ESR (erythrocyte sedimentation rate) showed significance between pre-treatment and post-treatment groups ($p < 0.01$). Other laboratory data did not show any significant difference (see Table 2)

The hyperbaric oxygen therapy averaged 20 daily sessions. Successful treatment was achieved in eight patients (80%). The mean length of treatment was 21 days. The preliminary results are comparable with other series.

DISCUSSION

Previous studies have reported high rates of osteomyelitis complications among hemodialysis-dependent patients.[3,4] It was associated with the presence of chronic vascular access and with the direct effect of hemodialysis on host immunity to bacteria infection, including uremia-associated phagocyte dysfunction[5] and iron overload.[6,7]

Refractory osteomyelitis is chronic osteomyelitis that has persisted or recurred after appropriate interventions have been performed, or where acute osteomyelitis has not responded to accepted management techniques.[8] Factors, either systemic or local, that compromise host responsiveness are invariably associated with refractory osteomyelitis.

Following initial case reports of successful adjunctive hyperbaric oxygen (HBO) use in cases of very difficult osteomyelitis during the 1960s,[9–11] controlled animal studies clearly verified the benefit of using adjunctive HBO.[12–16] Studies designed specifically to determine the mechanism of HBO action have revealed evidence that

Table 1
Demographic data of patients receiving hyperbaric oxygen therapy

Case	Sex	Age	Bone lesion	Culture result	Debridement	Antibiotics	Outcome
1	Male	45	Tibia	*S. aures**	+	+	Success
2	Male	53	Tibia	*S. aures*	+	+	Success
3	Female	62	Humerus	*S. aures*	+	+	Success
4	Male	40	Tibia	*S. aures*	+	+	Success
5	Female	58	Humerus	*S. aures*	+	+	Success
6	Female	42	Tibia	*S. aures*	+	+	Failure
7	Male	39	Tibia	*S. aures*	+	+	Success
8	Male	32	Humerus	*P. aeruginosa*†	+	+	Failure
9	Female	43	Tibia	*S. aures*	+	+	Success
10	Male	50	Tibia	*S. aures*	+	+	Success

Outcome definition is the success or failure in the arrest of the disease.
**S. aureus*: *Staphylococcus aureus.*
†*P. aeruginosa*: *Pseudomonas aeruginosa.*

Table 2
Comparison of laboratory data between pre-treatment and post-treatment groups

	Pre-treatment	Post-treatment	*p* value
WBC ($\times 10^3$/ul)*	9.01 ± 0.3	8.82 ± 0.4	NS
Hemoglobin (g/dL)	13 ± 2	14 ± 3	NS
Platelete ($\times 10^3$/ul)	353 ± 0.8	334 ± 0.4	NS
ESR (mm/hour)†	110 ± 22	32 ± 3	$p < 0.01$
Albumin (g/dL)	3.5 ± 1.3	3.6 ± 1.1	NS
GOT (U/L)	22 ± 3	21 ± 2	NS
GPT (U/L)	25 ± 4	22 ± 1	NS
Creatinine (mg%)	11.0 ± 0.5	11.1 ± 0.4	NS

*WBC = white blood cell.
†ESR = erythrocyte sedimentation rate.

justifies the adjunctive use of HBO. It has been demonstrated that the decreased oxygen tensions found in infected bone can be elevated to normal or above-normal bone oxygen tensions when animals breathe 100% oxygen in a hyperbaric chamber.[17,18] HBO provides the periodic elevation of bone and tissue oxygen tension from hypoxic levels to normal or above normal levels. The increased oxygen tension in hypoxic tissue promotes collagen production by fibroblasts[19,20] and capillary angiogenesis, as structural collagen provides support for the new budding capillaries.[21] Intermittent oxygen tensions of 30–40 mmHg are necessary for neovascularization in an ischemic environment.[22] Also, neutrophils require tissue oxygen tensions of 30–40 mmHg to kill bacteria by oxidative killing mechanisms at the focus of infection. Therefore, leukocyte killing of aerobic Gram-positive organisms including *Staphylococcus aureus* and aerobic Gram-negative organisms is returned to normal or above-normal levels when the osteomyelitic bone's low oxygen tension is increased to physiologic or supraphysiologic levels. Elevating the oxygen tension above 30–40 mmHg further improves leukocyte killing.[23]

HBO has proved effective as adjunctive therapy in animal models of chronic *S. aureus* and *P. aeruginosa* osteomyelitis.[24] The osteoclast function of removing the necrotic bone (microscopic surgical debridement) is an oxygen-dependent function. The osteoclast is very active metabolically, perhaps 100 times more active than the osteocyte. However, without adequate oxygen tensions, the osteoclast cannot remove dead infected bone. HBO is the single therapy that provides the optimum environment in which this host factor functions. Strauss and Jones observed the osteoclastic stimulation on the effect of HBO in a rabbit model.[25–27]

Published clinical series that utilized adjunctive HBO therapy, while adhering to strict criteria for disease designation as chronic refractory osteomyelitis and follow-up data, have confirmed the controlled animal data. Arrest of previously refractory osteomyelitis ranged from 70 to 89% in patients who bad already undergone parenteral antibiotic therapy and aggressive surgical debridement but remained infected.[28–31]

A retrospective study of osteomyelitis by Esterhai et al. on superficial inspection reportedly showed no value in adjunctive HBO therapy.[32–34] There was one failure in fourteen patients in the non-HBO group (93% arrested) and three failures in fourteen patients in the HBO group (78.6% arrested). Three of the four treatment failures refused further debridement surgery, and the fourth patient had extensive osteomyelitis that required an ablative procedure, which the patient refused. Thus, all four treatment failures were related to the refusal of these patients to have a surgery rather than a reflection on the ineffectiveness of HBO. Furthermore, with an arrest rate greater than 90% in the non-HBO group, the question is raised whether or not the patients in this study met the criteria for refractory osteomyelitis. In a subsequent manuscript, Esterhai et al. published a non-HBO arrest rate of 62%.[35] While the Esterhai paper is a good attempt at evaluating adjunctive HBO for osteomyelitis, it falls short of being evaluative.

The results of several open clinical trials indicate that adjunctive hyperbaric oxygen therapy is useful in the treatment of chronic osteomyelitis. Perrins[36] reported on 24 patients with chronic, recurrent osteomyelitis and cutaneous sinus tracts, in which previous sequestrectomy, antibiotics, or marsupialization had been unsuccessful. A combination of HBO and antibiotic therapy resulted in the healing of 17 of Perrins' 24 cases (71%). In four of the non-healed cases, drainage from the sinus tract diminished. In the remaining three cases, the sinus tracts were not influenced by the treatment. Depenbusch[37] reported on 50 patients who had not responded to adequate antibiotic and surgical therapy. Thirty-five of these patients (70%) had healed completely after HBO, while the other 15 patients reported some improvement.

Two studies in which the patients served as their own controls were reported by Morrey and Davis. Morrey's[38] patients met the following criteria: the infection persisted for longer than one month, at least one surgical debridement had been performed, at least two weeks of parenteral antibiotics had been administered, and the patients had been followed for at least one year after surgery. After HBO therapy, appropriate surgery, and treatment with antibiotics, 34 patients (85%) remained clinically free of disease, and six experienced recurrence of their osteomyelitis. Davis[39] reported on 38 patients with chronic osteomyelitis who had failed to respond to a previous course of antibiotic and surgical therapy under the same criteria used by Morrey. Thirty-four of these 38 patients (89%) treated with adjunctive hyperbaric oxygen, antibiotics, and

surgery experienced an arrest of disease. In our series, all ten patients met the criteria of Morrey's criteria.

To avoid the many variables of clinical osteomyelitis and objectively evaluate the effect of HBO in the laboratory, Mader[40] used the *Staphylococcus aureus* osteomyelitis rabbit model. All animals treated developed stage 4A osteomyelitis in the Cierny-Mader classification system. The results of 28 days of treatment with HBO, antibiotic (cephalothin), a combination of both, or no treatment (control) were compared. HBO was administered for a total of 20 treatments. At the end of the study, cultures of bone were positive for *S. aureus* in 91 percent of the control animals, 36 percent of the animals treated with HBO, 47 percent of the animals treated with cephalothin, and 40 percent of the animals treated with cephalothin and HBO. All three treatment groups differed significantly from the control group, but there were no significant differences among the treatment groups. Hyperbaric oxygen alone was as effective as cephalothin in the treatment of experimental *S. aureus* osteomyelitis.[41–43]

These studies provided evidence for the following conclusions:

1. hyperbaric oxygen, when administered under standard treatment conditions, was as effective as cephalothin in the eradication of *S. aureus* from infected bone;
2. osteomyelitic bone in the experimental model has decreased blood flow and a greatly decreased partial pressure of oxygen;
3. HBO does not directly affect this strain of *S. aureus*; and
4. HBO can restore intramedullary oxygen tensions to physiologic or supraphysiologic levels, but this short exposure does not acutely increase blood flow in osteomyelitic bone.

One mechanism for HBO's effectiveness in *S. aureus* osteomyelitis may be the increase of intramedullary oxygen tensions that maximize the efficiency of killing by phagocytes.[44,45]

Based upon the extensive data submitted supporting the use of adjunctive HBO therapy for chronic osteomyelitis, our preliminary results suggests adjunctive HBO to be clinically effective in hemodialysis patients with chronic osteomyelitis.

REFERENCES

1. Fowler VG, Justice A, Moore C, Benjamin DK, Woods CW, Campbell S, Reller LB, Corey GR, Day NPJ, Peacock SJ. Risk factors for hematogenous complications of intravascular catheter-associated staphylococcus bacteremia. *Clin Infec Dis*. 2005;40:695–703.
2. Cierny G, Mader JT, Pennick JJ. A clinical staging system of adult osteomyelitis. *Contem Ortho*. 1985;10:17–37.
3. Strauss MB. Chronic refractory osteomyelitis. Review and role of hyperbaric oxygen. *HBO Review*. 1990;1:231–235.
4. Priest DH, Peacock JE. Hematogenous vertebral osteomyelitis due to staphylococcus aureus in the adult: Clinical features and therapeutic outcomes. *South Med J*. 2005;98(9):854–862.
5. Vanhlder R, De Smet R, Jacobs V, et al. Uremic toxic retention solutes depress polymorphonuclear response to phagocytosis. *Nephrol Dial Transplant*. 1994;9;1271–1278.
6. Boelaert JR, Daneels RF, Schurgers ML, Matthys EG, Gordts BZ, Van Landuyt HW. Iron overload in hemodialysis patients increased the risk of bacteremia: A prospective study. *Nephrol Dial Transplant*. 1990;5:130–134.
7. Hoen B, Paul-Dauphin A, Hestin D, Kessler M. EPIBAC-DIAL: A multicenter prospective study of risk factors for bacteremia in chronic hemodialysis patients. *J Am Soc Nephrol*. 1998;9:869–876.
8. Strauss MB. Refractory osteomyelitis. *J Hyperbaric Med*. 1987;2:147–159.
9. Slack WK, Thomas DA, Perrins DJD. Hyperbaric oxygenation in chronic osteomyelitis. *Lancet*. 1965;1:1093–1094.
10. Perrins DJD, Maudsley RH, Colwill RR, Slack WK, Thomas DA. OHP in the management of chronic osteomyelitis. In: Brown IW, Cox BG, eds. *Proceedings of the Third International Conference on Hyperbaric Medicine*. Washington, DC: National Academy of Sciences-National Research Council; 1966: 578–584.
11. Goulon M, Rapin M, Letoumel E, Barois A. Five cases of suppurated pseudoarthrosis (osteomyelitis) treated by hyperbaric oxygenation. In: Brown IW, Cox BG, eds. *Proceedings of the Third International Conference on Hyperbaric Medicine*. Washington, DC: National Academy of Sciences-National Research Council; 1966:585–591.
12. Hamblin DL. Hyperbaric oxygen in treatment of osteomyelitis. *Proc R Soc Med*. 1971;64:1202–1203.
13. Hamblin DL. Hyperbaric oxygenation: Its effect on experimental staphylococcal osteomyelitis in rats. *J Bone Jt Surg*. 1968;5OA:1129–1141.
14. Mader JT, Guckian JC, Glass DL, Reinarz JA. Therapy with hyperbaric oxygen in experimental osteomyelitis due to *Staphylococcus aureus* in rabbits. *J Infect Dis*. 1978; 138:312–318.
15. Mader JT, Adams KR, Couch LA, Sutton TE. Potentiation of tobramycin by hyperbaric oxygen in experimental *Pseudomonas aeruginosa* osteomyelitis. Presented at the 27th Interscience Conference on Antimicrobial Agents and Chemotherapy, Anaheim, California, USA; 1987.
16. Mendel V, Scholz H, Nagel A. Hyperbaric oxygenation: Its effect on experimental chronic osteomyelitis in rats. In: Bakker DL, Schmultz J, eds. *Hyperbaric Medicine Proceedings: 2nd Swiss Symposium on Hyperbaric Medicine, 2nd European Conference on Hyperbaric Medicine*. New York: Marcel Dekker, Inc.; 1990:77–85.
17. Triplett RG, Branham GB, Gilhnore JD, Lorber M. Experimental mandibular osteomyelitis. Therapeutic trials with hyperbaric oxygen. *J Oral Maxillofac Surg*. 1982;40:640–646.
18. Mader JT, Brown GL, Guckian JC, Wells CH, Reinarz JA. A mechanism for the amelioration by hyperbaric oxygen of

experimental staphylococcial osteomyelitis in rabbits. *J Infect Dis*. 1980;142:915–922.
19. Niftaoski H, Hunt TK. Oxygen tensions in healing bone. *Surg Gynecol Obstet*. 1972;134:746–750.
20. Hunt TK, Pai MP. The effect of varying ambient oxygen tensions on wound metabolism and collagen synthesis. *Surg Gynecol Obstet*. 1972;135:561–567.
21. Knighton DR, Hunt TK. Regulation of wound angiogenesis: Effect on oxygen gradients and inspired oxygen concentrations. Presented to the Society of University Surgeons, Hershey, Pa., February 12–14, 1981.
22. Hohn DC, MacKay RD, Halliday B, Hunt TK. The effect of oxygen tension on the microbicidal function of leukocytes in wounds and in vitro. *Surg Fonim*. 1976;27:18–20.
23. Verklin RN Jr, Mandell GL. Alteration of effectiveness of antibiotics by anaerobiosis. *J Lab Clin Med*. 1979;89:65–71.
24. Strauss MB, Malluche MM, Faugere MC, Greenberg DA, Hart GB, Green S. Effect of hyperbaric oxygen on bone resorption in rabbits. Presented at the Seventh Annual Conference on the Clinical Applications of Hyperbaric Oxygen, Anaheim, Calif., June 9–11, 1982.
25. Mendel V, Reichert B, Simanowski HJ, Schulz HC. Therapy with hyperbaric oxygen and cefazolin for experimental osteomyelitis duo staphylococcus aurous in rats. *Uundersea Hyper Med*. 1999;26(3):169.
26. Jones JP, Lewis RH, Lewis T, Fauere MC, Mallunch HH. *The effect of hyperbaric oxygen on osteonecrosis*. Anaheim, Calif.: Orthopaedic Research Society; 1991.
27. Depenbusch FL, Thompson RE, Hart GB. Use of hyperbaric oxygen in the treatment of refractory osteomyelitis: A preliminary report. *J Trauma.* 1972;12:807–812.
28. Bingham EL, Mullen JE, Winans RG, Hart GB. The treatment of refractory osteomyelitis with hyperbaric oxygen: A progress report. In: Trapp WG, Banister EW, Davison EJ, Trapp PA, eds. *Proceedings of the Fifth International Conference on Hyperbaric Medicine*. Burnaby, Canada: Fraser University; 1973:264–269.
29. Davis JC. Refractory osteomyelitis of the extremities and axial skeleton. In: Davis JC, Hunt TK, eds. *Hyperbaric oxygen therapy*. Bethesda, Md.: Undersea Medical Society; 1978:217–227.
30. Morrey BF, Dunn JM, Heimbach RD, Davis JC. Hyperbaric oxygen in chronic osteomyelitis. *Clin Orthop*. 1979;144(39):121–127.
31. Davis JC, Heckman JD, DeLee JC, Buckwold FJ. Chronic non hematogenous osteomyelitis treated with adjuvant hyperbaric oxygen. *J Bone Jt Surg*. 1986;68A:1210–1217.
32. Esterhai JH, Pisarello J, Brighton CT, Heppenstall RB, Gelman H, Goldstein G. Adjunctive hyperbaric oxygen therapy in the treatment of chronic refractory osteomyelitis. *J Trauma*. 1987; 27:763–768.
33. Esterhai JL, Pisarello J, Brighton CT, Heppenstall RB, Gehnan H, Goldstein G. Treatment of chronic refractory osteomyelitis with adjunctive hyperbaric oxygen. *Ortho Rev*. 1988;17:809–815.
34. MacGregor RR, Graziani AL, Esterhai JL. Oral ciprofloxacin for osteomyelitis. *Orthopedics*. 1990;13:55–60.
35. Mader JT, Adams KR, Wallace WR, Calhoun JH. Hyperbaric oxygen as adjunctive therapy for osteomyelitis. *Infect Dis Clin North Am*. 1990;4:433–440.
36. Perrins JD, Maudsley RH, Colwill MW, Slack WK, Thomas DA. OHP in the management of chronic osteomyelitis. In: Brown IW, Cox BG, eds. *Proceedings of the Third International Conference on Hyperbaric Medicine*. Washington, DC: National Academy of Sciences-National Research Council; 1966:578–584.
37. Depenbusch FI, Thompson RE, Hart GB. Use of hyperbaric oxygen in the treatment of refractory osteomyelitis: A preliminary report. *J Trauma*. 1972;12:802–812.
38. Morrey BF, Dunn JM, Heimbach RD, David JC. Hyperbaric oxygen and chronic osteomyelitis. *Clin Ortho*. 1979; 144:121–127.
39. Davis JC, Heckman JD, DeLee JC, Buckwold FJ. Chronic non-hematogenous osteomyelitis treated with adjuvant hyperbaric oxygen. *J Bone Joint Surg*. 1986;68A:1210–1217.
40. Mader JT, Guckian JC, Glass DL. Therapy with hyperbaric oxygen in experimental osteomyelitis due to *Staphylococcus aureus* in rabbits. *J Infect Dis*. 1978;138:312–318.
41. Mader JT, Guckian JC, Glass DL, Reinarz JA. Therapy with hyperbaric oxygen for experimental osteomyelitis due to *Staphylococcal aureus* in rabbits. *J Infec Dis*. 1978;138: 312–318.
42. Mader JT, Adams KR, Wallace WR. Hyperbaric oxygen as adjunctive therapy for osteomyelitis. *Infec Dis Clin North Am*. 1990;4:433–440.
43. Mader JT, Ortiz M. Update on the diagnosis and management of osteomyelitis. *Clin Podiatr Med Surg*. 1996; 13(4):701–724.
44. Morey BF, Dunn JM, Heimbach RD. Hyperbaric oxygen and chronic osteomyelitis. *Clin Orthop*. 1979;144:121–127.
45. Waldvogel FA, Medoff G, Swartz MM. Osteomyelitis: A review of clinical features, therapy, considerations, and unusual aspects. *New Engl J Med*. 1980;282:198–206, 260–266, 316–322.