Clinical Commissioning Policy Proposition: Hyperbaric Oxygen Therapy for diabetic lower limb ulceration (diabetic foot ulcer)

Reference: NHS England

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

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Contents

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 Diabetic Foot Ulcer

A diabetic foot ulcer is an open wound or sore on the skin that is slow to heal (NHS Choices, 2016). People with diabetes mellitus are at increased risk of foot ulceration. Diabetes can reduce the blood supply to feet and cause a loss of feeling known as peripheral neuropathy (NHS Choices, 2015). This can mean foot injuries do not heal well, and a person may not notice if their foot is sore or injured.

About current treatments

The usual treatment of diabetic foot ulcers requires a team of health care professionals working together including foot and diabetic specialists. Treatment options include close monitoring of the ulcer, the use of antibiotic medicines, caring for the wound, and removing dead tissue. A treatment to help restore blood flow to the foot called revascularisation is also usually considered (National Institute for Health and Care Excellence 2015).

About the treatment

In addition to the standard care for diabetic foot ulcer, Hyperbaric oxygen therapy (HBOT) has been suggested as a helpful addition in cases where the normal treatment has failed to heal the wound. Hyperbaric oxygen therapy (HBOT) involves the inhalation of pure oxygen at a pressure higher than normal atmospheric pressure, usually 2 to 3 atmospheres absolute (ATA). During HBOT, the patient is in a pressure chamber, and when used for the treatment of diabetic foot ulcers, this is usually for 45 to 120 minutes on most days for several weeks.

What we have decided

NHS England has carefully reviewed the evidence supporting the addition of hyperbaric oxygen to the standard treatments for diabetic foot ulcers. Although there would be value in a further double-blind trial of HBOT for this indication, we have concluded that there is not enough evidence to make the treatment routinely 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 diabetic foot ulcers.

For the purpose of consultation, NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

3 Proposed Intervention and Clinical Indication

About diabetic lower limb ulceration (diabetic foot ulcers)

People with diabetes mellitus are at increased risk of foot ulceration. The ulcers are multifactorial, often caused or exacerbated by diabetic peripheral neuropathy and angiopathy. Diabetic neuropathy diminishes perception of pain, so that minor damage, such as localised pressure caused by unsuitable shoes, abnormal biomechanical stress or open wounds, is often not noticed. This makes early

treatment difficult and makes the development of a foot ulcer more likely. Poor circulation because of diabetic vessel damage, leads to faster tissue breakdown and impairs resistance to infection, and ulcer healing (Schaper et al., 2012).

Current treatment

Standard treatment of diabetic foot ulcers requires a multidisciplinary team comprising a podiatrist, an orthotist, a specialised nurse and a diabetologist. Treatment options include close monitoring, intensive systemic antibiotic therapy, wound dressings and removal of dead tissue (debridement). Revascularisation is also usually considered (National Institute for Health and Care Excellence 2015).

Proposed Intervention

In HBOT patients receive 100% oxygen inside a pressurised treatment chamber (Hoggan & Cameron, 2014). Hyperbaric oxygen therapy (HBOT) involves the inhalation of pure oxygen at a pressure higher than normal atmospheric pressure, usually 2 to 3 atmospheres absolute (ATA). During HBOT, the patient is in a pressure chamber, and when used for the treatment of diabetic foot ulcers, this is usually for 45 to 120 minutes on most days for several weeks.

Side effects of HBOT are mostly infrequent and most often completely reversible. Reversible myopia, due to oxygen toxicity on the lens, is the commonest side effect and can last for weeks or months. Epileptic fits are rare and usually cause no permanent damage. A suggested carcinogenic effect of hyperbaric oxygen has not been substantiated in extensive studies. (Leach, Rees & Wilmshurst, 1998). Irreversible serious harm or death is rare. Fire in the chamber is the most common cause of death and has been described in units with poor regulation and inadequate supervision. There have been no reports of fire in a UK therapeutic chamber in the past 50 years. Table 1 provides a summary of risks.

	UHMS 2018/ Camporesi 2014	**UHMS 2018**	**Leach et al 1998**	**Hadanny 2016**		
	% of patients			**% of patients**	**Incidence per HBO session**	Comments
Subjective barotrauma				3.4	174:100,000	
Symptomatic reversible barotrauma			15-20			

Objective middle ear barotrauma	2			9.2	410:100,000		
Sinus squeeze				0.7	27:100,000		
Hypoglycaemia				0.4	17:100,000		
Seizures			1-2	0.3	11:100,000	Usually cause no permanent damage	
	0.01 to 0.03					Elective treatments	
	1.8					Carbon monoxide poisoning	
		0.6				Decompression illness	
Dizziness/weakness				1.5	57:100,000		
Claustrophobia	2			0.3	11:100,000		
Chest pain				0.9	35:100,000		
Pulmonary barotrauma during decompression	Rare						
Pulmonary oedema		Rare					
Dyspnoea			15-20	0.3	13:100,000		
Visual changes	69		≤20	0.3		Can last for weeks or months	
	96					Extremely prolonged treatment series	
New onset cataracts	47					Extremely prolonged treatment series	

4 Definitions

Adjuvant treatment: a treatment carried out in addition to normal treatment.

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

Barotrauma: damage to the ear or other gas-filled spaces in the body caused by changes in pressure.

Debridement: surgical removal of dead tissue.

Diabetic peripheral neuropathy: nerve damage caused by chronically high blood sugar in diabetes. It leads to numbness, loss of sensation, and sometimes pain in the feet, legs, or hands. It is the most common complication of diabetes.

Haemorrhage: an escape of blood from a broken blood vessel

Metatarsals: a group of five long bones in the foot.

Myopia: near-sightedness (close objects look clear but distant objects appear blurred)

Placebo treatment: fake (or dummy) treatment given to patients in the control group of a clinical trial. It is indistinguishable from the actual treatment (which is given to patients in the experimental group). The aim is to determine what effect the experimental treatment has had - over and above any placebo effect caused because someone has had (or thinks they have had) care or attention.

Pulmonary oedema: excess accumulation of fluid in the lungs.

PICO: A framework for defining a clinical question that aids in finding clinically relevant evidence in the literature. PICO stands for Patient/Population/Problem, Intervention, Comparison and Outcome.

Randomisation: Assigning people in a research study to different groups without taking any similarities or differences between them into account. It means that each individual (or each group in the case of cluster randomisation) has the same chance of having each intervention.

Randomised controlled trials: a study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment or other intervention.

Refractory Ulcers: ulcers that are unresponsive to standard care.

Revascularisation: a surgical procedure to help restore blood flow to an area of the body.

Sham treatment: This is a form of placebo treatment. Sham treatments are methods used in medical trials to help researchers determine the effectiveness of a drug or treatment. In sham treatments, the doctor goes through the motions without actually performing the treatment.

Systematic review: A review that summarises the evidence on a clearly formulated review question according to a predefined protocol, using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, analyse, collate and report their findings.

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

5 Aims and Objectives

This policy proposition considered: the evidence underpinning the use of HBOT for diabetic lower limb ulceration (diabetic foot ulcers).

The objectives were to:

- consider whether, in the management of diabetic lower limb ulceration (diabetic foot ulcers) the evidence base supports the addition of HBOT as a routine adjuvant treatment.
- the evidence base identifies the place of HBOT in the care pathway
- there is evidence that HBOT is cost effective when used in this way.

6 Epidemiology and Needs Assessment

The annual incidence of foot ulcers among people with diabetes has been estimated at between 2.5% and 10.7%, and the annual incidence of amputation is 0.25% to 1.8% (Boulton, 2008). This translates into between 58,470 and 250,252 potential cases of foot ulcers in England (PHOF, 2017).

Regular foot examination, patient education, simple hygienic practices, provision of appropriate footwear, and prompt treatment of minor injuries can decrease ulcer occurrence by 50% and eliminate the need for major amputation in non-ischaemic limbs (Larsson et al., 1995; Lavery, Wunderlich, & Tredwell, 2005).

The majority (60–80%) of foot ulcers will heal, while 10–15% of them will remain active, and 5–24% of them will finally lead to limb amputation within a period of 6–18 months after the first evaluation (Alexiadou & Doupis, 2012). True estimates of the numbers of patients with refractory ulcers are difficult to make because of the variation in 'standard' care in clinical practice.

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 patients with diabetic lower limb ulceration (diabetic foot ulcer). 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:

- This evidence review found four randomised controlled trials and one cost-utility analysis.
- Two trials compared HBOT plus standard care with standard care only, and two compared HBOT plus standard care with sham HBOT plus standard care.
- They reported results in three categories: amputation or the emergence of indications for amputation, partial or complete ulcer healing and adverse effects of treatment.
- Fedorko et al 2016 conducted a double-blind randomised trial using air at slightly above atmospheric pressure as a sham alternative to HBOT. The authors reported no effect of HBOT on rates of meeting vascular surgical criteria for major amputation (95% CI 0.37 to 2.28, p = 0.846) or of recommendation of major or minor amputation (95% CI 0.52 to 2.43, p = 0.771) among their 103 participants. Major amputation was defined as a procedure below the knee or at the level of the metatarsals; minor amputations were at the level of the toes.
- Fedorko et al (2016) reported that at 12 weeks after starting HBOT, there was no significant effect of HBOT on wound size, the rate at which the wound edge advanced, the results of a wound assessment tool or the proportion of wounds that healed.
- In another double-blinded study, Löndahl et al (2010) randomised 94 participants between HBOT and hyperbaric air, both at 2.5 atmospheres. The authors reported rates of complete healing of the index ulcer of 52% in the HBOT group and 29% in the placebo group (p = 0.03). The longer follow up period of this study (1 year compared to 12 weeks in Fedorko et al) enabled the authors to report rates of death and actual major (above the ankle) and minor amputation. There were 3 major amputations (above the ankle) in the HBOT group and one in the control group, along with 4 minor amputations in each group. However, the statistical significance of these differences was not tested. By contrast, Duzgun et al's (2008) unblinded trial with 100 participants did not use a placebo treatment. These authors reported that more participants treated with HBOT had

ulcers that healed (66% vs 0%, $p < 0.05$) or were treated with a graft or flap (8% vs 0%, $p < 0.05$), while fewer had an amputation (distal: 8% vs 48%, $p < 0.05$; proximal: 0% vs 34%, $p < 0.05$).

- Ma et al (2013) reported a smaller, less reliable, unblinded study, with only 36 participants. They reported the same rates of completed ulcer healing with and without HBOT. Ulcer size was reported as reducing faster after HBOT, though not to the extent that significantly more ulcers had healed by the end of the study.
- Participants who underwent HBOT in Fedorko et al's (2016) trial reported 24 adverse events which had not been specifically solicited by the researchers, significantly more than the five events reported by the participants who had a sham treatment. Rates of reporting of solicited adverse events were similar in the two groups. Löndahl et al (2010) reported similar rates of adverse events in the two arms of their trial. The most common adverse events in these two trials included barotrauma, inability to equalise middle ear pressures and episodes of hypo- or hyper-glycaemia. Ma et al (2013) reported no adverse events in either arm of their trial.
- Fedorko et al (2016) reduced the risk of observer bias by the use of a placebo treatment with hyperbaric air, and double-blinding. The pressure of the air (125 kPa / 1.23 ATA) was asserted to be too low to have an adverse effect on wound healing. The authors argue that this was substantiated by the higher rate of adverse reactions in the intervention arm. The randomisation resulted in different proportions of participants with potential confounders in each arm: for example, the HBOT group participants had had their index ulcer for less time than those in the control group, but had had diabetes for longer. The authors reported no benefit from HBOT as assessed at 12 weeks.
- Löndahl et al (2010) also used a double-blind design, with control participants receiving placebo hyperbaric air. Randomisation in this trial resulted in no important differences between participants allocated to the two arms. Fedorko et al. suggest that the placebo pressure used by Löndahl et al (2.5 ATA vs 1.23 ATA in Fedorko) might be high enough to create a risk of adverse effects on ulcer healing in the control arm. However, neither the magnitude, nor the likelihood of this risk was estimated by Fedorko et al.

- The other two trials reported benefit from HBOT. However, both were at material risk of bias because the participants and the researchers were aware of whether HBOT had been used; this is a plausible explanation for their discrepant results.
- There are some additional concerns about Duzgun et al (2008). The authors appear to suggest that there may have been significant confounding, though the nature, extent and impact of this are not reported.
- Furthermore, none of 50 control participants' ulcers in Duzgun et al's (2008) trial were healed after 92 weeks of treatment. This is inconsistent with the other trials, despite the participation of people with Wagner grade 2 ulcers in all trials, and calls into question the effectiveness of standard care in this trial. Poor standard care would make this trial not generalisable to the NHS.
- Adverse events appear more common after HBOT.
- We found one cost-utility study. Chuck et al (2008) reported that HBOT was both more effective and less expensive than standard care.
- Chuck et al's (2008) analysis is of limited relevance and reliability.
- It used estimates of the effectiveness of HBOT from a study published in 2003 (Guo et al 2003), which predates the three randomised trials in this rapid evidence review. The model's assumptions about the effectiveness of HBOT are incompatible with this more recent evidence, which is derived from more reliable studies. Chuck et al (2008) themselves noted that the clinical data that they used were "*limited*". The costs are based on the Canadian health care system in 2008, and may be materially different from those in the NHS. The authors admitted that their data were not *"of high quality."* They went on to note *"Cost data for HBOT were based on data from only a few centers, and reporting was not standardized"*.

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Conclusion

There is inconsistent evidence that HBOT is effective in the treatment of diabetic foot ulcers. Taken as a whole, the evidence is insufficient and so does not support HBOT's routine use in the NHS for this indication. Two of the trials reporting benefit were at risk of placebo effects and observer bias because they were

unblinded; they are unreliable. Of the two double-blind trials, one reported no benefit from HBOT as judged at 12 weeks and a second reported benefit observed at 52 weeks. The study reporting benefit used a higher pressure for the sham treatment than was used for the sham treatment in the study reporting no benefit.

There would be value in a further double-blind trial of HBOT for this indication, with a control similar to that used in Fedorko et al (2016).

8 Proposed Criteria for Commissioning

Not for routine commissioning.

9 Proposed Patient Pathway

Not for routine commissioning.

10 Proposed Governance Arrangements

Not for routine commissioning.

11 Proposed Mechanism for Funding

Not for routine commissioning.

12 Proposed Audit Requirements

Not for routine commissioning.

13 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

14 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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