HYPERBARIC OXYGEN FOR OSTEOMYELITIS AND OSTEORADIONECROSIS

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HYPERBARIC OXYGEN FOR OSTEOMYELITIS
AND OSTEORADIONECROSIS

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# TABLE OF CONTENTS

FOREWORD

EXECUTIVE SUMMARY ................................................................. i

1.0 INTRODUCTION ..................................................................... 1
   1.1 General considerations ..................................................... 1
   1.2 Local availability of HBO and recent data on its use ............... 3

2.0 METHODS ............................................................................ 4

3.0 REVIEW OF THE LITERATURE: CHRONIC OSTEOMYELITIS ...... 5
   3.1 Reviews ........................................................................... 5
   3.2 Case series ..................................................................... 7
   3.3 Trials ............................................................................. 9
   3.4 Costs ............................................................................ 11
   3.5 Summary ....................................................................... 11

4.0 REVIEW OF THE LITERATURE: OSTEORADIONECROSIS ....... 12
   4.1 Reviews ........................................................................... 12
   4.2 Case series ..................................................................... 13
   4.3 Trials ............................................................................. 13
   4.4 Summary ....................................................................... 14

5.0 CONCLUSION AND COST CONSIDERATIONS ...................... 15
   5.1 Costs ............................................................................ 15
   5.2 Conclusion ..................................................................... 16

REFERENCES .............................................................................. 18
FOREWORD

The British Columbia Office of Health Technology Assessment (BCOHTA) was established on December 1, 1990 by a grant to the University of British Columbia from the Province to promote and encourage the use of assessment research in policy and planning activities at the government level and in policy, acquisition and utilization decisions at the clinical, operations and government levels. It is important to understand that the role of the Office is to appraise the scientific evidence only, and not to be involved in actual policy development.

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EXECUTIVE SUMMARY

This Technology Assessment Report from the B.C. Office of Technology Assessment (BCOHTA) was requested by the Vancouver General Hospital (VGH) in response to suggestions by Clinical Staff that Hyperbaric Oxygen (HBO) use for chronic osteomyelitis (COM) and osteoradionecrosis (ORN) should be assessed. Thus, the VGH felt it would be useful to obtain an overview of the available scientific evidence on the efficacy and effectiveness of HBO for these two conditions.

The literature was systematically searched, as per the B.C.O.H.T.A. routine database search strategy, for the use of HBO for the two indicated conditions for the years 1988-1991. Relevant additional papers from prior years were obtained from the reference lists of the papers identified and were reviewed in depth. This process yielded approximately 40 papers on the two topics of interest.

With two exceptions, all the papers identified were either review articles, case series, case reports, or animal studies. Animal studies and case reports are not included in this assessment of the literature. Two trials, one non-randomized in COM and one randomized in ORN, were found. Most reviews comment on the lack of prospective trials, although some go to great lengths to justify the absence of trials by pointing out how difficult they would be to carry out.

The paucity of well designed clinical trials makes assessment of HBO for COM and ORN difficult. Not only is the literature limited essentially to animal studies, case reports and case series but these, although relatively large in number, tend to be by the same authors (often reporting the same data, which in turn are cited in reviews and textbooks edited by the same authors), and thus provide little more than (often repeated) anecdotal evidence.

The two controlled trials were: 1) Esterhai et. al. with 14 patients in each group (non-randomly allocated) who had uncomplicated COM which found no difference between the HBO group and the control group in length of stay, rapidity of wound repair, initial clinical outcome or recurrence rate. These negative results must be viewed with caution since the power of the study to detect meaningful differences is low; and 2) Marx et. al., on the prevention of ORN, compared HBO with prophylactic penicillin in patients requiring tooth extraction following radiation of the mandible: 37 patients were randomly assigned to each group – there was a significant increase in socket wound healing at six months in the HBO group.
Data from case series is difficult to interpret because of poor descriptions of methodology (e.g. patient selection) and mixed results with success rates ranging from 50% to 100% both with and without HBO.

The Annual Report from the Division Head for HBO at the VGH was also reviewed. It provides utilization data for the year 1990-91, allowing an assessment of the relative importance of COM and ORN in terms of the use of the HBO chamber in BC. These two conditions make up only 20% of the case load for the year in question. The VGH Annual Report makes no comment on unmet need. Moreover, cost data were provided and these are discussed in the report.

In summary, for COM there is neither evidence that HBO clearly makes a difference in the outcome nor support to expand the use of HBO, although, as noted before, the literature is so poor that a definitive assessment is impossible. There is certainly no clear evidence that expanded use of HBO for COM is warranted, or indeed required. With regard to ORN, although the data are equally poor, the complex nature of the condition, the results reported in the case series, and the single randomized trial suggest that there may be stronger indications for HBO use than is the case with COM, although the trial was limited to the evaluation of prophylactic HBO in the context of tooth extraction for the prevention of ORN.

One conclusion is clear: all experts agree and the data support the fact that successful management of COM relies first on adequate surgical and antibiotic treatment. HBO is regarded by virtually all authors as an adjunct to this primary management. For ORN, differential success with and without HBO appears to be greater and although primary management is surgery and appropriate antibiotics, the complexity of the tissue injury in ORN (particularly of the mandible the site most often studied) suggests that HBO may be efficacious and effective. However, as noted above, the lack of evidence based on well designed trials makes this, at best, a tentative, conclusion.

The issue of the cost of managing COM and ORN and the components of these costs attributable to HBO is complex. On the one hand, HBO use for several conditions (e.g. decompression sickness, gas gangrene, etc.) is unquestioned so that operating costs, although not insignificant (on the order of $300,000), are justified by more than simply the treatment of COM and ORN. The specific overall management costs for COM and ORN are high (approximately $100,000 – $250,000), but estimates suggest that the subset of costs associated with HBO account for only 5% of the total cost per case. On the other hand, the HBO physician costs specifically for COM and ORN are not trivial (ranging between $5,000 to $14,000 for the average course of HBO treatment). Thus, while the impact of expanding the use of HBO for COM and ORN has definite cost implications, these
are relatively small compared with the basic and substantial total management cost associated with these conditions (including multiple hospitalization, multiple surgery, antibiotics, etc.)

Conclusions regarding the value of HBO, in terms of costs versus benefits, are currently not possible since these relationships for COM and ORN are complex and no formal economic evaluations were found in the literature.
1.0 INTRODUCTION

The first use of hyperbaric oxygen therapy (HBO) occurred in 1860 in North America when a chamber for increasing oxygen pressure was built in Oshawa Ontario, most likely for the treatment of decompression sickness (1). The first International Conference on the use of HBO was held a century later, in 1963, with eight subsequent conferences up to 1987 (including one in Vancouver in 1973). Over the last thirty years interest in, and knowledge about this form of therapeutic intervention has increased geometrically. Indeed, the HANDBOOK OF HYPERBARIC OXYGEN THERAPY published in 1988 cites about 1550 references (2). A recent textbook, "PROBLEM WOUNDS, THE ROLE OF OXYGEN", edited by Davis and Hunt, also provides a comprehensive overview of the use of HBO (3). This paper reviews the evidence for the use of HBO in chronic osteomyelitis (COM), also known as refractory osteomyelitis, and osteoradionecrosis (ORN), a common condition seen after radiation therapy, especially of the mandible. The pathophysiology of these conditions is similar in that both involve significant bone infection associated with severe tissue hypoxia, hence the use of HBO in their management.

1.1 General considerations

HBO has been proposed in the management of infection generally (except viral infections) and COM and ORN specifically because oxygen (O₂) has antibiotic properties (2,3). These are of two types: 1) leukocytes utilize hydrogen peroxide, superoxide, and other reduced O₂ components as part of their mechanism of bactericidal action; and 2) O₂ itself inhibits both gram + and gram – bacterial growth. The latter effect is of less importance since it is variable depending on the organism, the amount of pressure used, and other conditions. For example, aerobic bacteria show a biphasic response to O₂ with growth enhancement at 0.6-1.3 ATA, but growth inhibition above 1.3 ATA. Moreover, the killing action is time dependent. In addition, O₂ is also an indiscriminate killer of cells, hence its' toxicity for host cells.

The proposed mechanisms of HBO action are based on the fact that both COM and ORN are anoxic infections with tissue pO₂ usually less than 30mmHg (2,3). Thus, indirect action through leukocyte function is of primary importance; direct action on bacteria is said not to be a factor since HBO used prophylactically to prevent infection does not seem to work (2,3). In addition, optimal oxygenation of the infected bone enhances osteogenesis, collagen formation and neovascularization, which are critical in filling dead space and enhancing the entry of leukocytes and antibiotics into affected bone (2,3).
With regard to ORN, radiation therapy not only produces the direct effects of disrupting mitotic activity (the effect more pronounced in proportion to the mitotic activity of the target cells and surrounding tissue), but there is also a late effect: obliterative endarteritis which in turn produces profound hypoxia. HBO appears to work by two mechanisms. First by counteracting the anoxic effects of obliterative endarteritis (with HBO, although it produces vasoconstriction, pO₂ levels actually increase and initial vasoconstriction is followed by vasodilatation); and second, prolonged treatment with HBO produces neovascularization and collagen formation, the same beneficial effect seen in COM. Although COM and ORN share several pathogenic mechanisms, ORN of the mandible unlike COM has a continuous focus of bacteria (the teeth and gums). This difference is the basis for evidence to suggest that HBO is useful prophylactically in ORN of the mandible (see below).

HBO exposure is measured both in "dives", a term derived from its use in decompression sickness, the pressure related to each dive, and the percent oxygen (% O₂) used. Pressure is measured in atmospheres absolute (ATA). One ATA is equivalent to the air pressure at sea level (14.7 psi). During a "dive" the pressure gauge is set to 0, and thus a chamber pressurized to 14.7 psi represents the pressure felt at 33 feet under sea level or 2 ATA; similarly a 3 ATA "dive" represents the pressure felt at 66 feet below sea level. HBO is said to be well tolerated at 1.5-2.0 ATA (for up to 40-90 minutes), but tolerance is dependent on the (% O₂) used. Often in therapeutic situations 100% O₂ is used. However, O₂ is a toxic agent for multiple organs. Its toxic effects appear to be related to Mg++ and Ca++ effects since Mg++ and Ca++ blockers protect against HBO induced cellular injury. In addition, Vitamin E is often used prior to HBO, presumably to reduce the tissue damage by free oxygen radicals.

Specific toxic reactions to HBO include, oxygen seizures, otic barotrauma, pulmonary barotrauma, and myopia. Moreover, there is a long list of contraindications to its use, including: pneumothorax, upper respiratory tract infection, seizure disorders, emphysema, uncontrolled high fever, viral infections, malignant disease, pregnancy, optic neuritis, and others. It is useful to be aware of these since patients with COM or ORN may have any of these conditions.

The indications for use of HBO include: decompression sickness (HBO has been the mainstay of therapy for this condition for many years); burns; air embolism; carbon monoxide (CO), hydrogen sulfide (H₂S) and methane (CH₄) poisoning; as well as COM and ORN. However, as Jacobson et. al. note in their 1965 historical perspective of HBO (1),

"If this form of therapy is to achieve a worthwhile place in the medical armamentarium, it can only do so on a firm basis of accurate physiological data on the effect of both
pressure and oxygen obtained in experiments, as well controlled as clinical medicine will permit." (emphasis ours)

The purpose of this review is to examine the recent literature on HBO for COM and ORN to determine if the evidence is sufficient to: 1) support its use generally; and 2) to assist decision making regarding its use at VGH for these conditions.

1.2 Local availability of HBO and recent data on its use

In order to put the discussion of the literature in perspective, it is of importance to note that the Vancouver General Hospital has one of the two HBO chambers in the province (set up in 1966), and is thus a provincial resource.

Utilization of the VGH unit, over time and for 1990-91, has recently been summarized(4). There has been a steady increase in use since the chamber was installed: from less than 10 patients in 1967 to between 25-40 patients from 1968-77, to less than 10 in 1978 (due to refitting the chamber in that year), with a subsequent steady increase up to about 86 patients in 1990-91. For the year 1990-91, most patients were treated for osteonecrosis unrelated to radiation therapy-21, decompression sickness-17, CO poisoning-15, ORN-12, delayed wound healing-8, COM-5 and other conditions-8 (e.g. air embolism, gas gangrene, etc.). Thus, only 17/86 (20%) of patients had conditions of direct relevance to this report.

In 1990-91, the chamber operated at 80% capacity, with 46 outpatients and 40 inpatients, 48 elective and 38 emergency patients, for a total of 1348 treatments (an average of 16 per patient). No data are provided regarding ranges or number of treatments by diagnosis, age, sex, etc. There were 477 treatment dives (about 5.5 per patient, but again no breakdown by relevant variables), 1109 chamber hours, and an average of 2.8 patients per dive overall (3.2 on elective dives). Estimates of Unit operational costs were reported to be $300,000 per year of which $30,000 were recovered from the Workers' Compensation Board (WCB). These costs do not include physician fees. Thus the average operating cost per patient is about $3450, while the average cost per dive is $620, and the average cost per chamber hour (presumably chamber treatment hour) is $270. These are, of course, average costs and thus do not reflect variation across treatment groups which undoubtedly exists. Moreover, although on average about 10% of these costs are covered by the WCB, the proportion recovered may differ widely depending on

* This point is emphasized because many authors feel that randomized controlled trials are not possible to carry out for COM or ORN.

** The other chamber is at the Canadian Forces base at Esquimalt.
the patient's diagnosis, and thus treatment needs, in terms of numbers of dives and total hours for a course of HBO therapy. One issue not clear from these data is whether the chamber costs vary by the length or depth of the dive; i.e., by ATA into which the patient is placed. Physician fees do, however, depend both on the length of the "dive" and whether the physician is in the chamber or monitoring the patient from outside the chamber (the fees are higher for inside chamber time). The relevance of these variables to costs are discussed below.

The VGH data fail to provide any estimates of denominators. Thus rates of use by geographic region, age, injury or illness type (and therefore costing the utilization of the HBO chamber for COM and ORN) is difficult and can only be based on literature estimates of the number of dives and/or hours needed to treat these specific conditions. In addition, total management costs for COM or ORN also include hospitalization, surgery, antibiotics, and other direct patient care costs (not to mention indirect costs). Thus the figures cited in the VGH report are only a fraction of overall patient management costs.

2.0 METHODS

The standard B.C.O.H.T.A. literature search routine was undertaken for the years 1988-91 using the National Library of Medicine database (MEDLINE), and the Health Planning and Administration database (HEALTH), using the key words HBO, COM, ORN, bone infection, bone necrosis, infection, and necrosis. In addition, the relevant sections of the Handbook (2) and Problem Wounds (3) were reviewed to identify additional relevant citations published prior to 1988. This process yielded a total of 61 papers which were sorted regarding type of study: review articles; basic science and animal studies (these were excluded from our review); single case reports (also excluded from this review); case series (more than one patient); trials (controlled or uncontrolled); and randomized controlled trials (RCTs). Twenty papers or abstracts met the selection criteria (although not all papers were available locally or through inter-library loan), and thus 14 papers were available for in-depth review, and six abstracts were assessed. The 41 papers and abstracts not discussed in this review, aside from being case reports and animal studies, reported data on clinical conditions other than COM and ORN such as: soft tissue infections; pulmonary infections; air embolism; decompression; hematuria; psychological effects; nursing issues; and effects on physiological systems such as leukocytes in the immune system.

Of the 20 recent papers or abstracts reviewed here: five were review articles; two were review articles and case series; four were case series; and two were trials, one specifically on HBO in
COM, and one on the use of penicillin versus HBO in the management of ORN. Overall, 10 papers and four abstracts on HBO in COM, and four papers and two abstracts on ORN were assessed. Thus, although not an exhaustive review of all possible citations on either COM or ORN, the papers reviewed here are representative of the consensus among researchers in the field. Notwithstanding the approach taken for this paper, several case series published prior to 1988 (and thus not included in our search process) are briefly cited to enable the reader to get a more complete "feel" for the quality of this literature and the basis upon which clinical impressions of effectiveness have been formed.

3.0 REVIEW OF THE LITERATURE: CHRONIC OSTEOMYELITIS

Although HBO has been promoted as an intervention in the management of this condition, the mainstay of therapy is surgery (drainage, removal of foreign bodies, debridement and removal of dead spaces), and appropriate antibiotics. Proponents of its use therefore view HBO as an adjunct to the primary therapy described above. Since surgical and antibiotic therapy is reported to be effective in 70-80% of patients with osteomyelitis (2,3), HBO is seen as specifically useful in what is termed "refractory or chronic" osteomyelitis (COM). However, the proportion of these patients who might benefit from HBO is not clear. Since none of the clinicians currently actively involved in research on HBO consider it to be other than an adjunct to standard therapy, the key question for this review is whether HBO produces significant clinical improvement compared with standard therapy. While there are considerable animal and basic science data to suggest a positive therapeutic effect, studies in humans are less numerous and, with the exceptions noted above, are generally restricted to case reports, case series, or reviews.

3.1 Reviews

The four main recent reviews all refer to numerous case reports, case series and animal studies and all conclude that HBO is a useful adjunct to standard therapy (5-8). Being reviews, however, little is to be gained by describing them in detail since they provide no primary data. While the consistency of opinion is clear, it should be noted that three of the four reviews (5,7,8) are from the same institution (the University of Texas Medical Branch at Galveston) and, not surprisingly, these three reviews have at least two authors in common, thus the independence of opinion is rather limited. The fourth review (6) is from the University of Chicago. All of the reviews note

* In general, the literature on this topic is highly repetitive and is, as can be seen in the reference list, limited to relatively few authors (who tend to cite and recite their own work or the work of colleagues). On occasion, different papers which are supposed to be original articles, use previously published data.
the lack of randomized controlled trials of HBO. Despite this, the preface to a recent textbook (3) makes the following statement:

"There is no longer any question as to whether or not elevation of problem wound oxygen is efficacious - it is. Remaining questions are whether or not perfusion of a given wound is adequate to achieve therapeutic PO2 within safe limits of oxygen breathing and then to determine the optimal dose."

Despite the optimism of this statement, it would appear that even advocates of HBO therapy are still uncertain about the effectiveness of this intervention, and given the literature available such uncertainty is well founded.

Davis and Heckman (5), review the animal and laboratory evidence for the biological plausibility of HBO management of COM. They also review a number of case series, noting in the first section "Clinical Series" that: "The one common feature to all (emphasis theirs) treatment modalities for osteomyelitis is the absence of valid human prospective controlled clinical trials". They cite several case series using therapeutic interventions without HBO reporting success rates of 80% or more which provide useful background "control" data for the HBO papers (9-14).

Thus Kelly (9) for example, in a study of closed irrigation and suction, compared 40 patients who had this modality with 35 who did not. At 2-8 year follow up the closed irrigation and suction group had an 80% success rate compared to 57% in the control group. Davis and Heckman (5), although providing few details about this study, claim that it has many methodological flaws which, unfortunately, they do not detail. Similarly, Papineau (10) reported on the use of open bone excisions and bone grafting in 39 patients and showed a 93% success rate. Other non-HBO case series for COM (11-14); -using muscle flap transfer and antibiotics, showed results on the order of 90 to 100%. Case series of HBO cited by Davis and Heckman (5) will be discussed below.

Grim et. al. (6) provide a very general overview of HBO therapy in many conditions but make reference to only three papers regarding COM: one is a case report, one another review and one is a case series discussed below.

Mader et. al. (7) review the experimental literature and report on their own experimental work in rabbits. In addition, they cite three additional case series which are briefly considered below. They also discuss and criticize the only trial in the literature.
Finally, Calhoun et. al. (8) describe the same case series as the other reviews and cite but, curiously, do not comment on the only trial to date.

3.2 Case series

Slack et. al. (15) treated five COM patients with HBO at 2 ATA all of whom showed clinical improvement. However, in the two review articles citing this paper, no details on subject selection, number of treatments, or time to clinical improvement are provided.

Perrins et. al. (16) treated 24 patients with COM and sinus tracts in whom previous procedures (sequestration, antibiotics, and marsupialization) failed to resolve the condition. However, with HBO and antibiotics, 17/24 (71%) of these cases responded; four cases (16.6%) showed reduced sinus tract drainage; and three patients failed to respond at all (12.5%). Again, no details are provided regarding patient selection (other than they all failed to respond to conventional therapy), intensity of HBO treatment, or other patient characteristics.

Dupenbusch et. al. (17), in a larger case series, reported on 50 patients who had been unresponsive to antibiotics and surgery. With HBO therapy, 71% reported that their COM had completely healed and the remaining 29% reported improvement in symptoms. Details regarding HBO treatment are not described nor is prior therapy described in detail.

Davis and Hunt (18) reviewed 70 patients with chronic osteomyelitis in various sites (spine, pelvis, chest wall, skull, etc.) unresponsive to the usual therapy and found an average of 62% responded to HBO; the condition was arrested (a rather ambiguous term) and remained so at 5 year follow-up. However, the proportion of patients whose disease was arrested ranged widely from 37% with COM of the hip to 100% for the small number of patients with COM of the humerus, hand, and frontal sinus. The most common site, the tibia (26/70 patients-37%), had a success rate of 73%. The femur, the next most common site (15/70-21%), was reported to have a success rate of only 40%.

Further analysis presented by these authors (19), involving an additional 28 cases of COM of various sites and at least two years follow-up (hence the figure of 98 cases cited in many references), revealed a success rate of 71%.

Morrey et. al. (20) reported a case series of 40 patients and long term follow-up. All the patients had COM for at least 6 months, had at least one (often many) surgical procedure(s) prior to HBO, and had received parenteral antibiotics. The average duration of COM was 30 months (range 6
months to 23 years). All patients had contiguous focus, as opposed to hematogenous, disease. Treatment, in addition to HBO (which was used in all patients), included antibiotics and careful surgical debridement (all patients), autogenous bone grafting in 7 patients and soft tissue grafts in 7 patients. Patients were followed for a mean period of 23 months (range 21-53 months) during which 34 (85%) responded and remained clinically free of disease and 6 (15%) failed to respond or had a recurrence (mean time to recurrence was 4.3 months (range 0-12 months)). These patients received an average of 42 HBO treatments (range 9-208). The average number of treatments in patients without recurrence was 39 (range 9-208), while for patients with recurrence it was 78 (range 29-153). Recurrence rate was not correlated with the number of treatments, with the type of organism, or with the duration of COM prior to HBO treatment. Further analysis presented by these authors (20) with extended follow-up (average 8.4 years, range 7.5 - 10.5 years) revealed 4 additional relapses giving an overall success rate of 75%.

Eltorai (21) reported on the treatment of 44 patients, with HBO at 2 ATA for an average number of 50 sessions, who had COM resulting from spinal cord injuries, and pressure sores around the pelvis. Of these patients 30 (68%) were cured, although the length of time to resolution of the COM and the correlation with the number of treatments was not described.

Davis et. al (22) reported the results of HBO treatment in 38 patients followed for an average of 34 months (range 24 to 59 months) and enrolled between 1 November 1979 to November 1 1982 (reinforcing the relative rarity of this condition). All patients had non-hematogeneous COM and were treated with careful surgical debridement and long term parenteral antibiotics based on organism sensitivities. The mean duration of COM prior to enrollment was 8.9 years and many patients had multiple surgical procedures. HBO was initiated on the first post-operative day at 2.4 ATA per day with 100% humidified O2 (35 l/min) for three 30 minute periods each followed by 10 minutes of air breathing. The mean number of daily treatments was 48 (range 8-103) and treatment was stopped when the bone was fully covered by healthy vascular tissue. Three patients required tympanostomy tubes to prevent otic barotrauma and two patients had transient oxygen induced myopia. Thirty-four of 38 patients (90%) became and remained clinically free of COM over an average of 34 months. All the HBO failures had significant infections: three with Pseudomonas Aerogenosia and one with E. coli. These data are consistent with clinical experience that gram negative COM is more refractory to treatment with longer treatment periods and more surgical procedures. It is useful to note that, despite these apparently positive results, the authors were cautious in interpreting their results:

"We wish to emphasize that the therapy with hyperbaric oxygen cannot be given sole credit for the results in our patients. The daily debridement and meticulous care of the
wound by the experienced physician and the use of culture specific antibiotics played a large role in prolonging the disease-free interval in our patients. Finally, in spite of these encouraging results and similarly encouraging results in a previous series of patients, we are careful not to regard our patients as cured of the chronic osteomyelitis. A much longer follow-up period than that used in the present report is essential before a true rate of cure can be determined. We believe that it was the combined treatment protocol, not any one of its components, that was responsible for the reported success (emphasis mine)."

Hui-Chieh Lee et al. (23), in the largest case series of HBO patients published to date (N=1288), found over a 12 year period that for COM (not well defined) the cure rate was 59% with improvement (undefined) in a further 37.3%. However, in their series, COM accounted for only 83 of the 1288 patients (6.4%, not unlike the proportion of HBO patients treated for COM at the VGH for fiscal 1990-91- 5.8%); no cases of ORN were included in the series. The failure rate, including death, was 3.7% which was generally lower than for the other conditions in the series: like gas gangrene (22%); chronic skin ulcer (10%); and burn injury (23.9%).

In general, the Handbook (2), states that the overall success rate of HBO therapy for COM across various studies (not referenced) was between 68-85%. The range of success rates for the clinical series reported here was between 50% (Davis (18)) and 100% (Slack(15)). However, as noted above, although many of the patients in these case series served as their own controls (given their previous treatment history), it is also true that the success rate in patients treated with other modalities (mainly good surgical debridement and appropriate antibiotics) were on the same order of magnitude (9-14). Thus, without valid controls, the issue of whether HBO provides any benefit beyond clearly agreed upon primary surgical and antibiotic therapy is left unresolved by these papers since virtually all of these data are derived from weak study designs. The remarks by Davis et al. (quoted above) are therefore particularly pertinent to the role of HBO in the successful management of COM.

3.3 Trials

In terms of COM, a single trial is of interest. The study by Esterhai et al. (24) was a case-matched trial of 28 consecutive patients with COM uncomplicated by fracture nonunion, septic arthritis, total joint arthroplasty, or major systemic disease (tumors, immune deficiency, renal or hepatic disease, etc.) were treated from January 1980 through December 1985. Patients were classified using one of the several current staging systems (Cierny, Mader, and Penninck (25))
and were matched by stage, although how this was done is not discussed. Staging and matching were carried out after the initial debridement (and presumably after initiation of antibiotic therapy—although this is not explicitly stated). HBO consisted of 100% O$_2$, at 2 ATA, for one 2 hour dive per day, 6 dives per week, in the 14 HBO patients. The other 14 patients received no HBO. Outcomes included: length of hospitalization; rapidity of open wound soft tissue granulation repair; the initial clinical outcome (whatever that may mean); and the recurrence of infection. No patient was lost to follow-up and the patients were followed monthly for the first three months and evaluated at 3 and 6 months. Of the 28 patients, 24 (86%) demonstrated healing at six months, with no difference between the HBO and non-HBO group: three of the treatment failures were in the HBO group and one failure occurred in the non-HBO group. All failures were reported to have occurred because of insufficient surgical debridement: two patients refused a second surgical attempt; one patient had very extensive injuries; and one patient (who also had a tumor) refused amputation and preferred to live with his osteomyelitis. The mean length of hospitalization for the HBO group was 54 days (range 41-143) compared to the non-HBO group of 47 days (range 10-66). However, it should be noted that three patients in the non-HBO group went home on parenteral antibiotics quite early, at 10, 16, and 24 days respectively, thus skewing the length of stay data. Their removal increased the mean length of stay for the non-HBO group to 51 days. The large difference in the upper end of the range for length of stay, 66 vs. 143 days, suggests either a poor (biased) match or a possible untoward effect of HBO or both. There were "significant complications" for two extremely heavy individuals (330 and 250 pounds) but their treatment group was not specified. Three recurrences were reported after an average follow-up of 41.1 months (range 11-77 months): two in the HBO group and one in the non-HBO group. Thus, in the HBO group, a total of five patients ultimately failed (35%) while in the non-HBO group only 2 (14%) failed: Fischer's exact test, p = .38. It is not clear what this means since the protocol as initially described does not indicate continued follow-up past 6 months for the purpose of evaluation. Thus, the late follow-up results reported by the authors may represent a convenience sample. The authors concluded that HBO did not offer any significant additional benefit over standard therapy.

Despite many shortcomings, this is the only trial to date directly related to the management of COM with HBO. Thus, it is of more than passing interest that the reviews briefly discussed above, published after this study (the fourth was published prior to it in 1984) either: 1) give this trial only a brief mention and essentially ignore it (6); or criticize it (7); or ignore it completely (8). Indeed, Mader et. al. (7) raise the issue that, in the four failures, all the patients refused second surgical interventions (either further debridement or amputation) concluding that all four were doomed to fail anyway which begs the question since three of the failures were in the HBO.
group. Mader et. al. also complain that the recurrences (two which were in HBO treated patients) were due to patient refusal of further surgical intervention after HBO. Thus, they claim the trial to be inconclusive because the patients were non-compliant. However, one could suggest that HBO should reduce the need for second or third debridements (and recurrences). Moreover, the Esterhai et. al. trial found that the failure rate in the HBO group was just over double that in the control group, suggesting a potentially clinically significant negative effect of HBO in these patients. Thus the failure to demonstrate any statistically significant difference (even in the "wrong" direction) between HBO and control groups was not because of bias, but because of its' low power.

3.4 Costs

In terms of costs, Davis & Heckman (5) cite an example of a patient with COM whose total management costs were $240,000 over a 7 year period. Of this total cost, they estimated that HBO costs added an average of $11,600, based on their own experience. HBO costs, however, varied across studies with some estimates ranging from $10,000 to $12,500 or about 5% of overall management costs.

3.5 Summary

In summary, case series data all report fairly high recovery rates of COM with the use of HBO as an adjunct to standard therapy, and the only trial in a small number of patients (n=28) showed no beneficial (and possibly a deleterious) effect. Thus one is left with conflicting data regarding the efficacy and effectiveness of this intervention and little can be concluded until larger trials are undertaken. Moreover, COM would appear, fortunately, to be a fairly rare phenomenon based both on VGH and Chinese data. Since success rates (whether measured in cures or arrested disease) are highly variable and do not seem to be consistently higher with HBO than without it, and given that the expense of HBO has been estimated by some authors to be as high as $12,500 (whether this includes all chamber and physician costs or even the total HBO costs for a complete course of therapy which may occur intermittently over many months is not clear), HBO may not provide value for money in the management of COM. More compelling evidence of its effectiveness and greater understanding of its costs is needed for informed policy decisions.
4.0 REVIEW OF THE LITERATURE: OSTEO RADIONECROSIS

ORN is a complex clinical entity involving bone, skin and teeth. As noted above, radiation therapy for cancer produces significant necrosis and resultant hypoxia. Bone, because it is a continuously growing tissue, is particularly susceptible to radiation injury. The mandible, because of its idiosyncratic blood supply and its particular proximity to potentially pathogenic bacteria (i.e. the teeth and gums the integrity of which is compromised by the cancer being treated), is especially sensitive (2,3). Thus the literature available for review or cited either in the Handbook (2) or Davis and Hunt (3) refers almost exclusively to ORN of the mandible. These are mostly basic science or animal studies and case reports (excluded from consideration), and case series. A single randomized controlled trial on the effect of HBO vs. penicillin in the prevention of post-radiation osteonecrosis in the context of tooth extraction was reviewed.

4.1 Reviews

Myers and Marx (26) provide the most recent comprehensive discussion of the pathophysiological and clinical aspects of ORN. They cite several early studies in which HBO was used without adequate surgical management demonstrating that HBO alone was of little therapeutic value. In the late 1970's the basic pathophysiological problem of hypoxia was clarified and led to the same type of management approach used in COM: good surgical care, appropriate antibiotics, and HBO as an adjunct maneuver. This reference, essentially a review, (much of it of Marx's own work) provides little detail on the selection of patients or other methodological issues. Considerable space is devoted to the specifics of HBO treatment such as the management protocol developed by Marx for the several stages of ORN (Stage I, Stage II, Stage III, and Stage IIIIR). It is claimed that ORN was resolved in all 268 patients (38 in Stage I, 48 in Stage II, 182 in Stage III). In Stage I, the HBO treatment consisted of 40 dives at 2.4 ATA for 90 minutes each. If there was insufficient resolution, patients were considered to be in Stage II and given an additional 10 dives and if there was still no resolution patients were considered to be in Stage III and given a further 10 dives. Stage IIIIR patients were those who, following resection and adjunct HBO, were given more radiation. Resolution and cost data are provided for this large case series. Among the non-HBO patients (N=65) the average one-year cost was $31,000 with total average costs of $104,000 and a resolution rate of 8%. In contrast, among the 51 patients with HBO without surgery, the mean one-year cost was $20,000 and the mean total cost was $82,000, with a resolution rate of 17%. For the Marx protocol 130 patients had a mean
one-year cost of $35,000 and a mean total cost of $35,000 with a 100% resolution rate. All costs were estimated using 1985 dollars. Whether these costs include physician fees is not clear.

Del Core et.al. (27) have written a recent review (in Italian), but it adds little to the information already provided.

### 4.2 Case Series

Other case series reviewed or cited by Myers and Marx, and Marx and Johnson (28), report essentially the same results and will only be mentioned briefly.

Hart and Strauss (29) reported a large series (N=378) in 1986, with 336 patients completing HBO treatment and receiving 2 ATA for two hours daily (outpatients) or 1.5 hours per day (inpatients) for a total of approximately 120 hours. HBO was started no sooner than 2 months following radiation because of known complications with early HBO. The overall success rate is not reported in the Handbook but data are provided on the 235 patients with mandibular ORN which accounted for 62.2% of all the patients in this series. Of these 235 patients, 206 completed HBO treatment and 72% were said to have "excellent results", 10% "good results", 15% "a fair response", and 3% were "failures". How these outcomes were defined is not stated. Similarly, Mainous et. al. (30) reported on 11 cases of mandibular ORN and 22 cases of mandibular COM all of which were said to have healed completely. No specifics are provided regarding treatment regimen, patient selection, blindness, etc. Finally, Tobey et. al (31) reported in 1977 that 2 ATA appeared to be more effective in mandibular ORN than 1.2 ATA but no specifics are provided. Other case series report essentially the same results (32-35).

### 4.3 Trials

Marx et. al. (36), report the only randomized controlled trial of patients with ORN. There were 74 "high risk irradiated patients" requiring dental surgery which, as noted above, is a complicating factor in ORN of the mandible. The focus of this study was on the prevention of ORN and the contrast was between penicillin and HBO. The results revealed that in the penicillin control group, 11 patients (29%) developed ORN, while in the HBO group only 2 patients (5.4%) developed ORN. However, although this was a randomized trial it was not made clear whether the observers were blinded. As well, the exclusion criteria were severe (e.g. no significant co-morbidity etc.), which reduces generalizability.
Myers and Marx also cite an early study by Greenwood and Gilchrist (37) which was said to be a randomized trial of 104 patients with ORN who received 6400 Grays. The treatment group was given HBO at 2.4 ATA for 90 minutes daily for twenty days compared with a control group which received only air. The success rate in the HBO group was 92% (with a complication rate of 11%) compared to a non HBO group success rate of 66% (with a complication rate of 26%). No comments are made regarding the methodology employed (how patients were randomized, whether the groups were comparable at baseline or whether blinded assessment was used, etc.). These results seem impressive with a relative increase in success of almost 40% (an absolute difference of 26%) but no statistical assessment is reported. Assuming an equal numbers of patients in each group (N=52), the power may have been limited. Unfortunately, the reference cited by Myers and Marx is not a randomized controlled trial but a case series of 4 patients with additional animal data. Further searches have failed to find the randomized controlled trial of 104 patients they describe*.

4.4 Summary

In summary, HBO for ORN of the mandible would seem to have some support, particularly as an adjunct to surgery post irradiation of the mandible. However, the single controlled trial is small although its focus is on an important aspect of this disease: the prevention of ORN. Data from case series, although roughly consistent with regard to success rates, are poorly described in terms of methodology. Moreover, it is clear that for ORN of the mandible (and perhaps other sites) costs of HBO are substantial, although according to Myers and Marx (26), the costs are less expensive than alternative therapeutic regimens. Given the complexity of post radiation ORN from a physiological and clinical perspective, and since there would seem to be little else one can offer the patient, HBO may very well be a useful adjunct in this situation. However, as noted above, the costs are not trivial, even if less than the alternatives, and further research providing appropriate comparisons of treatment with and without HBO should be undertaken in order to provide more conclusive evidence than is available to date.

* In addition, the BCOHTA has contacted Marx to obtain the correct reference, but he has been unable to locate it, even after discussion with Myers.
5.0 CONCLUSIONS AND COST CONSIDERATIONS

COM and ORN are infrequent but difficult clinical conditions to manage. The literature reviewed (mostly case series in humans) suggests that HBO is a useful adjunct to sound surgical and antibiotic therapy. However, the overall failure rate in COM patients with HBO in the only trial to date was twice the failure rate in those without HBO. Moreover, success rates in case series with and without HBO were quite variable and on the same order of magnitude.

Although the evidence may be more convincing for ORN, it is still far from satisfactory. Data from the VGH indicate that local costs are far lower than those reported by Myers and Marx (26) (but the former do not include physician fees or other costs of care-only HBO chamber costs (see below)). Since the proportion of cases seen at the VGH for COM and ORN account for only 20% of all patients treated (at least in fiscal 1990-91), and although it is not clear how representative these utilization data are in terms of annual case mix over the last several years, it would seem that HBO for these conditions represents a relatively marginal cost.

There remains the uncertainty of whether HBO does more good than harm or significantly improves patient outcomes. Thus, the data at this stage are insufficient to provide clear directions for policy. Given the insufficient data regarding COM, it is possible that little is to be gained by expanding the utilization of the VGH chamber to include more cases. Indeed, if the 1991 data are representative of provincial need (and no argument is put forward by the Division Head that there is unmet need), there may be no unmet need. Conversely, since there are several other conditions for which HBO has been shown effective and is indeed the accepted treatment of choice, and given the substantial capital investment, it seems clear that the chamber at the VGH should continue to operate, and that small changes in the number of cases of COM either up or down would have a marginal effect on hospital costs although the effect on physician costs would be more dramatic.

The situation regarding ORN is less ambiguous but the fact remains that for both conditions population based data of potential provincial caseloads are currently unavailable, thus potential utilization rates are unknown.

5.1 Costs

The issue of costs for the management of these two conditions although hard to estimate warrants further discussion. As noted above, the costs identified in the VGH report are for the operation
of the HBO chamber only and do not include the costs of other management components such as surgery, antibiotics, general hospital care, diagnostic tests (e.g. CT scans) etc. In addition, physician costs were not included. Fees (according to the current BCMA fee schedule, p. 23) are $65.89 for the first hour and $33.86 for each additional fifteen minutes if the physician is inside the chamber, and $44.86 for the first 30 minutes and $23.86 for each additional 15 minutes if the physician is outside the chamber. In the Esterhai et. al. trial (23), the HBO group received one dive per day of two hours duration, six dives per week. Although the total number of weeks is not given, the physician fees for a week of therapy in BC would have be as high as $1178.58 if the physician was inside the chamber, assuming for each day’s dive the first hour was billed at the first hour rate and the second hour at the 15 minute rate x 4, or as low as $1110.24 if the physician was outside the chamber. According to Davis and Heckman (5), the average number of treatments for COM is between 30 and 60 (i.e. 5-12 weeks) depending on the rapidity of response, thus the total physician costs per patient would range between $5891 and $14,143 using inside chamber fees. However, as noted above, the number of treatment sessions reported in the literature may be much higher so that the figures estimated here may be conservative and, as reported in the literature, cost data may range widely.

With regard to ORN, Marx and Johnson (27) report that with appropriate staging the minimal cost would be for stage I patients who require at least of 30 dives (90 minutes a dive) at an approximate HBO cost of at least $4000 for these patients with the best prognosis.

While it is noted by many authors that HBO treatment may be carried out on an outpatient basis, thus shortening hospital length of stay and thereby reducing costs, it is also clear that the overall costs of managing patients with COM or ORN are not trivial and much higher than the average fixed chamber costs calculated from the VGH data. These estimates clearly do not represent a formal cost analysis but give a rough idea of what the minimal management costs of these patients are likely to be. A thorough cost analysis should be undertaken since, despite the suggestion of significant benefit in numerous case series, effectiveness data are poor and costs are high.

5.2 Conclusion

Thus, it is concluded that until a more convincing case can be made both for efficacy and effectiveness, and overall provincial rates of these two conditions is clarified, expanded utilization of HBO for COM (and probably also for ORN) is unwarranted. The uncertainty regarding the recent data on effectiveness might even suggest that current utilization may be of
little value for these conditions and should be discouraged, although the overall cost savings
associated with a reduction of such utilization are likely to be marginal (except for physician
fees) given the small number of cases, high fixed chamber operating costs, and the utility of
HBO for other conditions. However, the costing data provided in the VGH report are insufficient
to obtain a clear picture of the total costs of treating COM or ORN. Notwithstanding this lack of
data, evidence from the literature suggests that total management costs are substantial, possibly
as high as $250,000 to $300,000 per patient with COM (the higher figure for patients with
ORN), with 10% of these figures representing HBO costs. Thus there is an urgent need for data
to support, clearly and unambiguously, this therapeutic modality for these conditions.

What is perhaps most striking (and sobering) about the evaluation of HBO is that after 30 years
of intensive research including several thousand published papers, at least two decades of
symposia of various kinds, and development of unquestioned clinical expertise by a number of
key groups, the efficacy and effectiveness of this therapeutic intervention remains unclear. Only
the fact that it is an adjunct to other forms of management is unambiguous and represents a
consensus among workers in this field. The lack of appropriate randomized controlled trials
(despite the view of many authors that such trials cannot be undertaken- a view based on
insufficient evidence) and the absence of good economic evaluations would appear to leave us in
the clinical and policy equivalent of purgatory, where we shall remain until proper evidence is
produced.
REFERENCES


* Reference read by citation only – because unavailable locally.


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