Hyperbaric Oxygen Therapy in the Treatment of Chronic Refractory Osteomyelitis: A Preliminary Report

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Background: Hyperbaric oxygen (HBO) has been proven to enhance bone and soft tissue healing in ischemic tissue in vitro and in vivo studies. Although only a few reports have been proven using controlled studies, this treatment modality remains encouraging for chronic refractory osteomyelitis. In this retrospective study, we reported the clinical results of HBO therapy for chronic refractory osteomyelitis.

Methods: From January through August 2000, 14 patients with chronic refractory osteomyelitis of the tibias treated with HBO were available for follow-up examination. According to the Cierny-Mader classification, all patients were classified as type III or IV osteomyelitis. Adequate debridement and parenteral antibiotic treatment in conjunction with HBO therapy at 2.5 atmospheres absolute for 120 minutes, and 5 days per week regimen was used in all patients. The patients were followed-up for an average of 15 months after completion of HBO therapy.

Results: The most common infecting microorganism was *Staphylococcus aureus*. Mixed infections were usually found in patients with open fractures. The average number of operations before HBO therapy was 5.4 including soft tissue reconstruction in 11 patients. The average number of HBO treatments was 33.6 times. There were no HBO related complications. No recurrence of infection was noted in 11 patients, which resulted in a success rate of 79%.

Conclusions: Hyperbaric oxygen therapy is effective and safe for chronic refractory osteomyelitis provided that patients had received appropriate medical and surgical management.

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Key words: hyperbaric oxygen (HBO), chronic refractory osteomyelitis, atmosphere absolute (ATA).

The management of chronic refractory osteomyelitis remains a challenge to orthopedic surgeons. Not only is the recurrence rate high, but also the disease prolongs patients' disabilities. Chronic osteomyelitis is a surgical disease. Adequate debridement and antibiotic therapy remain the mainstay of the treatment.[1,2] Soft tissue reconstruction is necessary when there are soft tissue

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defects. The reported recurrence rate is estimated to be around 30%, even after aggressive medical and surgical treatment.[1] In a 1983 Mayo Clinic review, there had been a recurrence rate of 61.5% in patients with mixed aerobic/anaerobic osteomyelitis.[3] The treatment of chronic refractory osteomyelitis greatly increases the medical expenses because prolonged treatment is usually needed. Furthermore, optimal results are not always achieved.

Hyperbaric oxygen (HBO) therapy has been used for chronic refractory osteomyelitis since 1965.[4] The therapeutic effects have been widely reported in vitro and in vivo studies.[3,5-9] Although chronic refractory osteomyelitis is one of the indications which are approved by the Undersea and Hyperbaric Medical Society (UHMS), only a few reports have confirmed the effects using results of controlled studies.[6,10] However, this treatment modality remains encouraging for chronic osteomyelitis because of the high rate of wound complications and recurrence in this disease. The purpose of this study was to evaluate the effectiveness of HBO therapy in the treatment of chronic refractory osteomyelitis.

METHODS

From January 2000 through August 2000, 85 patients with tibial osteomyelitis were treated at authors' hospital. Fourteen patients with chronic refractory osteomyelitis treated with HBO were available for follow-up examination (Table 1). There were 12 men and two women with an average age of 50 years (range, 25 to 79 years).

The initial evaluation included a complete medical history, laboratory data, culture, antibiotic therapy, and operative treatment. Image studies included x-ray, bone scans/ Gallium scans, and computerized tomograms as indicated. Chronic refractory osteomyelitis was defined as bone infections that persisted longer than 6 months, in the patients where aggressive, adequate surgical debridement and antibiotic therapy had failed.[11,12] All patients enrolled in this study had met the following 3 criteria: (1) infection for at least 6 months, (2) had received at least three surgical procedures to eradicate the infection, and (3) treatment with parenteral antibiotics.

Chronic osteomyelitis was classified using the Cierny-Mader classification system.[4] All patients had anatomic type III or IV osteomyelitis. Nine cases resulted from open fractures, and five from closed fractures. The duration of infection before HBO therapy averaged 14 months (range, 6 to 48 months). The average number of surgical procedures before HBO therapy was 5.4 (range, 3 to 10). The choice of antibiotics was determined according to the latest culture and sensitivity tests. The duration of

Table 1. Data for Patients

Patient No.	Age (years)	Gender	Fracture type	Duration of infection (months)	+Osteomyelitis classification	Surgery (times)	HBO (times)	Follow-up (months)	Result
1	26	M	open IIIB	8	IVA	3	60	18	H
2	79	M	closed	14	IIIB	4	30	18	H
3	31	F	open IIIB	8	IVA	10	30	17	H
4	42	M	closed	48	IVB	8	40	17	H
5	73	F	closed	6	IVB	3	30	16	H
6	54	M	open II	7	IIIA	7	30	16	H
*7	64	M	closed	7	IVB	4	30	15	f
8	28	M	open IIIC	18	IVA	4	30	15	H
9	25	M	open IIIB	9	IIIB	3	40	15	H
*10	27	M	open IIIB	36	IVB	7	30	15	AK
11	75	M	open IIIB	7	IVB	4	30	15	H
12	66	M	closed	6	IIIB	4	30	14	H
*13	63	M	open IIIB	6	IVB	9	30	13	f
14	45	M	open IIIB	10	IIIA	5	30	12	H

Abbreviations: M: Male; F: Female; H: Healed; f: failed to heal; AK: above-knee amputation; +Cierny-Mader classification.

parenteral antibiotic therapy after operation was usually 2 weeks; followed by an additional 2 to 4 weeks of oral antibiotics.

In addition to surgical debridement and parenteral antibiotics, all patients had received adjunctive HBO therapy in a diving chamber (Haux-Starmed 2000 Hyperbaric Chamber, Germany). The treatment regimen was designed according to the suggestions by the UHMS.[13] In the hyperbaric chamber, 100% oxygen was delivered using a mask system, with 2.5 atmospheres absolute (ATA), for 2 hours with an intermittent schedule of 25 minutes of 100% oxygen breathing and 5 minutes of air breathing, one session per day, 5 days per week. All patients were followed for a minimum of 1 year with an average follow-up of 15 months (range, 12 to 18 months). Success of treatment was defined as patients who had good wound healing with no discharge and no recurrence of infection during the follow-up period after HBO therapy.

RESULTS

The average number of treatments with HBO therapy was 33.6 times (range, 30 to 60 times). None of the patients exhibited signs of oxygen toxicity or barotrauma during HBO therapy. The wounds healed in 11 patients with a 79% success rate. The average number of surgical procedures was 5.4 (range, 3 to 10) before HBO therapy, and 1.6 (range, 0 to 3) during HBO therapy. Debridement and flap or skin graft was performed in 11 patients.

The most common microorganism was *Staphylococcus aureus*. Mixed infection was more common in patients with open fractures (Table 2). Three patients failed to heal despite combined surgical debridement, parenteral antibiotic therapy and HBO therapy. The patients who failed the treatment protocol had also undergone 30 sessions of HBO. One patient had tibial osteomyelitis following an open type IIIB fracture. The culture results showed microorganisms with mixed flora. Multiple surgical procedures including free flap reconstruction were performed to preserve the tibia. However, the infection persisted despite surgical debridement, parenteral antibiotics and HBO therapy. The patient finally received an above-knee amputation to eradicate the infection. The other two patients with tibial osteomyelitis had decreased wound drainage after 30 sessions of HBO. The infecting microorganism was Oxacillin-resistant *Staphylococcus aureus*. The discharge sinus persisted during the follow-up, but both

Table 2. Microbiological Result from Surgical Specimens

Patient No.	Microorganism	Antibiotic beads	Antibiotics
1	Staphylococcus epidermidis	Y	Vancomycin
2	OSSA	Y	Oxacillin
3	Enterococcus	Y	Ampicillin
4	Serratia marcescens	Y	Ciproxin
5	OSSA	Y	Cefazolin
6	Pseudomonas aeruginosa ORSA	N	Vancomycin + Ciproxin
*7	ORSA	Y	Vancomycin
8	Pseudomonas, Enterococcus species Aeromonas sobria	Y	Piperacillin + Gentamicin
9	ORSA Serratia marcescens	N	Vancomycin + Gentamicin
*10	Enterococcus species, Serratia marcescens, Actinetu baumanni	Y	Ampicillin +
11	Escherichia coli Pseudomonas aeruginosa	Y	Piperacillin + Gentamicin
12	OSSA	N	Cefazolin
*13	ORSA	Y	Vancomycin
14	OSSA	Y	Oxacillin

*treatment failure; Y: yes; N: no

Abbreviations: ORSA: Oxacillin-resistant *Staphylococcus aureus*
OSSA: Oxacillin-sensitive *Staphylococcus aureus*

patients refused further debridement, preferring to live with the osteomyelitis.

The remaining 11 patients had wound healing and no recurrence of osteomyelitis after HBO therapy (Fig. 1). The length of treatment averaged 48 days (range, 42 to 84 days). There was no recurrence at a follow-up period of 15 months after the completion of HBO therapy.

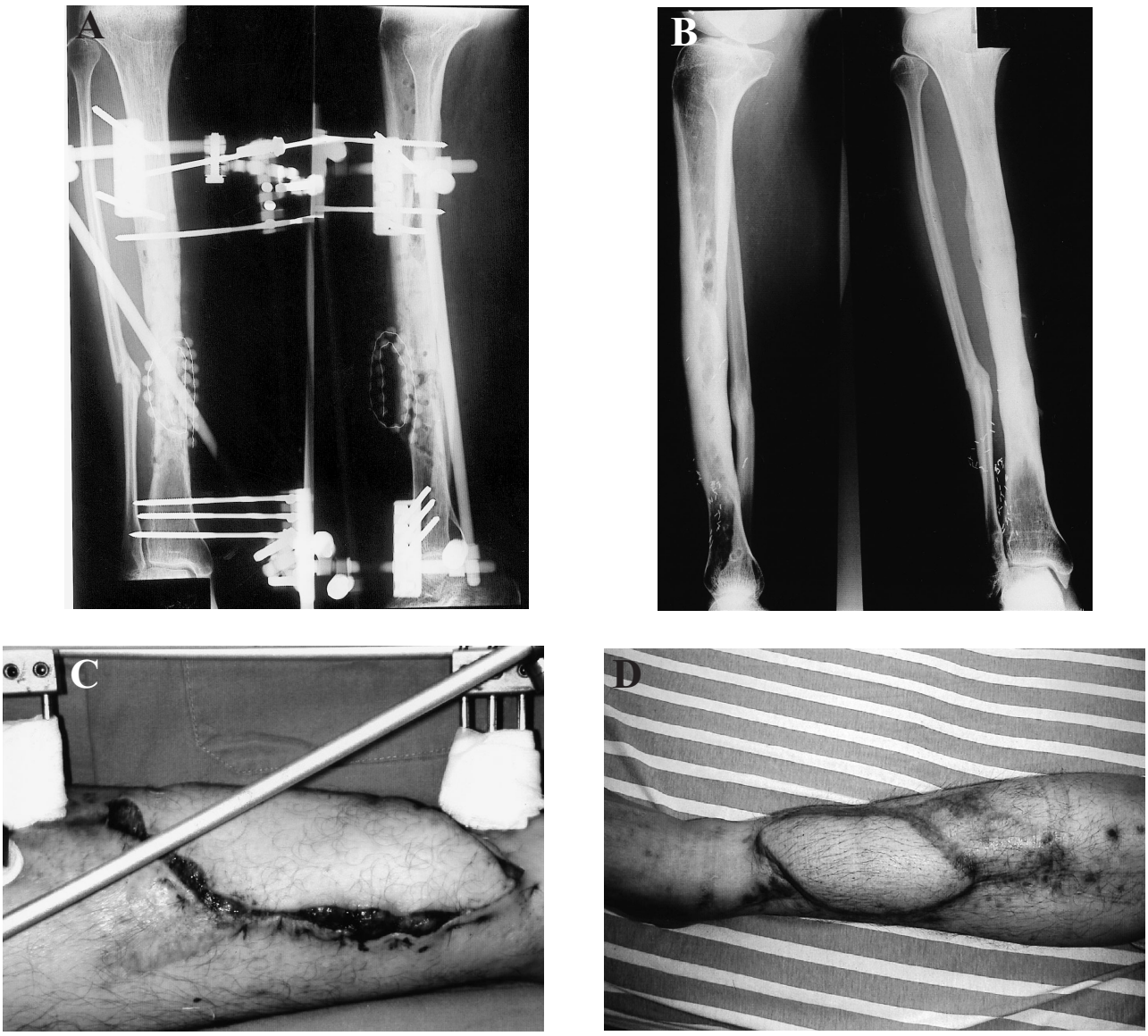

Fig. 1 (A) Radiographs of the tibia of a 26-year-old male shows external fixation and local antibiotic beads for infected nonunion of tibial shaft fracture. (B) Bone grafting and 30 sessions of hyperbaric oxygen therapy was performed to promote bone union. At 18 months of follow-up, radiographs show solid union of the tibia. (C) Photograph of the leg during the HBO therapy shows free flap for soft tissue defect and external fixation for stabilization of the tibia. (D) The wound was healed after HBO therapy. At 18 months of follow-up, no recurrence of the infection was noted and the ankle motion was normal compared with the unaffected extremity.

DISCUSSION

The basic principles of management for chronic osteomyelitis include adequate debridement and appropriate antibiotic therapy.[1,2,14,15] Soft tissue reconstruction or osteocutaneous transfer is necessary when there is soft tissue or bone defects. However, optimal surgical results are not always achieved, and this is one of the common causes of refractory infection. The recurrence rate in chronic refractory osteomyelitis is relatively high because the chronicity renders osteomyelitis resistant to conventional treatment.[16]

HBO therapy increases tissue oxygen tension and promotes bone and soft tissue healing in ischemic tissue which has been widely proven in vitro and in vivo studies.[7,10,17-19] The possible mechanisms of HBO in treating osteomyelitis are (1) HBO raises the tissue oxygen tension, (2) HBO enhances the leukocyte phagocytic mechanisms in bones and wounds with low oxygen tension,[5] (3) Optimal oxygen tension enhances osteogenesis or neovascularization to fill the dead space with vascular or bony tissue[17], and (4) HBO enhances osteoclastic activity to remove bony debris.[17] HBO also directly inhibits anaerobic organism growth in hypoxic tissue.

Normal oxygen tension in healthy bones is about 45 mmHg of oxygen under ambient conditions.[20] The infected bone and necrotic tissue produces an area of lower oxygen tension.[12] The level of oxygen tension under ambient conditions in chronic osteomyelitis is 23 mmHg or less.[20] The causes of low oxygen tension in chronic osteomyelitis include initial trauma, vascular compromise, dense fibrous scarring and undebrided infected bone. Intermittent oxygen tensions of 30 to 40 mmHg are necessary for neovascularization in an ischemic environment.[21] Also, elevating the oxygen tension above 30 to 40 mmHg further improves leukocyte killing.[22]

Although antibiotics help kill microorganisms in the soft tissue around the focus of infection and surgery removes the macroscopic portion of dead and infected bone, HBO improves host response by making the environment more favorable to leukocyte oxidative killing, neovascularization, and resorption of dead and infected bone. Small bone debris could be resorbed during HBO therapy, but persistent sequestrum should be surgically removed.[23] In addition, aminoglycoside transfer access to the bacterial wall is oxygen-dependent and is inhibited in conditions of a hypoxic environment. Therefore, HBO therapy enhances transport and augments the efficacy of the antibiotics.[24]

There were many reports of improvement for chronic osteomyelitis treated using HBO therapy. Davis reported a disease process arrested in 50% which remained so after 5 years of follow up in 98 patients treated with 2 ATA HBO.[25] In another report, Davis et al. found that 34 of 38 patients treated with 2ATA HBO plus wound debridement and antibiotics became free from clinical signs of osteomyelitis for 34 months.[7] Morrey et al. recommended that HBO be used as an adjunct to surgery and antibiotics. In their series of 40 patients treated with HBO, the cure rate at 2 years of follow-up was 85%.[11] In our series, 14 patients were treated with 2.5 ATA HBO. Eleven patients healed with a success rate of 79%. There was no recurrence at an average follow-up period of 15 months after the completion of HBO therapy.

All patients in our series were type III or IV osteomyelitis according to the Cierny-Mader classification system.[4] Three patients failed to respond to the treatment including one case with mixed infection, and two patients with *Staphylococcus aureus* infections. The first patient was a 64-year-old diabetic patient with multiple fractures. The second patient was a 27-year-old man who had large soft tissue defects combined with multiple flora infection. The third patient was a 63-year-old man who was an alcoholic and a heavy smoker. All of them were type IVB osteomyelitis. However, the number of patients who failed to heal after the treatment was too small to draw any conclusions concerning the poor results. The combination of infecting microorganism, duration and severity of infection, and underlying disease all contributed to the failure of the treatment.

Mader et al.[24] studied *Staphylococcus aureus* osteomyelitis using a rat tibial model to evaluate the effectiveness of HBO therapy. They found that HBO alone was as effective as Cephalothin in the treatment of experimental *Staphylococcus aureus* osteomyelitis. The best results were obtained in animals treated using a combination of HBO and Cephalothin. Therefore, they recommended that adjunctive HBO be used for stages 3B and 4B

osteomyelitis and not indicated for all clinical types of osteomyelitis.

In two identical publications, Esterhai et al.[6,10] reported no benefits of HBO therapy in their patients with chronic refractory osteomyelitis. This is the only study in which no effects of HBO in chronic refractory osteomyelitis were reported.

The limitation of this study was the fact that it was uncontrolled and retrospective. The treatment course was more complicated in the patients as compared with treatment for a simple fracture. The treatment was individualized, and no strict principles were adhered to. The treatment results were unpredictable and the treatment course was long. Although HBO therapy has been proven to enhance bone and soft tissue healing in ischemic tissue, the healing of chronic osteomyelitis may not be attributed solely to the HBO therapy, especially when combined soft tissue reconstruction was done for the patient. However, local wound condition before HBO therapy may serve as a control parameter in comparison with conditions after HBO therapy. The clinical responses to HBO therapy were used as guidelines for further treatment.

In conclusion, 11 of 14 patients with chronic refractory osteomyelitis were successfully treated with HBO therapy. No complications were associated with the HBO therapy in this series. The results were encouraging at 15 months of follow-up. HBO therapy is effective and safe for chronic refractory osteomyelitis provided there are appropriate medical and surgical management.

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高壓氧治療慢性復發性骨髓炎：初步報告

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背 景： 高壓氧治療慢性骨髓炎以促進骨折癒合及傷口癒合經由實驗已得到證實，雖然只有少許比較性的研究報告，此種治療對於慢性復發性骨髓炎仍是相當吸收人的治療方法。在此我們提出以高壓氧治療慢性復發性骨髓炎的臨床經驗。

方 法： 從2000年1月至2000年8月，我們共收集了14例脛骨慢性復發性骨髓炎在本院接受高壓氧治療並能夠追蹤檢查的病例。所有的病例均爲Cierny-Mader classification中type III及type IV的骨髓炎。病人除了接受清創手術及抗生素使用外，均再使用輔助性的高壓氧治療。治療以2.5絕對大氣壓，每次2小時，每週5天的方式進行。治療結束後病人接受平均15個月的追蹤。

結 果： 在我們的病例中最常見的致病菌爲金黃色葡萄球菌，而原先如爲開放性骨折則常見混合菌種感染。病人在接受高壓氧治療前平均接受5.4次的手術治療，有11位病人同時接受軟組織的重建手術。平均高壓氧治療的次數爲33.6次，治療中未有任何合併症發生。追蹤發現共有11位病人傷口癒合而無感染復發，成功率到達百分之七十九。

結 論： 對於慢性復發性骨髓炎的治療，如果能夠有適當的內科和外科處理，使用輔助性的高壓氧治療是一種有效又安全的方法。

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關鍵字： 高壓氧，慢性復發性骨髓炎，絕對大氣壓。

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