Hyperbaric oxygen therapy for complications of radiotherapy

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The increase in the available scientific evidence to support the use of hyperbaric oxygen therapy in the treatment of complications of radiotherapy has contributed to it being accepted in most treatment algorithms.

The goal of radiotherapy is to irradiate tumours with minimal adverse effects on the surrounding normal tissue. With the limitations of living tissue’s tolerance to radiation, optimal dosage schedules are followed that provide an acceptable benefit to damage ratio for the patient. Oncologists are acutely aware that their patients’ quality of life is as important as treating their malignancies. In spite of major improvements in the field of radiotherapy, side-effects of this therapy still occur. Oncologists have noticed that some patients are more sensitive to radiotherapy than others and that these patients are also more sensitive to radiation damage than those who do not respond to the treatment to the same degree. There is no way to accurately predict who will experience the worst side-effects.

The side-effects of radiotherapy can be divided into two categories:

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<th>Occurrence</th>
<th>Acute complications</th>
<th>Chronic complications</th>
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<td>Symptoms</td>
<td>Resolution with time</td>
<td>Benign, self limiting</td>
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<tr>
<td>Pathophysiology</td>
<td>Destruction of rapidly replicating cells</td>
<td>Dose dependent Damage and destruction of the blood vessels Fibrosis, necrosis of tissue due to ischaemia</td>
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<tr>
<td>Treatment</td>
<td>Symptomatic</td>
<td>Symptomatic Surgical removal of damaged tissue Hyperbaric oxygen therapy</td>
</tr>
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</table>

Patients who undergo radiotherapy remain at life-long risk of radiation-induced injury to normal tissues, also referred to as late radiation tissue injury. Chronic radiation damage is called “osteoradionecrosis” when the bone is damaged and “soft tissue radionecrosis” if muscle, skin or internal organs have been damaged by the radiation. Across all anatomic sites, the reported incidence of late effects ranges from 1–22%. Its true incidence is probably unknown, secondary to limited reporting and unrecognised cases.

For more than 30 years maxillofacial and head and neck surgeons have come to recognise the importance of hyperbaric oxygen therapy in the treatment and prevention of late radiation tissue injury. Hyperbaric oxygen therapy has been applied to treat chronic radiation damage of the mandible, brain, skeletal muscle and soft tissue of the chest wall, abdomen and pelvis. A recent prospective randomised trial confirmed that hyperbaric oxygen therapy is the treatment of choice for radiation proctitis.

Hyperbaric oxygen therapy’s value in the treatment of late radiation tissue injury is unique in that it is disease modifying. Most other therapies provide supportive care or are directed at relief of symptoms. Hyperbaric oxygen therapy, on the other hand, directly overcomes the progressive oblitative endarteritis which characterises late radiation injury's final common pathophysiologic insult. Oxygen is provided in the hyperbaric chamber at increased atmospheric pressure. The oxygen is dissolved in the patient's plasma and is carried in the circulation to the site of radiation injury to enable repair of the damage done by the destruction of blood vessels. Each treatment typically takes one to two hours and daily treatments are required over four to six weeks.

Studies done by Marx have conclusively demonstrated neovascularisation in irradiated tissue in response to hyperbaric oxygen therapy. They compared hyperbaric oxygen to normobaric oxygen (100% oxygen breathing in a non-hyperbaric setting, i.e. one that could be achieved in the normal clinical setting) to normobaric air. It was the hyperbaric environment, with oxygen breathing, that resulted in angiogenesis within previously irradiated tissue. The evidence was statistically significant when compared to oxygen and air breathing at normal atmospheric pressure.

In the South African context, not all medical aids provide financial cover for hyperbaric oxygen therapy for chronic radiation injury, in spite of the overwhelming evidence in support of this treatment modality. Hyperbaric oxygen therapy is available at various private hyperbaric facilities across the country, as well as the Steve Biko Academic Hospital (formerly the Pretoria Academic Hospital) and Tygerberg Hospital.
Radiation proctitis

Various authors have reported on the advantages of hyperbaric oxygen for injury to the rectum and anus after radiotherapy. Clarke and co-workers conducted a multi-centre, randomised, controlled, double-blind, crossover trial with long-term follow-up to evaluate the effectiveness of hyperbaric oxygen for refractory radiation proctitis. Patients with refractory radiation proctitis were randomised to hyperbaric oxygen at 2.0 atmospheres absolute (Group 1) or air at 1.1 atmospheres absolute (Group 2). The sham patients were subsequently crossed to Group 1. All patients were re-evaluated by an investigator who was unaware of the treatment allocation at three and six months and years one to five. The primary outcome measures were the late effects normal tissue subjective, objective, management, analytic (SOMA-LENT) score and standardised clinical assessment. The secondary outcome was the change in quality of life. Of 226 patients assessed, 150 were entered in the study and 120 were evaluable. After the initial allocation, the mean SOMA-LENT score improved in both groups. For Group 1 the mean was lower (p = 0.0150) and the amount of improvement nearly twice as great (5.00 vs 2.61, p = 0.0019). Similarly, Group 1 had a greater portion of responders per clinical assessment than did Group 2 (88.9% vs 62.5%, respectively; p = 0.0009). Significance improved when the data were analysed from an intention to treat perspective (p = 0.0006). Group 1 had a better result in the quality of life bowel bother subscale. These differences were abolished after the crossover. The authors concluded that hyperbaric oxygen therapy significantly improved the healing responses in patients with refractory radiation proctitis, generating an absolute risk reduction of 32% (number needed to treat of three) between the groups after the crossover. The authors concluded that hyperbaric oxygen therapy was effective, but also safe, with a low relapse rate. Chong et al recently published the largest series of patients up to date. They reported improvement rates of 90% with early treatment (within six months of onset of haemorrhage) vs 80% across all time frames. Due to the enduring nature of hyperbaric oxygen therapy, one year follow-up remained very encouraging, with very few relapses. Treatment efficacy was independent of prior intravesical therapy and the timing of radiotherapy.

Gynaecologic radionecrosis

Williams et al published a clinical series in which they reviewed vaginal vault radionecrosis involving 14 patients who were analysed retrospectively. Thirteen had complete resolution, while the one remaining patient succumbed to an overwhelming necrotising infection. This group subsequently reported on additional 67 patients, who had been prospectively followed. Of this number, 21 did not receive hyperbaric oxygen therapy. Reasons included patient refusal, unacceptable risk profile, cancer recurrence and transportation problems. Of the 46 who underwent hyperbaric oxygen therapy, 37 (80%) had significant improvement or complete healing. Of the remainder, one had tumour recurrence and eight were non-compliant to hyperbaric oxygen therapy. Feldmeier et al reported 44 patients treated with hyperbaric oxygen therapy for a variety of pelvic and abdominal radiation injuries. Thirty-one received at least 20 hyperbaric oxygen treatments for perineum, groin, vagina and pelvic bone involvement. Twenty-six had complete resolution. They concluded that hyperbaric oxygen is a useful adjunct in treatment of delayed radiation injuries of the pelvis and abdomen. Fink et al reported the response of 14 patients who suffered pelvic radiation injuries. Six involved the vagina, alone or in combination with other radiation damaged sites. One had complete resolution; four had greater than 50% resolution. Reedy reported on the improved wound healing following radical vulvectomy when hyperbaric oxygen therapy was used as an adjunctive therapy. Safra et al also reported on the improved quality of life associated with hyperbaric oxygen therapy in patients with late side-effects of radiotherapy of the pelvic region.

Head and neck radionecrosis

With appropriately fractionated radiotherapy, the incidence of laryngeal radionecrosis should be less than 1%. This incidence occurs as either a direct consequence of radiation exposure or secondary to surgical wounding, as would occur for biopsy to rule out local recurrence. A metaanalysis of hyperbaric oxygen therapy for laryngeal radionecrosis, (Richard Clarke unpublished), reported six failures out of 43 patients. As all of these hyperbaric treated cases were severe (Chandler Grade 3 or 4) this data, while non controlled and retrospective, represents a very high salvage rate when compared to any other management. Most cases of Grade 3 or 4 have a high likelihood of laryngectomy. Marx reported a controlled but non-randomised prospective study comparing hyperbaric oxygen therapy with standard care vs standard care alone in the treatment of soft tissue radionecrosis to the neck. In 160 patients, those receiving hyperbaric oxygen therapy experienced less infections (6% vs 24%), fewer instances of dehiscence (11% vs 48%) and fewer instances of delayed healing (11 % vs 55%). All differences were statistically significant. Feldmeier et al reported on the prophylactic use of hyperbaric oxygen for patients undergoing salvage for recurrent head and neck cancers following full course irradiation, with favourable results.
The Marx protocol advocates the use of adjunctive hyperbaric oxygen therapy for radiated tissues. In most cases this would include a total of thirty treatments: twenty treatments are administered preoperatively followed by ten treatments postoperatively. This reduces deformity, disability and length of hospital stay, resulting in an overall lowering of cost of care.

Dr Frans Cronje, former president of the Wound Healing Society of Southern Africa, wrote a review on the use of hyperbaric oxygen therapy for osteoradionecrosis. Due to the fact that this complication of radiotherapy deserves more than just a brief mention, readers are advised to refer to this review for more information.

**Trunk and chest wall radionecrosis**

When patients are irradiated after mastectomy, the radiation dose to the skin is intentionally high. As a result of this technique most women will suffer acute reactions and others will suffer both acute and late effects. Late effects often culminate in superficial ulceration which can pose a huge challenge. Attempts to resolve ulcerations surgically will occasionally produce larger and deeper ulcerations due to the injurious effects of radiation throughout its portal. Various published reports have demonstrated the benefit of hyperbaric oxygen therapy in resolving these problems. Feldmeier also published on hyperbaric oxygen as an adjunctive treatment for delayed radiation injury of the chest wall.

Radiation tissue injury to the extremities is very rare, due largely to the infrequent occurrence of primary malignancies of the extremities. Published information on hyperbaric oxygen therapy’s effects is, therefore, largely limited. Eleven of 17 (65%) patients treated with hyperbaric oxygen therapy had complete resolution of their soft tissue condition at completion of treatment. Of those patients who were followed over a longer period, 85% had fully resolved.

The results are consistent with other anatomic sites were evidence is more robust. As there is nothing to suggest that the injurious effects of radiotherapy on non-target tissues are anatomic specific, it is not surprising to find that hyperbaric oxygen therapy is broadly therapeutic.

**Summary**

Hyperbaric oxygen therapy for soft tissue radionecrosis has very encouraging outcomes in an otherwise complex management problem. Hyperbaric oxygen therapy is effective, safe and durable, irrespective of the anatomic site affected. If any of the complications of soft tissue radionecrosis is suspected, the patient should be considered for hyperbaric oxygen therapy.

Please contact the Southern African Undersea and Hyperbaric Medical Association for an accredited hyperbaric unit in your area. http://sauhma.co.za/