NHS England

Clinical Commissioning Policy Proposition: Hyperbaric Oxygen Therapy for soft tissue radiation damage in patients with a history of pelvic irradiation for malignant disease

Reference: NHS England 1778

Prepared by NHS England Specialised Services Clinical Reference Group for Hyperbaric Oxygen Therapy

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1 Executive Summary

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About Soft Tissue Radiation Damage in Patients with a History of Pelvic Irradiation for Malignant Disease

Radiation therapy to treat pelvic cancer can damage normal tissue. This will normally heal on its own following completion of the radiotherapy treatment. In some cases, however, serious radiation-related complications can develop months or years later (Bennett et al 2016). Late tissue radiation damage can significantly reduce quality of life and can be life threatening (Bennett et al 2016).
Areas that are particularly sensitive to soft tissue radiation damage are the pelvis, especially the rectum (Hoggan & Cameron 2014).

About current treatments

Treating tissue radiation damage can include symptom management and surgery to remove or repair the affected area (Bennett et al 2016).

Management strategies for patients whose condition fails to respond to standard interventions remain unclear and lacking in good quality evidence (NHS England 2017).

About the new treatment

In hyperbaric oxygen therapy (HBOT) patients receive 100% oxygen inside a pressurised treatment chamber (Hoggan & Cameron 2014). The aim of HBOT is to increase the number of blood vessels in irradiated tissue, improve tissue quality, promote healing and prevent breakdown of irradiated areas (Bennett et al 2016).

What we have decided

NHS England has carefully reviewed the evidence supporting the addition of hyperbaric oxygen to the standard treatments for soft tissue radiation damage in patients with a history of pelvic irradiation for malignant disease.

We have concluded that there is not enough evidence to make the treatment available at this time.

2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission hyperbaric oxygen treatment for soft tissue radiation damage in patients with a history of pelvic irradiation for malignant disease.

3 Proposed Intervention and Clinical Indication

About soft tissue radiation damage in patients with a history of pelvic irradiation for malignant disease

Radiation therapy to treat pelvic cancers can damage normal tissue in the radiated area. This normally heals spontaneously following completion of the radiotherapy treatment. However, in some cases serious radiation-related complications can develop months or years later (Bennett et al 2016). This can result in fibrosis, ulceration or areas of cell death (radiation necrosis). Late tissue radiation damage can significantly reduce quality of life and can be life threatening (Bennett et al 2016).

Areas that are particularly sensitive to soft tissue radiation damage are the pelvis, especially the rectum, and the skin and mucosa of the head and neck (Hoggan &

Cameron 2014).

Pelvic radiation disease is defined as “transient or long-term problems ranging from mild to severe, arising in non-cancerous tissues resulting from radiotherapy treatment to a tumour of pelvic origin” (van de Wetering et al 2016).

Radiation proctopathy is the most commonly investigated late-radiation effect to the pelvis with common symptoms including rectal urgency, rectal incontinence, pain, strictures, mucus discharge and rectal bleeding (van de Wetering et al 2016). Symptoms associated with pelvic radiation can also include bloating, flatulence and diarrhoea (Glover et al 2016). The pathophysiology and symptomatology of radiation proctopathy are complex because different anorectal sub-regions can be involved (van de Wetering et al 2016).

Haemorrhagic cystitis is a diffuse inflammatory condition of the bladder due to an infectious or non-infectious aetiology resulting in bleeding from the bladder mucosa and is a relatively common and potentially severe complication of high-dose chemoradiotherapy for the treatment of pelvic malignancies (Shao et al 2011). The clinical manifestation of this condition can vary from microscopic haematuria to severe haemorrhage with clot formation and urinary tract obstruction. This can lead to hydronephrosis and acute renal failure when it becomes chronic and recurrent” (Shao et al 2011). Symptoms can include urinary frequency, urgency and pelvic pain (Shao et al 2011).

Current treatment

Treatments for late tissue radiation damage include symptom management and surgery to remove or repair the affected area (Bennett et al 2016). Surgical intervention in an area that has received radiation therapy is associated with an increased incidence of delayed healing, infection or breakdown of the surgical wound (Bennett et al 2016).

Non-surgical options include aminosalicylic acid derivatives (such as sulfasalazine and mesalazine), short chain fatty acid preparations, sucralfate preparations, coagulation therapy, corticosteroids, formalin applications, pentoxyfilline, antibiotic treatment, hyperbaric oxygen therapy, retinol palmitate and Chinese traditional medicine in combination with Western medicine (van de Wetering et al 2016).

Management strategies for patients whose condition fails to respond to standard interventions remain unclear and lacking in good quality evidence (NHS England 2017).

Proposed Intervention

In HBOT patients receive 100% oxygen inside a pressurised treatment chamber (Hoggan & Cameron 2014). Treatments typically involve pressurisation of between 2.0 and 2.5 atmosphere absolute (ATA) (203 to 253 kilopascal (kPa)1) for between 60 and 120 minutes once or twice daily for a total of 30 to 60 sessions (Bennett et al 2016).

The aim of HBOT is to increase the number of blood vessels in irradiated tissue, improve tissue quality, promote healing and prevent breakdown of irradiated areas (Bennett et al 2016).

4 Definitions

Aminosalicylic acid: is a derivative of salicylic acid which is an active ingredient of aspirin.

Atmospheres absolute (ATA): a measurement used to describe atmospheric pressure; one ATA is roughly equivalent to sea level atmospheric pressure.

Coriticosteroids: anti-inflammatory medicines used to treat a range of conditions.

Fibrosis: the formation of excess fibrous connective tissue in an organ or tissue in a reparative or reactive process.

Hydronephrosis: a condition where one or both kidneys become stretched and swollen as the result of a build-up of urine inside them

Pentoxyfilline: a drug that makes blood cells more flexible and less likely to stick to vessel walls – it is used to treat muscle pain in people with artery disease.

Radiation therapy/Radiotherapy: a treatment where radiation is used to kill cancer cells. There are many different ways you can have radiotherapy, but they all work in a similar way. They damage cancer cells and stop them from

[1] 1 ATA = 101.3 kPa

growing or spreading in the body.

Retinol palmitate: a form of Vitamin A.

Ulceration: the formation of a break on the skin or on the surface of an organ.

Radiation proctopathy: a common complication following radiation therapy of pelvic malignancies. Symptoms include haematochezia (blood in stool), urgency, constipation, diarrhoea and rectal pain.

5 Aims and Objectives

This policy proposition considered: the evidence underpinning the use of HBOT for soft tissue radiation damage in patients with a history of pelvic irradiation for malignant disease.

The objectives were to:

consider whether, in the management of soft tissue radiation damage in patients with a history of pelvic irradiation for malignant disease:

- the evidence base supports HOBT as a routine adjuvant treatment.
- the evidence base identifies the place of HBOT in the care pathway
- there is evidence that the effect of HBOT varies in the following groups
    - those in whom there is no evidence of recurrence
    - those in whom HBOT is used to gain palliative control of symptoms
    - those who receive 30 or more HBOT treatments
- there is evidence that any beneficial effects are maintained in the medium or long term
- there is evidence that HBOT is cost effective when used in this way.

6 Epidemiology and Needs Assessment

Late radiation tissue injury affects between 5% and 15% of long time survivors who received radiotherapy with the incidence varying with dose, age and treatment site (Bennett et al 2016). In patients who have received radiotherapy for pelvic cancer, up to a third subsequently develop chronic moderate or severe gastrointestinal symptoms (Glover et al 2016).

No accurate data were identified to enable an estimation of the proportion of

patients that have symptoms that are not relieved or rendered manageable by standard interventions.

7 Evidence Base

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of this treatment for the indication.

Summary of Evidence

NHS England commissioned a review of the published evidence on the use of HBOT treatment for soft tissue radiation damage in patients with a history of pelvic irradiation for malignant disease. To aid in the search for clinically relevant literature, experts in the field of HBOT guided the development of a Population, Intervention, Comparison, Outcome (PICO) framework. Key findings were:

- The evidence review found two randomised controlled trials (RCTs) comparing HBOT to sham treatment, one randomised controlled trial comparing HBOT to intravesical hyaluronic acid instillation (HA) and one non-randomised controlled study comparing HBOT to argon plasma coagulation (APC).
- The studies considered different outcomes and reported outcomes at different time periods following treatment. Outcomes were those most commonly related to changes in the symptoms experienced by patients.
- The most recent trial with 84 patients considered outcomes of gastrointestinal symptoms, rectal bleeding and bowel dysfunction. This study did not find any significant differences in the outcomes for patients receiving HBOT and patients receiving sham treatment 12 months after the treatment (Glover et al 2016).
- The largest trial with 150 patients found a greater improvement in LENT SOMA score (a scoring system for severity of radiation-induced complications) for the HBOT group than the sham group immediately following treatment (an improvement of 5.00 points for HBOT and 2.61 points for sham) (Clarke et al 2008).
- This study also found that a greater proportion of HBOT patients showed at least some improvement on clinical evaluation immediately following treatment (89% vs 63%) (Clarke et al 2008). Four categories were used for clinical improvement: healed, significant improvement, moderate improvement or no improvement. The

proportion of patients that were considered healed in each group was 8% for HBOT and 0% for sham. No definition was provided to explain what was meant by a moderate or significant improvement.

- Quality of life outcomes were reported in one trial (Clarke et al 2008). This found no difference between HBOT and sham patients in general well-being assessed immediately after treatment. The study did find that the HBOT group had a greater improvement from baseline (14%) than the sham group (5%) on a bowel bother scale. However the HBOT group had a lower score at baseline and the bowel bother scores were similar for both groups immediately following treatment (approximately 60%).
- The evidence review also found two small studies that compared HBOT to other treatments. These were intravesical hyaluronic acid instillation (HA) in patients with haemorrhagic cystitis (Shao et al 2011) and argon plasma coagulation (APC) in patients with radiation proctopathy (Álvaro-Villegas et al 2011).
- Shao et al (2011) found no significant difference between HBOT and HA in the proportion of patients showing a partial or complete response to treatment (75% in both groups at final follow-up 18 months after treatment).
- No direct comparison of the two groups was done for the other outcomes reported by Shao et al (2011) of voiding (urinating) frequency and pelvic pain. An improvement from baseline was seen in both groups for voiding frequency at six months (by approximately one to three voids per day from a baseline of approximately 10 voids per day). However this improvement was not sustained over the 18 month follow-up period. An improvement in pelvic pain from baseline was seen in both groups at six, 12 and 18 months. This improvement was approximately one point on a 10-point pain scale from a baseline of approximately two to three points.
- Álvaro-Villegas et al (2011) found no significant difference between HBOT and APC for change in haemoglobin level at one, two or three months follow-up. For the other two outcomes assessed (number of transfusions and tissue toxicity) the improvement was greater in the APC group in the first two months. By three months the HBOT group had also improved and there was no significant difference between the groups. In both groups the number of transfusions required ranged from approximately four to five at baseline to less than one at

three months follow-up. The time period over which transfusions were received was not specified.

- One study reported a significantly higher incidence of urinary tract infection (UTI) in the HA group (43%) compared to the HBOT group (10%) at six months follow-up (Shao et al 2011). There was no significant difference between the groups at later follow-up with a UTI incidence of 50% for the HA group and 30% for the HBOT group at 18 months follow-up.
- Other studies did not report any analysis comparing the number of adverse events between HBOT and sham or other treatments.
- Common adverse events in patients receiving HBOT were eye changes including myopia (30% in one study) and ear pain (28% in one study).
- No studies assessing the cost effectiveness of HBOT for soft tissue radiation damage were identified.
- There were limitations in the studies reported. The two trials comparing HBOT to sham did not include all patients in their analysis, reducing confidence in their results, and the study authors did not always include enough information to enable the reader to understand the importance of their results.
- Direct comparison between the studies is not possible due to the different comparators used, the different outcome measures reported and the different time periods used for the assessment of outcomes following treatment.
- At present there is inconsistent evidence about the efficacy of HBOT compared to sham in the treatment of soft tissue radiation damage following pelvic irradiation. Further adequately powered trials comparing HBOT to sham may be warranted.

Conclusion

The evidence identified for HBOT for the treatment of soft tissue radiation damage after pelvic irradiation included three randomised controlled trials and one non-randomised controlled study.

Studies reported improvements from baseline following HBOT treatment. However, only one of the two studies comparing HBOT to sham provides evidence of better outcomes with HBOT treatment. This was the largest study identified, but only reported comparative outcomes immediately following treatment and the clinical

meaningfulness of the improvements observed with HBOT is unclear.

Two small studies comparing HBOT to other treatments also showed improvement with HBOT but HBOT was not superior to the alternative treatments.

At present there is inconsistent evidence about the efficacy of HBOT compared to sham in the treatment of soft tissue radiation damage following pelvic irradiation. HBOT was not superior to alternative treatments in two small studies. Given the discrepancy in the results of the two sham-controlled trials identified and the limitations of these studies, further adequately powered trials comparing HBOT to sham may be warranted.

8 Documents That Have Informed This Policy Proposition

This document updates and replaces the present policy - NHS England policy: Hyperbaric Oxygen Therapy April 2013 NHSCB/D11?P/a *https://www.england.nhs.uk/commissioning?s=hyperbaric+oxygen*

9 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned.

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