An observational trial to establish the effect of hyperbaric oxygen treatment on pelvic late radiation tissue injury due to radiotherapy

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Abstract
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Introduction: Rates of pelvic cancer are growing globally with around half of these patients receiving radiotherapy. In a small proportion, radiotherapy results in significant late radiation tissue injury (LRTI) to surrounding tissue, most commonly affecting the bladder and bowel mucosa. We conducted a combined prospective and retrospective observational trial to establish the effectiveness of hyperbaric oxygen treatment (HBOT) in improving the symptoms and signs of LRTI in these patients.

Methods: Fifty-two patients were included after receiving radiotherapy for cancers of the bowel, bladder, cervix, prostate or vulva. They received HBOT at 203–243 kPa (2.0–2.4 atmospheres absolute (atm abs)) for 90 minutes with the median number of treatments being 30 (IQR 1). Late effects normal tissues – subjective, objective, management, analytic (LENT-SOMA) scores were recorded before and after treatment.

Results: The mean LENT-SOMA scores before and after HBOT were 11.7 (SD 5.3) and 8.1 (5.1) respectively. This reduction in score of 3.7 (95% CI 2.6 to 4.8) was statistically significant ($P < 0.001$). For radiation cystitis the mean reduction was 3.7 (95% CI 2.4 to 5.0, $P < 0.001$) and for radiation proctitis was 3.8 (95% CI 1.4 to 6.1, $P = 0.004$). There were no significant adverse effects recorded.

Conclusions: Hyperbaric oxygen treatment may be an effective and safe treatment for pelvic late tissue radiation injury.

Introduction

Cancer is a significant issue worldwide, causing nearly one in six deaths globally.[1] Pelvic tumours make up the largest group of solid cancers in the USA.[2] One of the most frequent modalities of treatment is radiotherapy with around half of cancer patients receiving either curative or palliative radiotherapy. Whilst effective at eliminating cancer cells, there is unavoidable damage to surrounding tissues. These effects are often divided into early (within weeks) and late (months to years). The early phase involves DNA damage and cell death (commonly during mitosis or through apoptosis) and is usually self-limiting.[3,4] It characteristically affects rapidly proliferating cells such as the mucosa of the bowel and bladder. In contrast, the late phase is driven in part by chronic oxidative stress and abnormal cytokine cascades.[5] This leads to chronic inflammation, progressive endarteritis, hypoxia and fibrosis.[6] Once again, the most affected tissues are the mucosal surfaces. Of all patients receiving pelvic radiotherapy around 5–18% will develop symptomatic late radiation tissue injury (LRTI).[7]

The clinical manifestations of this process are organ specific. In the rectum, they vary from mild (minor bleeding, excessive mucus production, tenesmus, diarrhoea and urgency) to severe (major bleeding, ulceration, stricture and fistula formation). In the bladder, frequency, incontinence and haematuria with clot retention are common. In severe cases of both rectal and bladder injury, blood loss can result in significant anaemia and require repeated blood transfusion and/or surgical removal of the organ. The severity of these symptoms is largely dependent on cumulative radiation dose and the area of tissue affected, and is often responsible for a significant reduction in quality of life.[8–10] Despite this, there is wide variability between patients who have received the same radiation dose.[11]

Advances in cancer treatment mean an ever-increasing number of survivors, with around half of patients being long-term survivors.[12] This suggests an increasing number of patients may suffer from LRTI in the future and has led to an increased interest in methods to reduce this substantial burden. Conventional approaches involve either medical or surgical symptom control, the cost of which commonly totals tens of thousands of dollars per year.[13] Unfortunately, these have limited efficacy or unpleasant side effects of their own. Hyperbaric oxygen treatment (HBOT) has for some time been reported as useful in LRTI.[14–17] However, there are also

data to support the contrary view. For example, a randomised controlled trial (RCT) published in 2016 demonstrated no improvement in chronic bowel dysfunction with HBOT.[18] High quality trials involving HBOT are difficult to undertake for a number of reasons and to date the only other four RCTs published in pelvic LRTI were crossed-over in the short term,[17] unblinded,[19,20] or both.[21] The majority of reports are non-controlled retrospective or observational studies, often vulnerable to regression to the mean and placebo effect.[15] In light of this, multiple authors have suggested that further research is needed.[14,22]

The aim of this study was to evaluate the effectiveness of HBOT for ameliorating the symptoms and signs of pelvic LRTI presenting to our clinical service. We hypothesised that HBOT is an effective treatment for these patients. We also aimed to evaluate the use of a long proposed, but little used, system for grading these symptoms and signs: the 'late effects normal tissues – subjective, objective, management, analytic (LENT-SOMA) scoring system'. In particular, we want to evaluate both the ease of use and practicality of this score of clinical severity for incorporation into a prospective registry under development.

Methods

The study was approved by the Prince of Wales Human Research Ethics Committee (HREC 17/010(LNR/17/POWH/24). Informed consent was waived on the basis that all data is obtained routinely from all patients in our unit. The study was conducted at the Prince of Wales Department of Diving and Hyperbaric Medicine. We recruited patients retrospectively who completed treatment from July to December 2017 and prospectively from January to April 2018. The study subjects were drawn from patients accepted for treatment during the study period. Inclusion criteria were: a diagnosis of pelvic LRTI made by the referring physician based on symptomatology or objective findings on endoscopy. Endoscopic evaluation is preferred as it allows for exclusion of recurrence of cancer, which can present similarly to LRTI. It also allows for objective assessment of treatment response when repeated during the post-HBOT period.

TREATMENT PROTOCOL

Treatments were once a day Monday to Friday, for six weeks (30 treatments planned in total). Most patients were treated in a multiplace chamber breathing oxygen using a hood or mask at 243 kPa (2.4 atmospheres absolute [atm abs]) for 90 minutes. The remainder were treated in a monoplace chamber, breathing 100% O_2 at 203 kPa (2.0 atm abs) for the same length of time. Both groups had a 5-minute air break at 45 minutes. Historically these two treatments have been considered roughly equivalent in terms of oxygen dose; allowing for some ambient air entrainment in the multiplace system. We aimed to minimise any gaps in treatment but sometimes this was not possible due to patient circumstances, appointments at other medical facilities or complications such as two to three days off recovering from barotrauma to the middle ear. After completion of this initial course, patients were discharged home and reviewed one month later for the consideration of a further course of treatment if required, to a maximum total of 50 sessions.

DATA COLLECTION

Symptoms were evaluated before starting and after finishing treatment. Where possible this was performed by the same doctor. We used the 'bladder' and 'bowel' domains of the original LENT-SOMA scoring system. This system was created in 1995 to address a need for a uniform scoring system applicable to LRTI in a wide range of tissue sites.[23] It has been validated for scoring the severity of LRTI in the pelvis and has been shown to correlate well with other scales for bladder and bowel symptoms.[24–26]

The score is the sum of three numerical domains: *subjective* (asking about symptoms such as pain), *objective* (documenting signs such as bleeding or observations on endoscopy) and *management* (asking about medical management such as iron therapy). Each domain asks about several relevant symptoms, objective findings and interventions respectively. For each of these, there is a possible score between 1 (the least) to 4 (the worst) possible manifestation of that item. Any field for which there is no contribution (e.g., no pain) does not contribute to the score. It was not practical to include the objective domain as few patients underwent endoscopy at meaningful intervals before and after treatment.

Age, sex, type of malignancy, site and dose of radiation, comorbidities, length of HBOT, complications and reasons for any early termination of the course were recorded.

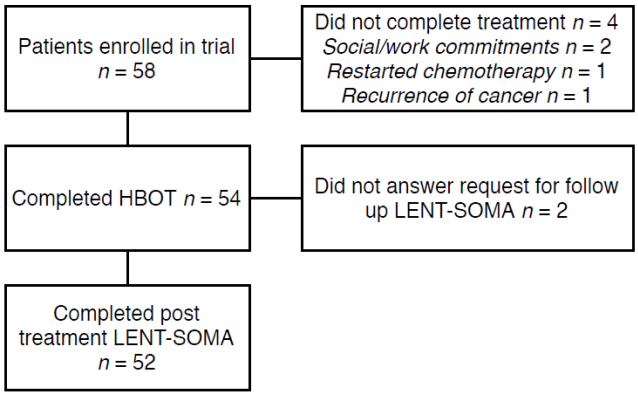
STATISTICAL ANALYSIS

Statistical analysis was performed using StatsDirect v3.1.11 (StatsDirect Ltd, Merseyside, UK). Parametric testing was deemed to be appropriate after visual inspection of the distribution of LENT-SOMA scores. Continuous data were assessed using paired *t*-tests and correlations were evaluated using simple linear regression and logistic regression as appropriate. A P-value < 0.05 was considered statistically significant. Data will be presented as mean and standard deviation or confidence interval, where appropriate. No formal sample size calculation was made on this opportunistic patient cohort.

Results

Fifty-eight patients were initially enrolled. Two withdrew because of work/social commitments. One had a recurrence of cancer and one had to restart chemotherapy. Two did not reply to our request for follow-up (see Figure 1). Data were therefore available for 52 patients. Of these,

Figure 1
PRISMA diagram demonstrating dropouts during the study



44 (84.6%) were male. The average age was 67.9 years (SD 10.1). The primary sites of LRTI were bladder (38 patients) bowel (13) and vulva (1). The primary malignancies were cancers of the prostate (41 patients), cervix (4), rectum (3), endometrium (2), bladder (1) and vulva (1).

Forty-eight of the 52 patients substantially completed the prescribed course of 30 treatments (27 to 31 sessions), while four completed a prescribed course of 20 treatments. Six of those completing an initial course of 30 treatments opted to have further sessions after the clinical evaluation of response (three had a further 20 sessions, two had eight and one had ten).

For the whole group, the mean LENT-SOMA score prior to HBOT was 11.7 (SD 5.3) while after completion of HBOT it was 8.1 (5.1). The maximum possible score was 44 in the rectum domain and 40 in the bladder domain. The mean reduction in score of 3.7 over the treatment period (95% CI 2.6 to 4.8) was statistically significant, $P < 0.001$. Subgroup analysis by affected site demonstrated a similar reduction for those with either proctitis or cystitis (mean reductions of 3.8 (95% CI 1.4 to 6.1); $P = 0.004$ and 3.7 (2.4 to 5.0); $P < 0.001$ respectively).

Simple linear regression demonstrated a statistically significant relationship between the severity of LRTI on presentation and the subsequent absolute reduction in LENT-SOMA scores ($P = 0.003$). There was no such clear relationship between the reduction in LENT-SOMA score and the number of HBOT sessions ($P = 0.71$), number of comorbidities ($P = 0.50$) or age ($P = 0.21$).

Thirteen of the 52 (25%) patients complained of ear pain during HBOT, of which two (3.8%) had clinically demonstrable barotrauma on examination. In both cases, this resolved and they were able to complete the course of treatment after a delay of two and three days respectively without further intervention. Four (7.7%) patients complained of myopia, which also resolved spontaneously. There were no other adverse events of therapy reported.

Discussion

The present findings are consistent with previous trials suggesting HBOT is an effective intervention for improving symptomatology in patients with LRTI. This was demonstrated by statistically significant improvements in scores using the LENT-SOMA grading system and our impression that the magnitude of these improvements is clinically important. A seemingly modest reduction of 3.7 can convey marked changes in a patient's quality of life. Examples from our series include a patient who had significant urinary frequency with recurrent admissions for clot-retention who became catheter-free and able to pass the night without having to urinate, and another who was housebound with social anxiety related to faecal incontinence is now able to socialise normally.

The most appropriate trial with which to compare the present proctitis scores is an RCT that demonstrated an improvement in LENT-SOMA scores after HBOT of 5.07 (from 12.55 to 7.48).[17] This is comparable to our mean improvement of 3.7 (from 11.7 to 8.1). We were unable to find any comparable trials using the LENT-SOMA system to assess symptoms of radiation cystitis. A recent RCT by Oscarsson et al. investigated HBOT treatment for radiation cystitis (as well as proctitis).[15] Their primary outcome was an improvement in expanded prostate cancer index composite (EPIC) scores, which have a large overlap with the subjective domain in the LENT-SOMA system. They observed an improvement in urinary symptoms of 22%, comparable to a 29.6% improvement in our group. We also demonstrated HBOT to be a safe intervention as evidenced by our low rate of side effects and absence of severe complications requiring early termination of the treatment course. HBOT has been shown to reduce the daily medical expenses for a patient with LRTI from AUD231.09 to AUD19.08.[13] The cost of a course of HBOT to treat LRTI at Prince of Wales Hospital has been estimated at AUD7153.[27] We believe this is a cost effective alternative to conventional treatments.

The present finding of a relationship between pre-treatment symptom severity and absolute improvement in LENT-SOMA scores makes clinical sense. The worst affected by any disease have the greatest potential for improvement. When we instead looked at the percentage improvement relative to the original score there was no trend, suggesting patients with worse symptoms did not improve disproportionately compared to those with mild disease. The absence of a relationship between number of treatments and change in LENT-SOMA scores probably reflects the fact that the majority received very close to 30 treatments (median 30, IQR one). It is also probable our study was not sufficiently powered to establish such a link. The six patients who had a further course of HBOT (an extra planned

10–20 treatments) had a smaller improvement in scores (1.5 vs. 3.9 for 'non-extenders') after completion of all treatments. Although this was not statistically significant it may represent a cohort of poor responders to HBOT.

THE LENT-SOMA SCORING SYSTEM

When the LENT-SOMA scoring system was released in 1995 the authors recommended taking the sum of all individual item scores and dividing by the number of items for which there was a score recorded, to give the overall severity score. Initial observations suggested this could lead to a misleadingly low overall score in a patient who had a high score in only one domain with low scores in all others.[28] It has become common practice over the years to report the sum of raw scores from each domain, as we have done in this report. This does not allow for comparison between different tissue types, as was the original aim of the system, but we feel it is a better representation of the impact of radiation injury on the individual.

Any system evaluating the side effects of a therapy must find a balance between high sensitivity and specificity for the diagnosis (e.g., mucosal changes on cystoscopy/sigmoidoscopy) and a representation of the impact on the patient (e.g., quality of life or functional assessments).[11] The four domains in the LENT-SOMA tables (subjective, objective, measured, analytic) was an attempt to strike this balance and it has been shown to have correlation with quality of life (QoL) scores.[29] Interestingly, several patients in the present cohort reported significant improvements during an informal discussion of QoL despite little improvement in their LENT-SOMA score and others reported the reverse.

Some studies have used cut-offs (e.g., an improvement of two points) as the minimum improvement likely to be important to an individual patient. Instead, we simply reported the mean changes in score, along with statistical significance testing of before and after scores. While any such assessment is very subjective, it is inferred from the observed changes over the course of treatment that many patients are improved in a clinically meaningful way. This investigation has prompted inclusion of a brief QoL assessment at first consultation, at treatment completion and at four week follow-up.

There were several other practical issues with the scoring system. Firstly, the scoring terminology was not very clear or intuitive, i.e., using criteria such as 'occasional' or 'intermittent' rather than clearly defined frequencies. Secondly, the inclusion of double criteria led to room for interpretation, i.e., dysuria could be 'occasional and minimal' (Grade 1) or 'persistent and intense' (Grade 3), but what if it was occasional yet intense? We feel in part this accounts for our anecdotal observations of inter-interpreter variability when different doctors scored symptoms in the same patient.

The objective and analytic domains in the LENT-SOMA tables were also sources of difficulty. Many patients had not had a recent cystoscopy/sigmoidoscopy or the results were very difficult to track down. As we re-assessed the patients shortly after they had completed treatment there was little opportunity for them to be re-evaluated objectively (on endoscopy).

Over the course of writing this paper, we have been introduced to an adaptation of the original LENT-SOMA tables that solve many of the above problems. For example, the separation of the frequency and severity of a symptom into two separate scores and the replacement of vague criteria such as 'occasional' with 'monthly'. In addition, the questionnaire has been divided into two sections. Subjective/management criteria are filled out as much as possible by the patient, removing interpreter bias. The clinician then fills out a questionnaire regarding objective findings (e.g., cystoscopic) where available. These are recommended for future use.[30]

LIMITATIONS

Aside from the difficulties with the LENT-SOMA scoring system, there were other issues requiring acknowledgement. The LENT-SOMA assessments were made by physicians involved in patient care and there was no comparator group with which to draw a comparison; either may bias the result favourably. As such, regression to the mean or a participation effect unrelated to any actual pathophysiological therapeutic benefit of HBOT cannot be ruled out. It is widely accepted that the 'ritual' of regular daily exposure over six to eight weeks to the chamber environment, supportive staff and one's fellow patients may make HBOT a powerful placebo procedure.[31] This effect may have been demonstrated in the Clarke et al. RCT, where 63% of the control group reported some response to sham treatment.[17]

Unfortunately having a control group is both technically challenging due to the nature of the treatment and highly consumptive of resources. Inevitably, in a busy service it means denying or delaying patients with accepted indications because of the fixed capacity of the chamber and attendant staff. A further ethical consideration surrounds the denial of what has become a routine accepted treatment to the putative control group. While we have demonstrated the effect we could anticipate in the active arm of a blinded, sham-controlled future study, we do not at this time have plans for a future controlled study.

A further limitation was the limited follow-up period of one month after treatment completion. This has two implications. Firstly, it has been shown that patients continue to improve for several months after HBOT, and there is potential to miss some improvements that manifested after follow-up.[17] Secondly, it is not possible to comment on whether or not any improvement in symptoms will have a lasting effect.

Conclusions

A review of the treatment outcome for LRTI patients in our unit suggests these patients are positively impacted by HBOT and this is consistent with most previous reports. There continues to be a good case for high quality, blinded and randomised trials, possibly in a group of patients for whom HBOT is not currently available due to geographical or regulatory constraints.

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