The Use of Hyperbaric Oxygen as an Adjunct in the Treatment of Radionecrosis

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SUMMARY

The rationale leading to the use of hyperbaric oxygen (HBO) in the treatment of radionecrosis is described. Between January 1975 and February 1977, 13 patients received HBO at Groote Schuur Hospital for radionecrosis, and the response is evaluated in terms of pain relief and wound healing.

The implications of these results are discussed.


Radionecrosis is a debilitating complication of therapeutic irradiation. It is usually associated with intractable pain, and local areas of ulceration and infection develop.

PATHOLOGICAL FINDINGS

Blood vessel damage is the major contributing factor to the development of radionecrosis. Endothelial swelling and proliferation result, with subsequent narrowing of the vessel lumina. Degeneration of the smooth-muscle cells of the media is followed by fibrosis and loss of elasticity. At a capillary level, other factors such as extracapillary fibrosis and swelling of the basement membrane contribute to the decreased capillary permeation, in addition to endothelial lesions. The overall picture resembles that of endarteritis obliterans with tissue hypoxia.

The overlying radiation-damaged epithelium is atrophic and less able to withstand insults such as minor trauma or infection, which can then precipitate radionecrosis. The subsequent healing of radionecrotic lesions is impaired, as the fundamental mechanisms in wound healing, i.e. vascular proliferation, the formation of granulation tissue and re-epithelialization, are inhibited by the previous irradiation and tissue hypoxia.

REASONS FOR THE USE OF HYPERBARIC OXYGEN

Hyperbaric oxygen (HBO) is used in the treatment of radionecrosis in an attempt to improve wound healing by reducing tissue hypoxia. Kivisaari and Niinikoski have shown that the healing of hypoxic wounds in experimental rats is accelerated by HBO, while in clinical situations it has been found to be of value in the treatment of...
hypoxic conditions such as peripheral vascular disease and ischaemic skin flaps.

**Mechanisms for Improved Wound Healing with HBO**

The mechanisms for improved wound healing with HBO are the promotion of tissue revascularization and re-epithelialization together with the inhibition of infection. The revascularization of avascular burn wounds in experimental rats treated with HBO has been demonstrated both angiographically and histologically by Ketchum et al. A histopathological study of patients with ischaemic gangrene in peripheral vascular disease treated with HBO and amputation has been done by Stansell. He observed restoration of capillary function in hypoxic zones adjacent to the gangrenous areas and the presence, on histological examination, of capillaries which were not usually apparent in the absence of HBO.

Winter and Perrins have studied the effect of HBO on shallow wounds in pigs used experimentally. The rate of epithelialization was determined by serial histological sections, and an accelerated rate was found with HBO.

The inhibiting effect of HBO on infection has been documented for aerobic as well as anaerobic microorganisms. HBO has been used extensively in the treatment of gas gangrene.

**SUBJECTS AND METHODS**

Between January 1975 and February 1977, 13 patients with radionecrosis confirmed on histological examination were treated at Groote Schuur Hospital. All the patients had failed to respond to conservative therapy, which comprised systemic and local measures such as antibiotics, analgesics, correction of anaemia, a high-protein, high-energy diet, and wound irrigation.

HBO was administered by a Vickers Mark IV HBO chamber at a pressure of 3 ATA. The pressurizations were planned for daily administration and the duration of each treatment was 1½ - 2 hours.

In 8 of the 13 patients the response of the radionecrosis to HBO could be assessed. The 5 patients excluded from the analysis comprised 2 patients referred from other centres who were lost to follow-up, 1 patient who had convulsions during the initial stages of therapy and in whom the pressurizations were discontinued, and 2 patients who could not be evaluated because of the onset of rapidly progressing cancer.

**RESULTS**

The data on the 8 patients eligible for analysis can be seen in Table I. The subjective response was evaluated in terms of complete, partial or failed pain relief. The extent of healing was assessed objectively, and could be complete, partial or failed. Complete healing consisted of complete re-epithelialization which was maintained at follow-up, and partial healing consisted of a more than 50% re-epithelialization of the radionecrosis.

Patients 1 - 3 were regarded as complete responders. The first 2 patients had no evidence of disease at follow-up, while patient 3 had pulmonary metastases. Patients 4 - 6 are regarded as partial responders. Patient 4 had a small area of residual ulceration, patient 5 developed locally recurrent carcinoma 3 months after treatment with HBO was completed, and patient 6 had complete re-epithelialization which broke down 2 months after HBO therapy.

Patients 7 and 8 failed to respond to HBO treatment. Patient 7 developed local tumour recurrence 3 months after treatment and died 6 months later, while patient 8 died from unknown causes 6 months after HBO administration.

The dose rate of HBO administration expressed as the total number of hours of HBO treatment divided by the overall treatment time is plotted against the overall treatment time in Fig. 1.

**DISCUSSION**

The value of HBO in the treatment of radionecrosis as reported by Hart and Mainous and Greenwood and Gilchrist is substantiated in this series. The treatment protocol used at this hospital contrasts with that of Hart and Mainous in terms of the mean duration of HBO administration (41.7 hours as opposed to more than 100 hours) and the absolute pressure of HBO (3 ATA as opposed to 2 ATA) indicating that the total number of hours of HBO required for a beneficial result will depend on the oxygen pressure.

The dependence of the clinical response on the total number of hours of HBO treatment is suggested by the observation that 5 of the 6 patients who responded to treatment received HBO for more than 45 hours, while both failures received HBO for less than 33 hours.

The dose rate of HBO administration as expressed in Fig. 1 may be significant, since all the cases above the arbitrary line A-B responded to HBO, while both the cases
TABLE I. SUMMARY OF DATA FROM 8 PATIENTS TREATED WITH HBO FOR RADIONECROSIS

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>Sq. Ca uvula (T1 N0)</td>
<td>(a) 4 900 rad by implant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(b) Rec — excision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(c) Rec — 7 000 rad by implant</td>
</tr>
<tr>
<td>2</td>
<td>47</td>
<td>Sq Ca tonsil (multicentric)</td>
<td>(a) Excision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(b) Rec — MTX and bleo. + 4 200 rad in 14 triweekly</td>
</tr>
<tr>
<td>3</td>
<td>43</td>
<td>Chondrosarcoma pelvis</td>
<td>Incomplete excision + 4 500 rad in 10 biweekly</td>
</tr>
<tr>
<td>4</td>
<td>47</td>
<td>Sq. Ca tonsil (T3 N0)</td>
<td>(a) 2 000 rad in 5 d + 3 400 rad in 17 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(b) Rec — 5 200 rad by implant</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>Sq. Ca floor of mouth (T4 N3)</td>
<td>MTX + 2 000 rad in 5 d + 3 500 rad by implant + 3 400 rad in 17 d</td>
</tr>
<tr>
<td>6</td>
<td>68</td>
<td>Sq. Ca mouth (T4 N0)</td>
<td>MTX + 2 000 rad in 5 d + 3 500 rad by implant + 2 400 rad in 12 d</td>
</tr>
<tr>
<td>7</td>
<td>52</td>
<td>Sq. Ca mouth (T4 N0)</td>
<td>MTX + 2 000 rad in 5 d + 5 000 rad by implant</td>
</tr>
<tr>
<td>8</td>
<td>63</td>
<td>Sq. Ca floor of mouth (T3 N0)</td>
<td>2 000 rad in 5 d + 3 600 rad in 18 d</td>
</tr>
</tbody>
</table>

Bleo = bleomycin; d = daily fractions; MTX = methotrexate; Rec. = recurrence; CPR = complete pain relief; CH = complete healing; PPR = partial pain relief; PH = partial healing; FPR = failed pain relief; FH = failed healing.

below it indicate treatment failure. Although the total number of cases is small and no firm conclusions can be drawn, this dose-rate relationship merits further investigation, since increasing the duration of daily pressurization might accelerate the healing process.

Patients in this series who had developed radionecrosis after treatment for advanced disease were offered HBO even though the possibility of latent active cancer was recognized, since it was found that palliation could result. The fear that HBO might stimulate tumour growth has been shown to be unwarranted by Glassburn et al. who concluded, after a review of the literature, that HBO does not significantly affect the incidence or growth rate of metastatic disease, and by McCredie et al. who found that HBO had no effect on local tumour growth rate in experimental mice.

The benefit that patients with radionecrosis which is unresponsive to conventional therapy derive from HBO therapy is a strong indication for this form of treatment.

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REFERENCES