Original Article

Improved Quality of Life with Hyperbaric Oxygen Therapy in Patients with Persistent Pelvic Radiation-induced Toxicity

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ABSTRACT:
Aims: We report the results of hyperbaric oxygen therapy (HBOT) used in the treatment of radiation-induced persistent side-effects after the irradiation of pelvic tumours.

Materials and methods: Between January 2001 and December 2005, 13 women (median age 60.3 years) with radiation combined proctitis/cystitis (n = 6), longstanding vaginal ulcers and fistulas (n = 5) and longstanding skin injuries (n = 2) underwent HBOT in a multipurpose chamber for a median of 27 sessions (range 16–40). The treatment schedule was HBOT 100% oxygen, at 2 absolute atmospheres, for 90 min, once a day. For radiation-induced toxicity grading we used the National Cancer Institute Common Toxicity Criteria (CTC) grading system, before and after HBOT.

Results: Thirteen patients underwent an adequate number of HBOT sessions. The mean CTC grading score before HBOT was 3.3 ± 0.75, whereas the mean CTC grading score after HBOT was 0.3 ± 0.63. The scores showed a significant improvement after HBOT (P = 0.001; exact Wilcoxon signed-rank test). Rectal bleeding ceased in five of six patients with proctitis and dysuria resolved in six of seven cystitis patients. Macroscopic haematuria stopped in seven of seven patients. Scar complications resolved in two of two patients. None reported HBOT-associated side-effects.

Conclusion: HBOT is apparently safe and effective in managing radiation-induced late side-effects, such as soft tissue necrosis (skin and vagina), cystitis, proctitis and fistulas. Safra, T. et al. (2008). Clinical Oncology 20, 284–287

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Key words: Hyperbaric oxygen therapy, pelvis, radiation, side-effects

Introduction
Pelvic irradiation is an essential part of the curative treatment of pelvic malignancies, including rectal, uterine and cervical carcinoma. In spite of all the precautions and advances that are taken in the implementation of radiation therapy, the adjacent healthy tissues do get damaged. The damage mechanisms include outright cell demise or lethal cellular damage with later cell death, as well as inappropriate cell reproduction or collagen production. Injuries are divided into two basic categories: those of soft tissue (fibroblast, endothelium, muscle, nerve, etc.) and radiation osteonecrosis (bone injury). Late complications appear in 5% of the irradiated population and up to 10% when surgery and radiation are combined [1].

The urinary and gastrointestinal systems are the main sites of post-radiation pelvic complications [2–4]. Radiation cystitis presents as haematuria (recurrent), urinary urgency and pain. The primary treatment modality for haemorrhagic cystitis is bladder irrigation. Oral and intravenous agents, such as aminocaproic acid, oestrogens and sodium pentosanpolysulphate, have been tried with limited success [4]. Intravesical treatments with alumsilver nitrate, prostaglandins or formalin are sometimes used if bleeding persists [5]. Finally, selective embolisation of the hypogastric arteries, urinary diversion and cystectomy may be carried out as necessary in the most severe cases. Radiation proctitis presents as irregularity of bowel function, rectal blood loss and pain [6], and primary treatment includes anti-inflammatory agents in combination with rectal steroids, rectal sulphate, short-chain fatty acid enemas and different types of thermal therapy [7].

In hyperbaric oxygen therapy (HBOT), patients are breathing 100% oxygen at pressures greater than normal atmospheric (sea level) pressure. Instead of topical application of oxygen into tissues at levels only slightly higher than atmospheric pressure, HBOT consists of the systemic (patients are breathing the oxygen into their body) delivery...
of oxygen at levels two to three times higher than atmospheric pressure.

There are a number of well-established indications for HBOT, such as decompression sickness, air embolism or carbon monoxide poisoning. Since the mid-1980s, experiences dealing with the treatment of radiation-induced changes at various sites have been published [8]; encouraging results were reported in the case of radionecrosis of the mandible [9], complications of wound healing after surgery in irradiated head and neck regions [10], radiation-induced necrosis of the brain [11], as well as radiation-induced proctitis and cystitis [12,13].

We present the results of HBOT in patients with pelvic tumours suffering radiation-induced late side-effects, such as soft tissue necrosis (skin and vagina), cystitis, proctitis and fistulas.

Materials and Methods

Patients' Characteristics

Between January 2001 and December 2005, 108 patients underwent pelvic surgery and adjuvant postoperative pelvic radiotherapy for pelvic malignancy at the Institute of Radiotherapy, Tel-Aviv Sourasky Medical Center, Israel.

Twelve per cent of the patients (n = 13), with a median age of 60.3 years (range 32–88 years), suffered chronic radiation-induced toxicity after pelvic radiation. This group of patients was referred for HBOT. The clinical details are provided in Table 1.

Radiotherapy

All of the patients who were referred to radiation therapy underwent computed tomography simulation (Marconi Philips Simulator) and three-dimensional conformal planning (XiO planning system of SMS) of the pelvis. The standard prescription of treatment involved megavoltage energy of 6–8 MV (Electa), supine position, four-field arrangement: AP; PA; right and left opposed lateral fields.

A total of 5000 cGy was provided in standard fractionation of 200 cGy per fraction five times a week. Patients with cancer of the cervix also received three applications of high-dose rate brachytherapy (500–700 cGy per treatment, 1 week apart) by VariSorce Ir 162.

Hyperbaric Oxygen Therapy

The mean time between the completion of radiation therapy and the start of HBOT for persistent symptoms was 32 months (range 4–60). All patients underwent imaging studies and biopsies to exclude disease recurrence as the reason for the symptoms. All patients were already treated with conventional methods to alleviate symptoms, such as sigmoidoscopy followed by steroid enemas, laser cauterisation or cystitis with cystoscopy, and pain with pain medications.

Hyperbaric oxygen was given in a multiplace chamber. The protocol used was: 2.0 absolute atmosphere (ATA) pressure, 100% oxygen, and a treatment duration of 90 min on consecutive days. The study patients received an average of 27 HBOT (range 16–40) sessions.

Statistics

The patients were assessed by reviewing both the medical records taken during routine follow-up investigations at the Department of Oncology and the reports of the respective gynaecologist. The Common Toxicity Criteria (CTC) were graded in retrospect, based on the data from the patients’ records; the Wilcoxon matched-pairs signed-rank test was carried out to compare pre- and post-HBOT CTC morbidity scores using the StatXact computer program.

Results

The median time to occurrence of late radiation-induced toxicity was 10.1 months. Six patients suffered from proctitis/cystitis, five patients suffered from longstanding vaginal ulcers and fistulas and two patients suffered longstanding skin injuries (Table 1).

For radiation-induced toxicity grading we used the National Cancer Institute CTC grading system [14] (Table 2).

We used this grading system before and after HBOT. Details are shown in Table 3.

Table 1 – Patients’ characteristics

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Type of tumour</th>
<th>Age</th>
<th>Type of radiation-induced toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Endometrial carcinoma</td>
<td>82</td>
<td>Cystitis and proctitis</td>
</tr>
<tr>
<td>2</td>
<td>Cervical carcinoma</td>
<td>49</td>
<td>Cystitis and proctitis</td>
</tr>
<tr>
<td>3</td>
<td>Cervical carcinoma</td>
<td>53</td>
<td>Cystitis and proctitis</td>
</tr>
<tr>
<td>4</td>
<td>Cervical carcinoma</td>
<td>47</td>
<td>Cystitis and proctitis</td>
</tr>
<tr>
<td>5</td>
<td>Cervical carcinoma</td>
<td>76</td>
<td>Cystitis and proctitis</td>
</tr>
<tr>
<td>6</td>
<td>Rectal carcinoma</td>
<td>78</td>
<td>Cystitis and proctitis</td>
</tr>
<tr>
<td>7</td>
<td>Vaginal carcinoma</td>
<td>57</td>
<td>Recto-vaginal fistula</td>
</tr>
<tr>
<td>8</td>
<td>Bladder carcinoma</td>
<td>88</td>
<td>Vaginal ulcer</td>
</tr>
<tr>
<td>9</td>
<td>Cervical carcinoma</td>
<td>52</td>
<td>Vaginal ulcer</td>
</tr>
<tr>
<td>10</td>
<td>Cervical carcinoma</td>
<td>32</td>
<td>Vesico-vaginal fistula</td>
</tr>
<tr>
<td>11</td>
<td>Endometrial carcinoma</td>
<td>73</td>
<td>Vaginal ulcer</td>
</tr>
<tr>
<td>12</td>
<td>Cervical carcinoma</td>
<td>49</td>
<td>Wound healing complications</td>
</tr>
<tr>
<td>13</td>
<td>Cervical carcinoma</td>
<td>37</td>
<td>Wound healing complications</td>
</tr>
</tbody>
</table>

Table 2 – The National Cancer Institute Common Toxicity Criteria grading system (general definitions)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No adverse event or within normal limits</td>
</tr>
<tr>
<td>1</td>
<td>Mild adverse event</td>
</tr>
<tr>
<td>2</td>
<td>Moderate adverse event</td>
</tr>
<tr>
<td>3</td>
<td>Severe and undesirable adverse event</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening or disabling adverse event</td>
</tr>
<tr>
<td>5</td>
<td>Death related to adverse event</td>
</tr>
</tbody>
</table>
Henry's Law states that the amount of an ideal gas dissolved in solution is directly proportional to its pressure. Thus, the dissolved plasma oxygen concentration of 0.3 ml/dl at sea level (1.0 ATA) increases to 1.5 ml/dl upon administration of 100% oxygen, whereas hyperbaric oxygen delivered at 3.0 ATA yields a dissolved oxygen content of 6 ml/dl. The elevated pressure within the hyperbaric chamber results in a 10- to 15-fold increase in plasma oxygen concentration (arterial oxygen values of 1500–2000 mmHg), thereby producing a four-fold increase in the diffusing distance of oxygen from functioning capillaries. The latter figure is sufficient to meet resting tissue oxygen extraction requirements irrespective of the adequacy of the haemoglobin-bound oxygen pool [19]. The ability of HBOT to augment oxygen content and independently meet resting tissue oxygen requirements has led to its use in conditions of compromised oxygen delivery, such as profound anaemia, carbon monoxide poisoning, and both acute and chronic tissue ischaemia.

In vitro HBOT modulates local and systemic effects in both acute and chronic injury, ischaemia, and inflammation. Local hyperoxia induces vasoconstriction and reduces vasogenic oedema after acute trauma. HBOT ameliorates ischaemia-reperfusion-induced leukocyte influx and reduces the indirect component of injury by preventing such activation through a down-regulation of leukocyte receptor sites. By altering conditions of local hypoxia, HBOT facilitates fibroblast proliferation, angiogenesis, and wound healing [20,21] and it is reasonable to consider that it might improve radiation-induced damage.

Few controlled trials are available using HBOT for radiation-induced damage with different rates of response and lack of evaluation of the main factors for success [7,18]. Important parameters influencing the activity of HBOT include: atmospheric pressure, duration of exposure, oxygen percentage and interval between treatments, and lack of evaluation of the main factors for success with small non-randomised studies it is difficult to evaluate the most important factor or the best schedule of administration. In our group of patients we noticed an improvement in pelvic pain, necrosis and wound healing. The patients did not experience any side-effects. Moreover, none had local recurrence.

Despite our small group of patients, this schedule of HBOT suggests a method that might have a low level of toxicity and a high rate of symptom relief and quality of life improvement. We observed a high rate of pain relief and significant improvement in vaginal necrosis, discharge and bleeding, with moderate but significant relief of proctitis and cystitis and vaginal fistulas after failure of conventional methods. These features taken together makes HBOT an attractive modality for quality of life improvement in the treatment of patients with pelvic radiation toxicity. Further investigation with a larger sample size is warranted to confirm and improve the efficacy of HBOT in this setting.

**Discussion**

Late radiation damage is often characterised histologically by a loss of parenchymal cells and an overproduction of collagen. The classic theory of late radiation injury states that it is the depletion of these parenchymal cells that leads to late injury, and that the latent period preceding the development of late effects is caused by the long cell cycle time of many of these target cells. Recent evidence has highlighted the importance of microvascular endothelial damage as a major contributor to normal tissue injury after radiation [15]. The endothelium has been shown to be an important target for radiation in the lung, brain and gut [16]. Apoptosis of the microvascular endothelial cell seems to be the earliest lesion in the gut after radiation and leads to stem cell dysfunction [17]. Thus, a method that would cause neovascularisation (angiogenesis) should improve tissue functioning.

Conventional treatment of pelvic pain, cystitis, proctitis and vaginal discharge after radiation is generally not sufficient [18]. HBOT involves the systemic delivery of oxygen at levels two to three times greater than atmospheric pressure in order to enrich damaged tissues with oxygen and enhance endothelial and tissue healing. Most of the benefits of HBOT are explained by the simple physical relationships determining gas concentration, volume and pressure. Henry’s Law states that the amount of an ideal gas dissolved in solution is directly proportional to its partial pressure. Thus, the dissolved plasma oxygen concentration of 0.3 ml/dl at sea level (1.0 ATA) increases to 1.5 ml/dl upon administration of 100% oxygen, whereas hyperbaric oxygen delivered at 3.0 ATA yields a dissolved oxygen content of 6 ml/dl. The elevated pressure within the hyperbaric chamber results in a 10- to 15-fold increase in plasma oxygen concentration (arterial oxygen values of 1500–2000 mmHg), thereby producing a four-fold increase in the diffusing distance of oxygen from functioning capillaries. The latter figure is sufficient to meet resting tissue oxygen extraction requirements irrespective of the adequacy of the haemoglobin-bound oxygen pool [19]. The ability of HBOT to augment oxygen content and independently meet resting tissue oxygen requirements has led to its use in conditions of compromised oxygen delivery, such as profound anaemia, carbon monoxide poisoning, and both acute and chronic tissue ischaemia.

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