Rapid Recovery Hyperbarics

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Research on Radiation Injury

Hyperbaric oxygen in the treatment of delayed radiation injuries of the extremities

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Hyperbaric oxygen in the treatment of delayed radiation injuries of the extremities. Undersea Hyper Med 2000; 27(1)15-19.-Hyperbaric oxygen (HBO2) is used as an adjunct in the treatment of radiation injury at many sites, including the mandible, larynx, chest wall, bladder1 and rectum. In these disorders, HB02 is effective in stimulating neovascularization and reducing fibrosis. No previous publications report the application of HB02 to radiation injuries of the extremities. From 1979 until 1997, 17 patients were treated at the Southwest Texas Methodist and Nix Hospitals for nonhealing necrotic wounds of the extremities within previously irradiated fields. All but one wound involved a lower extremity. Most of the patients had been irradiated for soft tissue sarcomas or skin cancers. The rest were irradiated for a variety of malignancies. HB02 was delivered in a multiplace chamber at 2.4 atm abs daily for 90 min of 100% oxygen at pressure. This report is a retrospective, uncontrolled review of these patients. Eleven patients (65%) healed completely whereas five (29%) failed to heal and one (6%) was lost to follow-up. Three (60%) of those who failed were found to have local or distant recurrence of their tumor early in their course of hyperbaric treatment and were discontinued from therapy at that time. When last seen in the clinic, the wound of the patient who was lost to follow-up was improved but not completely healed. Four of those who failed (including the two with local tumor recurrence) required amputation. If we exclude those with active cancer and the patient lost to follow-up, the success rate was 11 of 13 or 85%. HB02 was applied successfully with complete wound healing and the avoidance of amputation in a majority of these patients. The consequences of failure in patients suffering from radiation necrosis of the extremities (some complicated by the presence of tumor) are significant, with 80% of the five failures requiring amputation. In radiation injuries of the extremities as in delayed radiation injury at other sites, HBO2 is a useful adjunct and should be part of the overall management.

One of the most successful and best documented indications for hyperbaric oxygen (HB02) has been its application to the treatment and prevention of mandibular

osteoradionecrosis (1-3). Hyperbaric oxygen for the treatment of soft tissue and bony necrosis at other sites is an indication approved by the Hyperbaric Oxygen Therapy Committee of the Undersea and Hyperbaric Medical Society, and reimbursement is approved for this indication by Health Care Finance Administration and other third-party payers. A number of papers report success in applying HB02 to radiation injuries at anatomic sites other than the mandible, including chest wall, abdomen, larynx, small bowel, large bowel, and bladder (419). However, a review of the literature fails to discover any reports of HB02 applied to delayed radiation injuries of the extremities. The postulated mechanism for HBO2 in the treatment of radiation necrosis of the extremities is the induction of angiogenesis and the reduction of fibrosis. In turn, these changes provide the oxygen necessary to support healing and resolution of necrosis. Marx and colleagues (20,21) have shown an increased density of vasculature after HBO2 in both clinical histologic specimens and in an animal study with microangiography. Feldmeier and associates (22,23) have demonstrated a reduction of fibrosis in an animal model of enteritis when HB02 is delivered to animals who have received radiation exposures likely to cause significant delayed complications.

MATERIALS AND METHODS

Since 1979, we have treated nine women and eight men with HB02 for radiation necrosis of the extremities. Sixteen of these 17 patients are available for follow-up. Malignancies irradiated included several different types and are listed in Table 1. The patient's ages ranged from 21 to 87 with a median age of 64. The interval from radiation therapy to injury varied from 4 wk to 17 yr, with a median time of 21 mo. The time from the manifestation of the injury to the referral for HB02 varied from immediately to 3 yr, with a median time of 6 mo. None of the patients had had any progression to healing in that time interval using a variety of conservative therapies including wound care and antibiotics. Two of 17 patients were referred less than 2 yr after their irradiation. Radiation doses varied from 3,600 to 6,000 cGy with a median dose of 6,000 cGy. Five of 17 patients had doses less than 6,000 cGy. The vast majority of injuries (17 of 18) involved the lower extremity. One patient had radiation necrosis of the upper extremity. Seventeen of the 18 wounds demonstrated only soft tissue involvement while the one patient with upper extremity involvement had bony as well as soft tissue involvement. Patient number 16 was treated for an original ulcer over the anterior tibia, with resolution after 43 treatments. About 9 mo. after this first course of therapy, the patient had a recurrence of the wound, although smaller. This recurrent wound was treated with a second course of HB02. Table 2 gives a complete description of pretreatment characteristics.

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Table 1: Pre-Treatment Characteristics

	Malignancy		Radiation to Injury	Time From to HBO	Time From Injury Radiation Dose	Patient	Age	Sex
1	74	M	Kaposi's sarcoma	5 yr	1yr	3,600		
2	62	F	malignant fibrous histiocytoma	1 yr	2 yr		6,000	
3	84	M	soft tissue sarcoma	8 yr	8 mo	5,000		
4	46	F	unknown	1 yr	6 mo	3,600		
5	77	F	soft tissue sarcoma	9 mo	1 yr	6,000		
6	56	F	mycosis fungoides	9 yr	3 yr	3,000		
7	63	M	basal cell	6 mo	6 mo 6,000			
8	54	M	mycloproliferative disease		4 wk immediately		unknown	
9	31	M	soft tissue sarcoma	1 yr	8 mo	6,000		
10	72	F	fibrosarcoma	3 yr	2 yr	6,000		
11	55	F	malignant fibrous histiocytoma	6 mo	3 mo	6,000		
12	56	M	soft tissue sarcoma	10 yr	6 mo	6,000		
13	21	M	soft tissue sarcoma	8 mo	immediately	6,000		
14	65	F	basal cell 18 mo	6 mo	6,000			
15	87	M	basal cell 2 yr	10 mo	6,000			
16	82	F	soft tissue sarcoma	2yr	6 mo	6,000		
16A	83	F	soft tissue sarcoma	2.75 yr	immediately	6,000		
17	73	F	soft tissue sarcoma	17 yr	immediately		6,000	

Key: STSG split thickness skin graft; aDose approximated from standard radiation therapy guidelines.

The HB02 exposures consisted of 90 min of 100% oxygen at 2.4 atm abs in a multiplace hyperbaric chamber. Treatments were typically given in three periods of 30 min 02 breathing with l0-min air breaks interposed between 02 periods. A medical attendant was always present in the chamber during the treatment. Daily wound care was an important part of the patients' therapeutic regimen. Typically, wounds received high-pressure irrigation with normal strength saline solution. Sharp debridement was done as necessary and as tolerated to remove superficial necrotic tissue. Wounds were then usually dressed with a "wet-to-dry" dressing using dilute boric acid.

Surgical intervention was used as appropriate in each case. Nine of the 17 patients underwent at least one surgical procedure as part of the therapy designed to preserve their limb. The specific surgical interventions are listed in Table 2.

RESULTS

Sixteen patients (94%) with 17 wounds were available for analysis. The full details of the patients' outcome are included in Table 2. One patient was lost to follow-up. This patient had shown significant improvement at 43 treatments. A flap was planned for this patient and complete resolution was expected but not documented. Eleven of the remaining 16 patients had complete healing of their necrotic wounds. The successfully treated patients were all followed to healing which was completed by the final HB02 treatment or within a week or two after treatment. As noted above,

patient number 16 had initial resolution of her wound, but it recurred and required a second course of HB02 for permanent resolution. The successfully treated patients included the one with bony as well as soft tissue involvement of the upper extremity. In the 11 patients who healed completely, 3 of 11(27%) required no surgery; 3 of 11(27%) had skin grafting; 2 of 11(18 %) had surgical debridement and 1 of these had delayed primary closure. 1 of 11(9%) had had a surgical resection of recurrent tumor just before beginning HB02; 1 of 11(9%) had debridement along with bone and skin grafting; and 1 final patient (9%) had both a myocutaneous flap and split thickness skin graft. *(Note:* The numbers do not add up to 100% due to rounding.) The timing of surgery relative to the course of hyperbaric treatments is included in Table 1. Since these patients were not treated according to a planned prospective trial, considerable variation in relative timing of surgery to HB02 is seen. Surgery was accomplished when the referring surgeon felt that the timing was optimal for each patient. However with the exception of patient number 12, all patients had at least 20 HBO2 treatments before any surgical intervention. No flap or graft loss was experienced in our group of patients.

Table 2: Wound Characteristics, Treatment, and Outcome

Patient	Wound Characteristics	Surgical Intervention	# of Treatments	Outcome
1	2 ulcers (each 4 x 5 cm)	none	12	amputation (persistent tumor)
2	6 x 3cm ulcer	none	8	discharged to hospice(lung matastases)
3	2 x 2cm ulcer	myocutaneous flap at 42 95 plus STGS at 90 Tx		healed
4	5 x 6cm ulcer	STSG at 43 Tx	55	healed
5	5 x 5cm ulcer	surgical debridement at 20 Tx	29	healed
6	13 x 16cm ulcer	none	24	healed
7	7 x 7cm ulcer	none	41	healed
8	not recorded	none	1	amputation (persistent tumor)
9	12 x 12cm ulcer	none	36	amputation
10	bone plus soft tissue	debridement and bone graft at 20 Tx	50	healed
11	2 x 4cm ulcer	none	43	significant improvement (flap planned)
12	soft tissue only	resection of recurrence just before Tx	50	healed
13	4 x 4cm ulcer	STSG at 11 Tx	29	healed
14	1 x 1cm ulcer	none	53	healed
15	54 x 5cm ulcer	flap attempted after HBO_2	74	amputation
16	3 x 10cm ulcer	previously failed growth factors; STGS at 38 Tx	43	healed
16A	4 x 5 cm recurrent ulcer	none	32	healed
17	9 x 10cm recurrent ulcer	flap just before HBO_2 which was failing; surgical debridement with delayed primary closure at 46 Tx	58	healed

The number of HB02 treatments varied from 1 to 95. For those who healed, the number of treatments varied from 24 to 95 with a median number of 47. For those who failed to heal, the number of treatments varied from 1 to 74 with a median number of 24. Patients' treatments were continued until clinical judgment determined that maximum benefit had been obtained or until biopsy of the lesion demonstrated tumor presence in the wound or, in one case, lung metastases was detected.

Of the five (29%) who failed to heal, four underwent amputation. Two (12%) of these (patients numbers 1 and 8) were found to have persistent or residual tumor in their wounds and were discontinued from hyperbaric treatment as soon as recurrence was demonstrated after 12 and 1 treatments, respectively. Another patient (6%) in this group was found to have lung metastases after eight HB02 treatments and was placed in hospice care at that time. If we exclude those with local or metastatic malignancy, only two patients failed. Including only these failures and excluding the patient lost to follow-up, the success rate was 85%(1l of 13).
The results of treatment are exemplified by patient number 10 whose serial wound photographs are depicted in Fig. 1. This case was selected for several reasons: her injury involved damage to both soft tissue and bone, and therefore successful intervention was a more significant accomplishment than closure of a soft-tissue only wound. Furthermore a long-term follow-up photograph taken 14 yr after successful intervention was available and confirmed that the effects of HB02 in the treatment of radiation damage of the extremities provides a durable repair of the injury.

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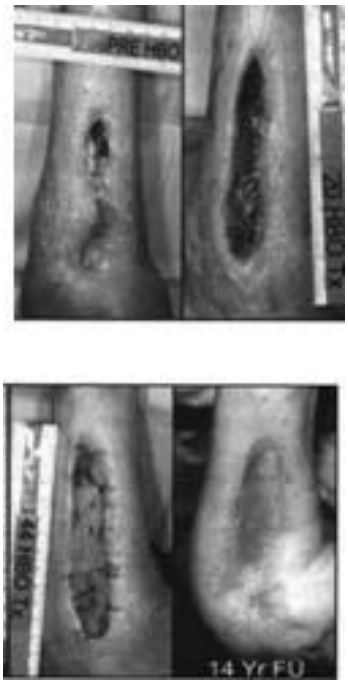

FIG. 1 -Patient 10. *Top left:* at the time of initial consultation for HBO2; *top right:* after 30 HB02 treatments status post debridement and bone graft at 20 treatments; *bottom left:* after 44 HBO2 treatments status post-STSG at 40 treatments; *bottom right* 14 yr after completion of HBO2 with a functional and cosmetically reasonable outcome.

DISCUSSION

The above report is a retrospective review of all patients treated by the Methodist-Nix Hospital group in San Antonio since 1979 for a diagnosis of radiation necrosis of the extremities. A search of the literature failed to discover specific reviews of radiation injury of the extremities. Several publications do discuss radiation injuries of the skin and subcutaneous soft tissues in general. Necrosis of the skin as a late complication of irradiation has been reviewed recently by Emami et al. (24). In this review for a 10 x 10 cm field, a 5% incidence of necrosis occurred at a dose of 5,500cGy. Fajardo (25) indicates that late skin ulceration occurs in 5% of patients at a dose of 6,000 cGy and 50% at a dose of 8,000 cGy. In our report most patients had been irradiated for skin cancer or soft tissue sarcomas and only 5 of 17 had doses of radiation less than 6,000 cGy. Two patients who had radiation exposures in the lower dose range had ulcerated wounds due to persistent tumor rather than to radiation injury. Radiation damage to bone and skin overall is less likely with today's techniques than it had been in the pre-cobalt days of radiation therapy. (25,26). This decrease is due to the physical characteristic of modern radiation modalities which

provide a lower dose in the skin relative to deep seated tumors and avoid selective deposition of the radiation dose in bone. With an increased emphasis on limb preservation in soft tissue sarcomas of the extremities, we may actually see an increase in necrosis of the extremities in the future (27). Gurlek et al. (27) have reported their results in using free tissue transfers to treat a variety of delayed radiation injuries of the head and neck, chest wall, groin, and extremity. A total of 33 patients are reviewed in this paper which 4 had injuries of the extremities. HB02 was not use in this series. Thirty-three flaps were accomplished in this group with an eventual success rate of 97%. However. three flaps were endangered by thrombosis and one was lost. A total of 40% of patients suffered complications including flap loss, partial flap loss, dehiscence, cellulitis, and seroma.

Our series also suggests that the lower extremity is higher risk than the upper extremity for delayed radiation injury, although this relative increase may be due to higher incidence of tumors of the lower extremity, which undergo irradiation as part of their management (28). Our experience with diabetes suggests that the lower extremity is more likely to develop non-healing wounds when a pathology (either radiation injury or diabetes) that induces small vessel damage is superimposed on the inherent relatively diminished blood supply of the lower extremity.

In those patients treated for radiation injury of the extremities who were cancer free, resolution of necrosis with healing of the necrotic wound occurred 85% of the time with avoidance of amputation and maintenance of a useful limb. In the three patients with demonstrated active malignancy it is impossible to say whether an intercurrent depression of their immune response contributed to their wounds and failure to heal. None of the patients were undergoing chemotherapy or radiation therapy at the time of their HB02 treatments. All were also deemed to have adequate nutritional status to support wound healing. All three of these patients had 12 or fewer hyperbaric treatments and two the three had biopsy proven tumor in the wound itself Only two patients (numbers 9 and 15) failed without evidence of recurrent tumor. Both of these had sizable ulcers before HB02 and both had doses of 6.000 cGy.Theyboth failed in spite of adequate trials of hyperbaric treatment. Their failures indicate that though effective in most cases HB02 is not universally successful in the treatment of radiation injuries. HB02 is recommended as part of the management of delayed radiation injuries of the extremities. Care must be taken to rule out recurrent or persistent tumor as an etiology of apparent necrosis and non-heating wounds. Our review also suggests that preoperative HB02 decreases the likelihood of surgical complications as compared to at least one publication where HBO2 was not used (27).