Hyperbaric oxygen therapy in orthopedic conditions.

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BACKGROUND

Since 1972, Japan and the United States have operated a cooperative program focusing on the research of diving and physiology. I have attended these meetings since 1973. The US-Japan Cooperative Program in Natural Resources (UNJR) meeting is held every two years, in both countries on an alternating basis. At each meeting Dr. Christian J. Lambertsen has given me very valuable advice about how to design our research and present our papers (Figure 1).

Fig. 1. UNJR Meeting – Yokosuka 1987

I have also attended the Undersea and Hyperbaric Medical Society annual meetings of the since 1975. He has told me many things about research and the presentations of papers. I am extremely grateful to him for his help. Today, I will present my paper on hyperbaric oxygen therapy in orthopedic conditions.

From 1972 to 1981, I worked in Kyushu Rosai Hospital in Kitakyushu City. My primary research involved dysbaric osteonecrosis in divers. We treated more than 400 shellfish divers and performed radiological investigations on the divers in Ohura. Dysbaric osteonecrosis was found in 268 of 450, or 59.5%, of the divers (1, 2). Within that group, 73.1% were known to have been treated for bends. Thus, bends were significantly related to the occurrence dysbaric osteonecrosis.

We have also undertaken cooperative research with Dr. Charles E. Lehner, from the University of Wisconsin in Madison. We sent our diver's diving profile to Dr. Lehner who succeeded in producing experimental dysbaric osteonecrosis in sheep (3). We have taken part in productive, cooperative research with scientists in the US through the UJNR program.

At Kyushu Rosai Hospital at that time, the indications for HBO_2 therapy were very limited. HBO_2 therapy was approved only for carbon monoxide poisoning, decompression illness and gas gangrene. Had we treated other diseases, our insurance system would have cut all reimbursement for HBO_2. This was our most significant problem with HBO_2 therapy. However, the Japanese Society for Hyperbaric Medicine gained political power through the efforts of Dr. Sakakibara and others. We can now treat many kinds of diseases with HBO_2 therapy.

Fig 2. Prof. Juro Wada President of the 4th International Congress on Hyperbaric Oxygenation in Sapporo (1969)

The first diving bell was imported from Holland in 1834 and placed at the Mitsubishi Heavy Industry Nagasaki Ship Product Factory. Mankichi Masuda used helmet diving to collect abalone in the Chiba Prefecture in 1877. Diving fishermen in Oura, Ariake Sea, continue the same style of helmet diving.

In 1958, Saito reported HBO_2 therapy for stroke (4). An HBO_2 chamber was built in Kyushu Rosai Hospital for Decompression Illness (DCI) and carbon monoxide (CO) poisoning in 1961. In 1965, Professor Juro Wada reported HBO_2 therapy for carbon monoxide poisoning and severe burns caused by the fire from a 1965 coal mine gas explosion (5). He organized the fourth International Congress on Hyperbaric Medicine in Sapporo in 1969 (Figure 2).

In 1966, the Japanese Society for Hyperbaric Medicine was established. In 1994, Mahito Kawashima organized the 29th Annual Meeting in Nakatsu. In 2002, Sugiyama held the 37th Annual Meeting, in Tokyo. As of June 30, 2001, there were 903 monoplace HBO_2 chambers and 54 multiplace chambers in Japan. The indications for the emergency use of HBO_2 therapy of the Japanese Society of Hyperbaric Medicine are as follows: CO poisoning, gas gangrene, decompression illness, air embolism, crush injuries, severe burns, shock, myocardial infarction, ileus, cerebral embolism, cerebral edema, brain ischemia, acute retinal artery occlusion, and spinal cord injuries. Indications for non-emergency use include malignant tumor treated with chemotherapy or radiotherapy, refractory ulcer, ischemic skin flap after skin graft, SMON (Kinohorm Poisoning), one week after the onset of emergency cases of cerebral ischemia, refractory osteomyelitis, and sudden deafness.

HBO_2 Therapy in Kawashima Orthopedic Hospital

The history of HBO_2 therapy at Kawashima Orthopaedic Hospital in Nakatsu is as follows: In 1981, an HBO_2 chamber was built and now two multiplace chambers are used for HBO_2 therapy (Figure 3).

Fig. 3. Chamber for HBO_2 at Kawashima Orthopaedic Hospital

In 1987, the tenth meeting of Japanese Bone and Joint Infection Society was held in Nakatsu. In 1990, the third Kyushu-Okinawa Society for Hyperbaric Medicine was held in Nakatsu. In 1994, The 29th Meeting of Japanese Society for Hyperbaric Medicine was held in Nakatsu. The 2001 International Seminar was also held in Nakatsu (Figure 4).

In terms of therapy from 1981 to 2001, the hospital performed 145,700 treatments in 4035 patients (Figures 5, 6 and 7). In an orthopedic hospital, infectious diseases are an important indication.

Fig. 4. 2001 International Seminar in Nakatsu

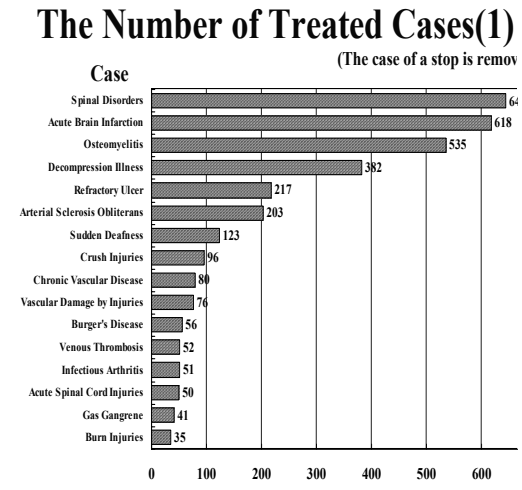

Fig. 5. The number of treated cases (1)

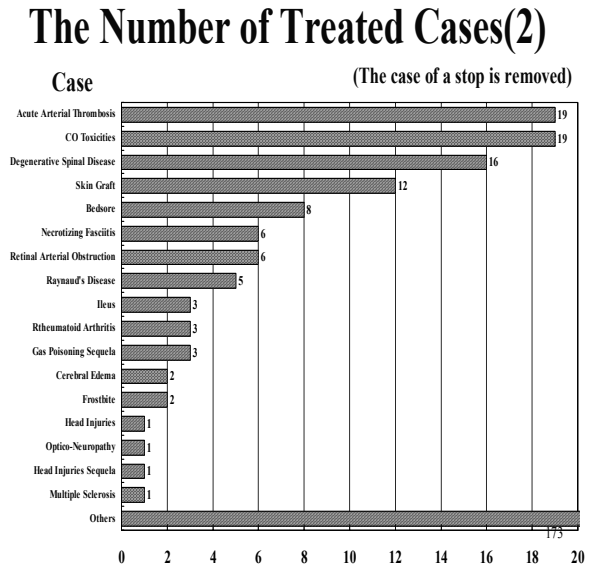

Fig. 6. The number of treated cases (2).

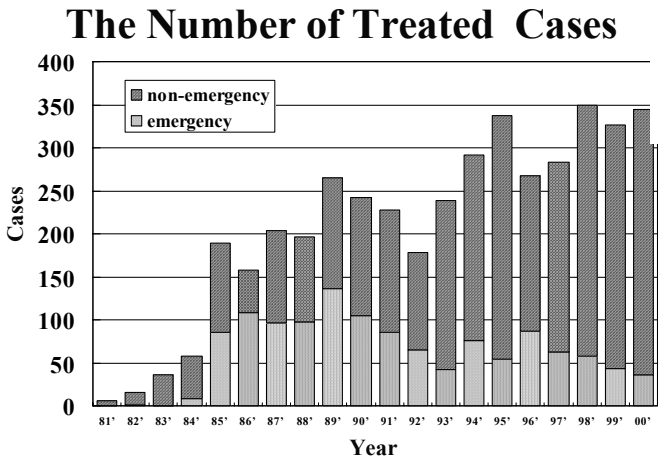

Fig. 7. The number of treated cases (3)

Crush Injuries

Crush injuries are traumatic ischemia that cause such severe damage to tissues from the energy transfer that tissue survival is in question (6). Usually, two or more tissues are injured severely enough that their survival is unsure. Edema due to tissue hypoxia has detrimental effects on wound healing and infection control. It interferes with oxygen availability for cells that already

have increased oxygen needs. A second harmful effect of edema is the collapse of capillaries. The edema fluid increases the interstitial pressure around the capillaries. Once the interstitial fluid pressure exceeds the capillary perfusion pressure in a closed space, the capillary bed collapses, and flow in the microcirculation ceases.

Bacteria grow almost without restraint if circulation is disrupted at the site of injury. With the disruptions of the blood supply, antibiotics can no longer reach the injury or infection site. In the hypoxic environment, neutrophils lose the ability to generate the reactive oxygen species that kill bacteria. As tissue oxygen is much reduced in acute traumatic peripheral ischemia and decreases a local site's ability to handle infection, impaired wound healing, and wound contracture are additional secondary problems. A wound will not heal unless there are sufficient oxygen tensions for fibroblasts to function (8). A tissue oxygen tension of 30mmHg is required for fibroblasts to mobilize and produce the collagen matrix needed for neovascularisation and wound repair.

Vasoconstriction is a secondary effect of HBO_2. This leads to edema reduction. Hyperbaric oxygen exposure causes a 20% reduction in blood flow. With decreased blood flow, extravasation of fluid in the area of injury is decreased. Since capillary resorption of extracellular fluid continues, the net effect is edema reduction. Edema reduction of 20% or more has been observed in laboratory studies (9). Increased oxygen content in the blood from HBO_2 compensates for the decreased flow. Moreover, flow in the microcirculation is improved as edema decreases and reduces external pressure around the microcirculation. HBO_2 reduces the amount of skeletal muscle necrosis. It also reduces post-injury muscle necrosis and edema. HBO_2 for crush injuries should be started as soon as feasible. It is also used as an adjunct for the management of compartment syndromes and other acute traumatic peripheral ischemias. We have treated many crush injuries with severe swelling, edema and infections, and the wounds completely healed.

Osteomyelitis

The oxygen tension in osteomyelitic bone is low, rarely exceeding 25mmHg of oxygen. Using animals, Mader, *et al.* have shown that oxygen tensions in normal, as well as infected, tissue are increased by HBO_2 (10). In the Mader studies, the therapy increased the oxygen tensions in both normal and osteomyelitic bones (10). Under ambient conditions, the oxygen tension in the osteomyelitic bone was 23mmHg, whereas oxygen tension in the normal bone was 45mmHg. HBO_2 increased the oxygen tension to 104mmHg in osteomyelitic bone, and to 322 mmHg in normal bone.

The polymorphonuclear leukocyte (PMN) is primarily responsible for fighting bacterial infection. Using an *S. aureus* model, Mader showed a proportional relationship between oxygen tensions and phgocytic killing ability. Increasing the oxygen to 150mmHg and 760mmHg killed the greatest number of *S. aureus* (10). The study showed improved treatment of experimental staphylococcal osteomyelitis with the adjunctive use of HBO_2, probably as the result of enhanced oxygen-dependent killing mechanisms.

Fibroblasts cannot synthesize collagen or migrate to the affected area when oxygen tensions are less than 20mmHg. Elevating oxygen tensions to levels greater than 200mmHg allows a return to normal function (8). Increasing oxygen tensions with HBO_2 therapy is a means of returning fibroblastic activity to normal. Following differentiation from fibroblast-like mesenchymal cells, osteoblasts deposit a layer of coarse immature fibrillar bone. This immature

bone is then replaced by mature lamellar bone, which is functionally reconstructed by resorption and deposition by osteoclasts and osteoblasts (11).

Barth, et al demonstrated the beneficial effects of HBO_2 therapy on bone healing by showing that the metaphyseal defects in the cortex of rat femurs were healed by primary ossification when rats were treated once-a-day for 90 minutes with HBO_2 at two atmospheres (12). Vancomycin, quinolones, sulfomides, and the aminoglycoside class of antibiotics have been shown to be far less active in the hypoxic environment (13). Mader has shown that with HBO_2 therapy, the bactericidal activity of aminoglycosides is enhanced (10).

We have treated 256 cases of osteomyelitis without HBO_2 therapy by debriding the infected area with closed irrigation. We achieved good results in 226 cases (88.3%), fair results in 7 cases (2.7%), and poor results in 23 cases (9.0%). We treated 433 cases of osteomyelitis with HBO_2. Good results were obtained in 398 cases (91.9%), fair results in 10 cases (2.3%), and poor results in 25 cases (5.8%). The results of the treatment with HBO_2, therefore, were better than the treatment with non-HBO_2 ($p<0.01$) (Table 1).

The result of the Treatment for 668 Cases of Osteomyelitis

	Non-HBO (Closed Irrigation only)	HBO
Good	226(88.3%)	398(91.9%)
Fair	7(2.7%)	10(2.3%)
Poor	23(9.0%)	25(5.8%)
Total	256	433

($P<0.01$)

Table 1

In the case of H.M., a consistent discharge was present from the tibia area. A skin and bone defect near knee joint was readily observable. We treated the condition with closed irrigation suction treatment and a skin muscle graft. Then, we started HBO_2 therapy. Two months later, the wound was completely healed.

The case of F.H., the victim of a traffic accident, was very serious. One hospital treated him, but delayed union, consistent discharge, and a defect of the tibia were seen. He was sent to our hospital, but he refused admission and operation. We treated him with HBO_2 therapy only. Three months later, the discharge stopped and the bone was healed. After six months, an almost-fusion of the tibia bone was observed, without any kind of the bone graft or other operation.

Gas Gangrene

Gas gangrene is a fulminating myonecrotic infection caused by clostridial species of bacteria. Untreated, this characteristically has a rapidly fatal outcome. Brummelkamp and associates first reported the use of HBO_2 in the treatment of gas gangrene in 1961. Demello, et al reported greater survival in dogs with experimental gas gangrene when three treatment modalities were used together compared with the use of one treatment modality or in combinations of two (14). Of more than twenty exotoxins produced by six species of clostridial organisms 7 are capable of producing lethal gas gangrene in man (15). When *C. perfringens* is the offending organism, one of these, alpha toxin, is of chief clinical significance. Alpha toxin is a lecithinase C that hydrolyzes the intact lecithin molecule to produce phosphoryl chlorine and a water insoluble diglyceride. The progressive nature of gas gangrene depends on the continuous production of alpha toxin by the organism.

Demello *et al.* did a comparative study on gas gangrene in dogs of the outcomes of all combinations of HBO_2, antibiotics, and surgery. They found that when all three treatment modalities were used together, the mortality was significantly lower than when only one or two were used (16). Hill and Osterhout saw a significantly increased survival rate in mice treated with HBO_2, when compared with controls not so treated (17). Stevens found that oxygen tensions of 40mmHg suppress clostridial growth, and oxygen tensions of 80mmHg suppress toxin synthesis. The cumulative mortality of their series was approximately 25%, while the disease specific fatality rate approximates fifteen percent. When patients were started in treatment within 24 hours of the presumptive diagnosis of gas gangrene, the disease-specific fatality rate was reported as five percent (18).

We have treated 32 cases of gas gangrene. Twenty-nine (90.6%) patients had good results and 3 (9.4%) had poor outcomes. We had one amputation and two cases were fatal.

Necrotizing Fasciitis

Necrotizing fasciitis, originally called hemolytic streptococcal gangrene, Meleny's ulcer or acute dermal gangrene, is a progressive, generally rapid spreading, inflammatory process in the deep fascia with secondary necrosis of subcutaneous tissues and skin. Skin necrosis occurs due to thrombosis of subcutaneous blood vessels. The whole area may become anesthetic by necrosis of nerve fibers. Riesman reported a mortality rate of 66% in necrotizing fasciitis in those not treated with HBO_2 and 23% in HBO_2-treated cases (19). Primary and aggressive surgical debridement is the cornerstone in the management of this disease. Early and extensive incision of the skin and subcutaneous tissue, wide into healthy tissue, followed by the excision of all necrotic fasciae, nonviable skin, and subcutaneous tissue, is necessary. Antibiotic treatment has an important place in the combined management of necrotizing fasciitis, although it is adjunctive to surgery. Mader and Thom have extensively outlined the rationale for the use of adjunctive hyperbaric oxygen and the mechanisms (20, 21). The main goals are a) the improvement of tissue pO_2, b) the improvement of phagocytic function through stimulating the oxygen-dependent killing mechanisms, either directly or indirectly, and c) the diminishing of edema and improvement of circulation in affected areas. This can be roughly summarized as the stimulation of the host defense and repair mechanisms (22).

Diabetic Foot

One of the most difficult complications of diabetes is foot infection. It has been reported that of the total diabetic population requiring hospitalization, 20% are admitted for foot problems and 30% have evidence of peripheral vascular disease (23). The peripheral neuropathy associated with diabetes leads to hypesthesia, which allows the unperceived development of traumatic pedal wounds. In addition, diminished pedal pain perception allows for the development of severe infections before patient become aware of them. Ulceration can develop and become secondarily infected. Even without the development of infection, these atrophic ulcerations are difficult to heal because of continued weight bearing. The accelerated atherosclerosis of infra-inguinal arteries observed in diabetics can produce significant, asymptomatic ischemia of the foot (24).

In a large clinical series of 168 patients with grades three and four diabetic foot lesions, Davis (25) reported a 70% success rate with the combined management protocol of daily debridement, metabolic control, and daily HBO_2 for 30 to 60 days. Oriani, et al (26) reported on the effect of the HBO_2 group which consisted of 62 patients while the matched control group had eighteen patients. In the HBO_2 group, 96% of the patients healed, while 4% underwent

amputation. In the control group, 66% achieved primary healing, and 33% required amputation ($p < 0.001$). We have treated 51 cases. Primary healing occurred in 44 cases (86.3%).

Other Indications

Oxygen is necessary for bone viability, healing, and remodeling. Osteocytes have the lowest requirement for oxygen. Osteoblasts, the bone-forming cell, have an intermediate oxygen requirement. This is reflected in an eight-fold or greater increase in blood flow in healing fractures. Osteoclasts, the bone-resorbing cells, have the highest oxygen requirement. Their metabolic activity may be a hundred times as great as that of the osteocytes (27). Basset reported that multi-potential cell precursors of fibroblastic origin form bone when exposed to high oxygen tensions and compressive forces. However, when oxygen tensions were low, cartridge was formed instead (28). Many studies have shown beneficial effects of HBO_2 on the mobilization of bone precursors, osteoid formation, and fracture healing. Increased oxygen enhances bone resorption and remodeling through stimulation of the osteoclasts. HBO_2 treatment is used for delayed union of fracture, radionecrosis, and idiopathic femoral head necrosis. Hyperbaric oxygen may be beneficial, especially when used in conjunction with other orthopedic interventions, such as core decompression, bone grafting, and electrical stimulation (29).

Hyperbaric oxygen was also used for various kinds of brain and spinal cord neurosurgical pathology. The main mechanisms of the effectiveness of HBO_2 in neurological disorders are the relief of hypoxia, improvement of microcirculation, relief of cerebral edema by vasoconstrictive effect, preservation of partially damaged tissue, prevention of further progression of secondary effects of cerebral lesions, and improvement of cerebral metabolism.

Lumbar spinal stenosis is a disorder of the spinal cord caused mainly by compression. Clinical results estimated by “criteria of the result of treatment lumbar part disease” (Japanese Orthopedic Association) for 143 cases treated by HBO_2 therapy from 1995 to 1999 showed an improvement in 125 cases (87.4%).

SUMMARY

As is well known, the origins and development of hyperbaric medicine are closely tied to the history of diving medicine. Our HBO_2 studies stemming from diving medicine date back to 1972. We concentrated our early basic research on dysbaric osteonecrosis. There are now good indications that HBO_2 is helpful in a variety of orthopedic conditions. However, hyperbaric medicine in orthopedics is still relatively new and some aspects of it remain controversial.

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