Hyperbaric oxygen as prophylaxis or treatment for radiation myelitis

J. J. FELDMEIER, J. D. LANGE, S. D. COX, L. J. CHOU, and V. CIARAVINO

Department of Radiation Oncology, Wayne State University, Detroit, Michigan 48201; and The University of Texas Health Science Center, San Antonio, Texas

Feldmeier JJ, Lange JD, Cox SD, Chou LJ, Ciaravino V. Hyperbaric oxygen as prophylaxis or treatment for radiation myelitis. Undersea & Hyperbaric Med 1993; 20(3):249–255.—This animal study was designed to investigate HBO as a treatment or prophylaxis for radiation myelitis. All animals received identical spinal cord radiation doses of 69 Gy in 10 daily fractions. Group I received no HBO; group II began HBO at the onset of signs of myelitis; group III received HBO with prophylactic intent beginning 6 wk after irradiation; and group IV received both modalities on the same day, but radiation always preceded HBO by at least 4 h. HBO consisted of 90 min oxygen at 2.4 atm abs for 20 daily treatments. Animals were objectively assessed for the loss of certain neurologic reflexes indicative of four levels of myelitis. Although all animals progressed to severe myelitis, group III animals had group-averaged levels of myelitis consistently less than control. The differences were statistically significant for several weeks. Group IV animals progressed to severe myelitis much more rapidly than any other group. Additional study is justified by this trial. Key questions to be answered include the optimal timing of HBO to produce a beneficial rather than detrimental effect.

hyperbaric oxygen, radiation tolerance, radiation myelitis, late radiation effects

One of the most devastating late complications of radiation therapy is radiation myelitis which results when the tolerance of the spinal cord to irradiation is exceeded. Radiation myelopathy is a potential complication of therapeutic irradiation whenever the spinal cord is included within the radiation treatment field (1–12). Fortunately, in modern radiation therapy, careful planning and meticulous dosimetry permit close monitoring of the spinal cord dose and modification of the treatment plan to ensure that spinal cord tolerance is not exceeded.

Several models, some requiring complex mathematical relationships, have been developed to estimate the limits for spinal cord tolerance (7, 12–14). These have been adapted to accommodate various dose fractionation schemes. For a standard dose fractionation scheme of 180–200 cGy (1 centigray = 1 rad) per day, a generally well-accepted guideline is that 4,500–5,000 cGy represent the practical clinical limit
of the spinal cord to irradiation (1, 4, 7, 10, 11). Such a limit results in an underdosage of a tumor located in close proximity to the cord unless that tumor is microscopic or unusually radiosensitive.

In spite of great care and the elegant models of spinal cord tolerance that have been developed, radiation myelitis still occurs occasionally. Palmer (6) estimated an incidence of 2.9% in his review of cases reported in the medical literature from 1948 to 1969. Wara et al. (12) have reported an incidence of 2.8% in the cervical cord and 9.2% in the thoracic cord. In another report, Reagan et al. (9) found only one case in 290 patients (0.3%), and Abbatucci et al. (1) reported 12 cases in 1,715 patients. Kaplan (15) has suggested that fewer than 1% of patients treated for Hodgkin’s disease with extended field irradiation and matching fields should be at risk for radiation myelitis.

The likelihood of radiation myelitis increases markedly when neutron therapy is utilized. Several studies report significantly increased levels of myelitis when neutrons or neutron/photon mixed beams have been delivered (16–18). Larramore et al. (19) reported that 5 of 10 patients who received neutron radiation for advanced oropharynx tumors and survived more than 10 mo. developed cervical radiation myelitis culminating in at least partial paralysis. Once radiation myelitis occurs, no effective treatment is available to reverse or prevent further neurologic deficits (4, 7, 16). Corticosteroids are usually prescribed in desperation without evidence of consistent benefit (5, 20). Depending on the spinal level of their injury, between 30 and 70% of patients with radiation myelopathy will die as a result of this occurrence (21, 22).

Some disagreement exists as to the pathophysiology of transverse myelitis. Some authors have proposed that myelitis occurs due to direct toxic effects of radiation on neuronal or glial cells (23). Others have proposed that radiation of the spinal cord triggers an autoimmune reaction that is responsible for the damage to and dysfunction of the spinal cord (24). Presently, most investigators would concur that late and progressive vascular damage secondary to radiation is primarily responsible (6, 25, 26).

Hyperbaric oxygen is receiving increased utilization for the treatment of late radiation necrosis of bone and soft tissue (27–31). It is postulated that HBO is primarily effective in these instances by inducing neovascularization at the microscopic level. Through this improved microvascular network, an increased supply of oxygen is made available to the tissues for their metabolic demand (32–34). If indeed tissue ischemia and hypoxia secondary to radiation endarteritis is the predominant cause of myelitis, a process that induces neovascularization at the microvascular level might ameliorate or even prevent transverse myelitis.

Hyperbaric oxygen has been used in the treatment of patients suffering from transverse myelitis, with some improvement (21, 30). A previously reported animal study showed no efficacy for HBO in the treatment of radiation myelitis (8). However, in this study a large single dose of radiation (from 2,000 to 2,800 cGy) rather than a fractionated regimen was used to induce the myelitis. Also, the number of animals in the study groups was very small (three or fewer). For these reasons, an adequate trial of the efficacy of HBO was not achieved.

MATERIALS AND METHODS

This study was a controlled animal trial using the adult female C3H mouse as the experimental animal. Four groups, each of 15 animals, were begun in the study and
irradiated in an identical fashion. The radiation scheme was patterned after a previous report by Goffinet et al. (35). The dose fractionation scheme was expected to cause a 50% incidence of myelitis in the control group of animals. It consisted of 10 fractions of 690 cGy each for a dose of 69 Gy in 12 days.

A General Electric Maxitron orthovoltage unit operating at 15 mA and 200 KVP with a filter of 0.25 mm Cu and a resultant HVL of 1.5 mm Cu was employed. Parallel opposed lateral portals with both fields treated every day were used. A lucite jig with lead shielding was fashioned to position the animals, to expose the desired 12-mm segment of spinal cord in the mid-thoracic region, and to shield surrounding organs. Animals were anesthetized with intraperitoneal ketamine before treatment to prevent movement within the jig.

Group I animals constituted the control group and these animals received no HBO. Group II animals received no HBO until they manifested overt signs of myelitis; as each animal demonstrated signs of myelitis, it began its course of HBO and completed 20 HBO treatments over the succeeding 4 wk. All group III animals began HBO 6 wk after completion of their course of irradiation; these animals also went on to complete a total of 20 HBO treatments in 4 wk. Group IV animals began HBO the same day as the initiation of their radiation course, and for the first 2 wk these animals received both radiation and HBO; when both were given on the same day, radiation preceded HBO by a minimum of 4 h. After completion of their course of irradiation, these animals continued to receive HBO for an additional 2 wk to complete 20 HBO treatments in 4 wk.

Hyperbaric oxygen treatments were given in a small-animal research hyperbaric chamber pressurized with bottled compressed 100% oxygen. Each hyperbaric exposure consisted of a compression phase which lasted 3–5 min. This was followed by the treatment proper that was composed of 90 min oxygen at a pressure of 2.4 atm abs. The resultant inspired partial pressure of oxygen was 1,824 mmHg. The HBO exposure ended with the decompression phase, during which the compressed oxygen was allowed to exhaust from the chamber under its own force. This final portion of each HBO treatment lasted approximately 5 min.

Goffinet (5) identified and described four distinct levels of transverse myelitis in mice. Level I represents the loss of the hind leg extension reflex when animals are lifted by their tails. Level II myelitis is noted when animals lose the grasp reflex of their hind limbs as they are suspended over the rim of their cage. Level III represents monoplegia or bilateral lower extremity paresis. Level IV is manifested by paraplegia, tail and lower extremity muscular wasting, and urinary and fecal incontinence.

The study animals were examined at weekly intervals beginning 8 wk postradiation exposure. The presence and numeric grade of myelitis were recorded for each animal. Scoring in this fashion was continued until either animals expired or a level IV myelitis was detected, at which time the animals were euthanized.

RESULTS

A number of animals expired due to untoward reactions to ketamine during sedation for irradiation. Eleven animals were evaluable for groups I and II. Ten were evaluable for group III and 13 were evaluable for group IV. Group-averaged levels of myelitis
for each group are plotted against weeks postradiation in Fig. 1. No animals exhibited signs of myelitis before Week 17. Several features of the plot are notable: group IV animals (concurrent) proceeded to high levels of myelitis very rapidly. By Week 18, the group-averaged level exceeded 3.0 and stayed at a plateau, gradually approaching a group average of 4.0 by Week 30. Group I (control) and group II (therapeutic) are virtually identical for the first 20 wk. Group II animals began HBO when signs of myelitis were detectable, and the plot suggests that for a short time (Weeks 21–24) these animals had some benefit from HBO because group-averaged scores are less than control for these weeks. Group III animals (prophylactic) are consistently lower in group-averaged scores of myelitis from Weeks 17 through 30. These differences are most marked for Weeks 17 through 25.

An analysis of variance was done to detect whether differences in myelitis scores were statistically significant when all four groups were compared. The P values for this analysis of variance are given in Table 1. P values were calculated utilizing the weekly individual scores for each animal. Animals were euthanized at level IV myelitis, and animals who were euthanized or died due to their myelitis were carried along as a level IV for the remainder of the analysis. Differences in myelitis scores are highly significant for weeks 17 through 25.

Pathologic, microscopic postmortem examination was done on the spinal cords of animals from each group. Findings reported were demyelination, spongiosis, and petechiae. This examination showed no real differences among the groups. Inasmuch as all animals had progressed to at least a level III myelitis before death, it is not surprising that microscopic findings were consistent for all animals in all groups.

DISCUSSION

This study was designed as a pilot trial to determine whether HBO could affect the occurrence or intensity of radiation myelitis. The study demonstrated a statistically

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FIG. 1.—Plot of group-averaged level of myelitis vs. weeks postirradiation. Error bars shown for Weeks 18, 20, 22, and 24 represent SE. Solid down triangle = group I, shaded triangle = group II, solid up triangle = group III, shaded square = group IV.
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Table 1: *P* Values for Analysis of Variance Comparing Individual Myelitis Scores for Each Evaluable Animal on a Weekly Basis

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<th>Week</th>
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<td>18</td>
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There is a significant difference in the degree of myelitis for Weeks 17 through 25. This difference was temporary, however.

Figure 1 suggests that group II animals, who received HBO therapeutically at the onset of signs of myelitis, seem to deteriorate more slowly than the control group. Figure 1 also demonstrates that group IV animals (concurrent radiation and HBO) progressed much more rapidly to severe levels of myelitis. The curve for group IV animals demonstrates a rapid climb to severe levels of myelitis at Week 18, with a very gradual increase thereafter. This rapid progression of myelitis for animals treated with both modalities concurrently suggests a sensitization of the spinal cords to radiation by HBO. This is a surprising finding because classical radiation biology predicts that oxygen must be present within milliseconds of the radiation exposure to have radiosensitizing properties. The results of this trial suggest that even after 4 h, oxygen can sensitize some normal tissues and that, at least in the mouse, the repair of sublethal radiation damage to the spinal cord is not complete until sometime after 4 h. A report by Luk et al. (36) in a rat model has also shown an increase in myelitis in animals who received HBO immediately after radiation.

This study depended heavily on the model borrowed from Goffinet et al. (35). It predicted a 50% level of myelitis for animals radiated according to the dose fractionation scheme selected. Unfortunately, 100% of the animals in all groups ultimately achieved a severe level of myelitis. The reason for the difference in the incidence achieved in our trial compared to that predicted by the borrowed dose fractionation scheme is not known. Although the dose fractionation scheme selected for the study was flawed, the model is much more clinically relevant than previous reports because a fractionated course of radiation was given rather than a large single dose. Certainly 690 cGy per fraction for 10 daily fractions far exceeds human spinal cord tolerance. However, significant variation of tolerance for a given organ system exists from one species to another.

The increased utilization of neutron beam therapy in a broad spectrum of tumors makes the development of preventive or therapeutic measures for radiation myelitis or other late radiation complications all the more necessary. Neutron beam therapy has given a higher incidence of complete responses and more durable duration of
complete responses in several primary tumors. Not only must we be concerned about a relatively higher biologic impact on the spinal cord (i.e., higher radiation biological effectiveness), we must also be concerned that more effective treatment leads to longer survival, which means more patients survive to be at risk for developing myelitis after a characteristic latent period of 6 mo. to 2 yr.

Due to the steep slope of the dose–response curve for normal tissues at or near curative doses, a reasonable expectation for any therapy to ameliorate or prevent radiation myelitis would be to extend spinal cord tolerance by only a small additional dose of radiation. It is possible that such severe spinal cord damage was done with our dose fractionation scheme that even a modality with a positive therapeutic impact could at best only delay the onset of myelitis.

The ultimate clinical significance of HBO as a preventive or therapeutic measure for radiation myelitis has not been established by this trial. The study has demonstrated a temporary, slight, but statistically significant difference in the intensity of myelitis when HBO is used. Final conclusions must await additional animal and, ultimately, human clinical trials. Based on our experience and a previous paper by Luk et al. (36), patients who are receiving therapeutic irradiation should probably avoid concurrent HBO therapy if the spinal cord is encompassed within the radiation treatment volume. Inasmuch as radiation myelitis is a rare occurrence, clinical trials resulting in significant data will require the cooperative effort of several HBO centers.

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REFERENCES

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