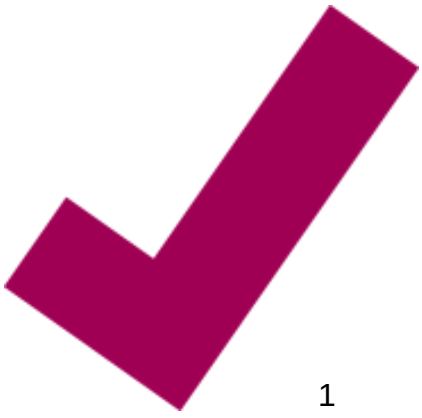
Clinical Commissioning Policy Proposition: Hyperbaric Oxygen Therapy for Carbon Monoxide Poisoning

Reference: NHS England



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

Published by NHS England, in electronic format only.

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 carbon monoxide poisoning

Carbon monoxide is an invisible poisonous gas that has no smell or taste. Breathing it in can cause illness and it can be fatal if a person is exposed to high levels. After carbon monoxide is breathed in, it enters your bloodstream and mixes with haemoglobin (the part of red blood cells that carry oxygen around your body), to form carboxyhaemoglobin. When this happens, the blood is no longer able to carry oxygen, and this lack of oxygen causes the body's cells and tissue to fail and die. (NHS Choices, 2016).

About current treatments

Standard oxygen therapy in hospital will be needed after exposure to a high level of carbon monoxide. 100% oxygen is given through a tight-fitting mask (normal air contains around 21% oxygen). Breathing in concentrated oxygen enables the body to quickly convert carboxyhaemoglobin back into the normal form of haemoglobin which can then deliver more oxygen around the body (NHS Choices, 2016) For those patients who have any residual symptoms, follow-up will be organised.

About the treatment

Hyperbaric oxygen therapy (HBOT) has sometimes been used for a small number of severely affected patients with significant carbon monoxide poisoning. HBOT is delivered by giving a patient oxygen to breathe while in a pressurised chamber so that a higher level of oxygen can be dissolved in the patient's blood plasma. HBOT further hastens the conversion of carboxyhaemoglobin, which is formed as a result of exposure to carbon monoxide, to normal haemoglobin. It may decrease an inflammatory process which is thought to be triggered by severe carbon monoxide (CO) poisoning. HBOT has been used mainly to treat acute CO poisoning of varying levels of severity within hours of exposure (Smollin and Olson 2010).

What we have decided

NHS England has carefully reviewed the evidence to treat carbon monoxide poisoning with hyperbaric oxygen therapy. 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 carbon monoxide poisoning.

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 Carbon Monoxide Poisoning

Carbon Monoxide (CO) poisoning is the most common cause of fatal poisoning in the USA and Europe (Ritchie et al 2008). CO is a colourless, odourless, tasteless gas generated during incomplete combustion of carbon-based compounds. It binds to haemoglobin (Hb) with an affinity 210 times that of oxygen, forming

carboxyhaemoglobin (COHb), and also increases[1] the affinity of the remaining Hb sites for oxygen, thus reducing the oxygen carrying and oxygen delivery capacity of blood. It has also been shown to lead to harm by other mechanisms including disruption of cellular oxidative processes resulting in marked cellular stress and inflammatory responses (Buckley et al 2011). The latter has been argued to only be countered by hyperbaric oxygen and not by normobaric oxygen (Weaver et al., Thom et al.).

The main symptoms of CO poisoning are non-specific and varied and relate to effects on the brain and heart, which are most sensitive to hypoxia. They include headache, fatigue, malaise, "trouble thinking", confusion, nausea, dizziness, visual disturbance, chest pain, shortness of breath, loss of consciousness and seizures (Smollin and Olson 2010). Delayed neurological syndrome (DNS) presents unpredictably with mild to severe neurological and or psychological symptoms and signs in a number of patients.

Poisoning is considered to have occurred at COHb levels of over 10%, and severe poisoning is associated with levels over 20-25% plus symptoms of severe cerebral or cardiac ischemia (Smollin and Olson 2010), although there is variation in these definitions. Severe poisoning can be fatal and up to a third of survivors are thought to have delayed neurological sequelae (Smollin and Olson 2010). People with comorbidity, the elderly, very young and pregnant women are most susceptible (Smollin and Olson 2010).

Current treatment

Standard treatment for CO poisoning includes removal from the site of exposure, administration of supplemental oxygen and general supportive care. The elimination half-life of COHb (approximately 320 minutes in room air) is shortened approximately five-fold by administration of 100% oxygen at atmospheric pressure (normobaric oxygen, NBO) (Buckley et al 2011).

Proposed Intervention

Hyperbaric oxygen treatment (HBOT) refers to administration of 100% oxygen at

[1] This means that the oxygen that is able to bind to Hb is not easily released in the tissues.

pressures higher than atmospheric pressure. This is achieved in a hyperbaric chamber. A wide range of protocols have been used involving different pressures, duration and frequency of treatments (Buckley et al 2011). In instances where HBOT has been used in the UK, it is in line with the protocol described by Weaver et al 2002.

HBOT hastens the elimination of COHb. For example, HBOT at three atmospheres absolute pressure (ATA) reduces the half-life of COHb in blood to 15-30 minutes, and this is one of the theoretical bases for use of HBOT in promoting the supply of oxygen to tissues following CO poisoning (NHS QIS 2008). In addition, there are several other theories as to why HBOT might be effective in treating CO poisoning. For example, cerebral vasoconstriction and reduction in cerebral oedema may prevent CO-induced lipid peroxidation and blocking of leukocyte adhesion (Neubauer et al 2006, Thom et al).

HBOT has been used mainly to treat acute CO poisoning of varying levels of severity within hours of exposure (Smollin and Olson 2010), although it has occasionally been used to treat DNS days to weeks after CO exposure (Coric et al 2017). Where HBOT has been used in the UK, patients have been treated in the acute phase and most often within 24 hours.

There are a number of potential risks and side effects of HBOT. Most are often mild and reversible but some can be severe and life threatening (Leach, Rees & Wilmshurst, 1998). Overall, severe central nervous system symptoms occur in 1-2% of treated patients, symptomatic reversible barotrauma in 15-20%, pulmonary symptoms in 15-20%, and reversible optic symptoms in up to 20% of patients (Leach, Rees & Wilmshurst, 1998). Reversible myopia, due to oxygen toxicity on the lens, is the commonest side effect and can last for weeks or months (Leach, Rees & Wilmshurst, 1998). Table 1 provides a summary of risks.

Table 1: Summary of Risks

General	Claustrophobia, Reversible myopia, Fatigue, Headache, Vomiting
Oxygen Toxicity	Convulsions, Psychological, Lung, Pulmonary oedema haemorrhage, Pulmonary toxicity, Respiratory failure
Barotrauma	Ear damage, Sinus damage, Ruptured middle ear, Lung damage

4 Definitions

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

Carbon Monoxide (CO): a poisonous gas that has no smell or taste.

Carboxyhaemoglobin (COHb): a product of reaction between carbon monoxide and haemoglobin.

Cellular oxidative processes: the process by which cells make energy.

Cerebral or cardiac ischemia: an inadequate blood supply to an organ or part of the body; cardiac (heart) and cerebral (brain).

Cerebral oedema: excess accumulation of fluid in the brain.

Cerebral vasoconstriction: tightening and narrowing of the blood vessels in the brain

Delayed neurological sequelae (DNS): new neurological symptoms and signs that appear or reappear after a period of days to weeks following CO poisoning

Haemoglobin (Hb): part of the red blood cells that carries oxygen from the lungs to the body's tissues and returns carbon dioxide from the tissues back to the lungs.

Hypoxia: deficiency in the amount of oxygen reaching the tissues.

Leukocyte adhesion: a response of white blood cells caused by tissue damage or injury, characterized by redness, heat and swelling.

Nystagmus: refers to repetitive involuntary eye movements.

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.

Tympanic membrane rupture: a hole or tear in the thin tissue that separates your ear canal from your middle ear (eardrum).

5 Aims and Objectives

This policy proposition considered: the evidence underpinning the use of HBOT for carbon monoxide poisoning.

The objectives were to: consider whether, in the treatment for carbon monoxide poisoning:

- the evidence base supports the use of HOBT as an adjuvant treatment
- the effects of HBOT produce different outcomes for pregnant women than others.
- it is possible to identify a group of patients in whom the benefits of HBOT are greatest
- there is evidence that the HBOT regimes in use in the UK produce different outcomes to other regimes
- the evidence indicates that any benefits from HBOT are sustained in the medium and longer term
- the evidence indicates that HBOT is cost effective in this indication

6 Epidemiology and Needs Assessment

CO poisoning is the most common cause of fatal poisoning in the USA and Europe (Ritchie et al 2008).

In 2015 and 2016, there were 102 deaths from accidental carbon monoxide poisoning in England and Wales (2015: 53 deaths; 2016: 49 deaths). It is estimated that every year 4,000 people are diagnosed with CO poisoning at A&E. Even though the 4,000 individuals were not admitted to hospital, this sub-lethal poisoning may lead to lasting neurological harm. Department of Health figures have shown that there are in excess of 200 non-fatal cases that require hospitalisation.

In addition to deliberate self-harm, poorly maintained boilers and cooking equipment are also significant sources of exposure to CO.

People with diseases that affect the delivery of oxygen to the heart or brain, such as those with coronary heart disease, angina, asthma or anaemia are particularly at risk from carbon monoxide poisoning as the amount of oxygen being carried to the heart or brain is further reduced by carbon monoxide. Children, pregnant women and older people are more at risk of harm following exposure to carbon monoxide. Altitude, activity, existing and previous exposure to carbon monoxide may also affect how sensitive a person is to the negative effects of carbon monoxide (Public Health England, 2016).

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 carbon monoxide poisoning. 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 is based on two randomised controlled trials (RCTs) of the use of HBOT following CO poisoning in non-pregnant adults, and one Cochrane systematic review which included these two studies (and which also included four further RCTs which do not meet the criteria for inclusion in this current review).
- The most commonly reported outcomes were neurological sequelae at four to six weeks following CO poisoning, including persistent neurological sequelae (PNS) and delayed neurological sequelae (DNS). DNS are new neurological CO poisoning-associated symptoms and signs that appear or reappear after a period of days to weeks. They may be non-specific, ranging from subtle personality changes, mood disorders and memory loss to (much less commonly) focal neurological injuries and severely disabling manifestations of hypoxic brain injury, such as cortical blindness and epilepsy, and may appear abruptly (Buckley et al 2011, Pepe et al 2011, Thom et al 1995).
- The presence of neurological symptoms and signs at four to six weeks following CO poisoning in non-pregnant adults was not found to be affected by HBOT administered in the hours after CO exposure in the Cochrane systematic review meta-analysis of six studies (odds ratio (OR) 0.78; 95% confidence interval (CI) 0.54-1.12; n=1361; Buckley et al 2011). However, four of the six studies included in the Cochrane systematic review do not meet the requirements of the PICO due to differences in population, treatment protocol or only being published in abstract form. Consequently, the two RCTs that do meet the PICO requirements compared HBOT with 100% normobaric oxygen (NBOT) (Weaver et al 2002 and Thom et al 1995) were assessed further..

- Delayed neurological sequelae: one RCT found that DNS developed in 0% of the HBOT group and 23% of the control NBOT group (95% CI for the difference in proportions 8.2% to 38.4%; p<0.05; n=65; Thom et al 1995). However, by 77 days post CO poisoning, DNS symptoms had resolved in all patients in this study.
- Cognitive sequelae: one RCT found significantly fewer cognitive sequelae at six weeks, six months and one year after CO poisoning in the HBOT group compared to the control NBOT group (25.0% vs 46.1%, OR=0.39, p=0.007 at six weeks; 21.1% vs 38.2%, OR=0.43, p=0.02 at six months; 18.4% vs 32.9%, OR=0.46, p=0.04 at one year; n=152; Weaver et al 2002). The HBOT group also had significantly fewer patients reporting difficulties with memory at six weeks compared to the group that received NBOT (28.0% vs 51.4%; p=0.004).
- No significant benefit of HBOT was found at six weeks for most of the other outcomes measured by Weaver et al (2002), including neuropsychological test scores, apart from one subset test (Trail Making Test Part A[2], p=0.03), Geriatric Depression Scale, Katz index of activities of daily living scores and SF 36 scores for quality of life. In this study, neurological abnormalities on examination after the third chamber session were also not significantly different between HBOT and NBOT groups apart from more nystagmus in the HBOT group (12% vs 2.7%; p=0.05).
- No studies of cost effectiveness were identified.
- Adverse events: although major adverse events have been reported following HBOT in other studies, they were not seen in these studies for which the most common adverse events reported were anxiety (seven patients), cough (one patient), tympanic membrane rupture (one patient) and difficulty equalising middle ear pressure (four patients).
- Overall, the findings of this evidence review suggest that HBOT is more effective than 100% normobaric oxygen therapy in preventing DNS and cognitive sequelae at 6 weeks, 6 months and 12 months post CO poisoning. (symptoms in both groups resolved). The findings do not suggest an effect on DNS in the

[2] The Trail Making Test Part A requires subjects to draw a line as quickly as possible connecting a series of numbers in sequence.

longer term (symptoms in both groups resolved) nor on activities of daily living, quality of life, depression or various neuropsychological tests.

- This review includes only two studies, both of which had a number of methodological issues which may have biased the results. The study by Thom et al (1995) was relatively small (n=65), was unblinded and was stopped early due to observed benefit, which tends to bias results in favour of the intervention. The study by Weaver et al (2002) was of higher quality in that it was double blind and larger (n=152). However, changes were made to the outcomes measured over the course of the study to rely increasingly on self-reported measures (Buckley et al 2011), control patients had more cerebellar dysfunction and longer average exposure to CO, assumptions were made about missing data, and the trial was stopped early due to observed benefit.
- Although the evidence suggests a benefit of HBOT, most of the evidence is based on one RCT with several methodological issues Replication of the results in at least one further good quality RCT would provide more certainty regarding whether HBOT should be routinely used for people with CO poisoning.

Conclusion

CO poisoning is a relatively common cause of poisoning in the UK and there are a number of plausible theories as to why HBOT might reduce the incidence and severity of neurological sequelae. This has led to ambiguous national guidance and to HBOT often being used to treat CO poisoning despite a lack of clarity regarding the evidence for its use. This evidence review found two RCTs. These studies suggest a benefit of HBOT following CO poisoning with respect to DNS, although this effect was not sustained, and a benefit with respect to cognitive sequelae at six weeks, six months and one year. However, other measures such as quality of life and activities of daily living were not found to be affected and both studies had a number of significant methodological limitations. This means that the results should be interpreted with caution. Replication of the results in at least one further good quality RCT would provide more certainty regarding whether HBOT should be routinely used for people with CO poisoning.

8 Proposed Criteria for Commissioning

Not routinely commissioned

9 Proposed Patient Pathway

Not applicable

10 Proposed Governance Arrangements

Not applicable

11 Proposed Mechanism for Funding

Not applicable

12 Proposed Audit Requirements

Not applicable

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.

15 References

Annane D, Chadda K, Gajdos P, Jars-Guincestre MC, Chevret S, Raphael JC. 2011. Hyperbaric oxygen therapy for acute domestic carbon monoxide poisoning: two randomized controlled trials. *Intensive Care Med.* 37(3):486-92

Buckley NA, Juurlink DN, Isbister G, Bennett MH, Lavonas EJ. 2011. Hyperbaric oxygen for carbon monoxide poisoning. *Cochrane Database Syst Rev.* 13(4):CD002041.

Coric V, Oren DA, Wolkenberg FA, Kravitz RE. 2017. Carbon monoxide poisoning and treatment with hyperbaric oxygen in the subacute phase. *J Neurol Neurosurg Psychiatry* 1998;65:245–247.

Leach RM, Rees PJ, Wilmshurst P. Hyperbaric oxygen therapy. *BMJ : British Medical Journal*. 1998;317(7166):1140-1143.

Mathieu D, Wattel F, Mathieu-Nolf M, Durak C, Tempe JP, Bouachour G, Sainty JM. 1996. Randomized prospective study comparing the effect of HBO vs. 12 hours NBO in noncomatose CO-poisoned patients: results of the preliminary analysis. *Undersea & Hyperbaric Medicine.* 1996;23 Suppl:7

Neubauer RA, Neubauer V, Ko Chi Nu A, Maxfield WS. 2006. Treatment of late neurologic sequelae of carbon monoxide poisoning with hyperbaric oxygenation: a case series. *J Am Phys Surg.* 2006;11:56-59.

NHS Choices, 2016. Carbon monoxide poisoning [online] Available at: http://www.nhs.uk/conditions/carbon-monoxide-poisoning/pages/introduction.aspx [Accessed 16 Oct. 2017].

NHS Commissioning Board Clinical Reference Group for Hyperbaric Oxygen Therapy. 2013. NHS Commissioning Board clinical commissioning policy: hyperbaric oxygen therapy. NHS Commissioning Board, 2013:14-16

Pepe G1, Castelli M, Nazerian P, Vanni S, Del Panta M, Gambassi F, Botti P, Missanelli A, Grifoni S. 1989. Delayed neuropsychological sequelae after carbon monoxide poisoning: predictive risk factors in the Emergency Department. A retrospective study. *Scand J Trauma Resusc Emerg Med*. 2011, 17;19:16. doi: 10.1186/1757-7241-19-16.

Public Health England, 2016. Carbon monoxide general information. [online]. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/561063/carbon_monoxide_general_information.pdf [Accessed 16 Oct. 2017].

Raphael JC, Elkharrat D, Jars-GuincestreM-C, Chastang C, Chasles V, Vercken J-B, Gajdos P. 1989. Trial of normobaric and hyperbaric oxygen for acute carbon monoxide intoxication. *Lancet.* 1989;2:414–9.

Ritchie K, Baxter S, Craig J, Macpherson K, Mandava L, McIntosh H, Wilson S. 2008. The clinical and cost-effectiveness of hyperbaric oxygen therapy. *NHS Quality Improvement Scotland, HTA Programme.* Systematic review 2 – July 2008.

Scheinkestel CD, Bailey M, Myles PS, Jones K, Cooper JD, Millar IL, Tuxen DV. 1999. Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomised controlled clinical trial. *Medical Journal of Australia.* 1999; 170:203–10.

Smollin C, Olson K. 2010. Carbon monoxide poisoning (acute). *BMJ Clin Evid.* 10:2103

Thom SR, Taber RL, Mendiguren II, Clark JM, Hardy KR, Fisher AB. 1995. Delayed neurologic sequelae after carbon monoxide poisoning: prevention by treatment with hyperbaric oxygen. *Annals of Emergency Medicine.* 25: 474–80.

Weaver LK, Hopkins RO, Chan KJ, Churchill S, Elliott CG, Clemmer TP, Orme JF, Thomas FO, Morris AH. 2002. Hyperbaric oxygen for acute carbon monoxide poisoning. *New England Journal of Medicine.* 347(14):1057–67.