Anthem

Medical Policy

Subject: Hyperoxemic Reperfusion Therapy
Document #: MED.00098
Status: Reviewed

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Description/Scope

This document addresses the use of hyperoxemic reperfusion (HR) therapy. This treatment is known by other names including:

- Intracoronary hyperoxemic perfusion (IHP)
- Supersaturated oxygen infusion therapy
- Superoxygenation therapy
- Aqueous oxygen (AO) therapy
- SSO2

HR therapy is a treatment in which arterial blood is removed, supersaturated with oxygen, and then reinfused into the person's blood stream at the site of cardiac injury. The intent of this treatment is to decrease myocardial damage following percutaneous placement of an intravascular coronary artery stent for the treatment of myocardial infarction (MI).

Position Statement

Investigational and Not Medically Necessary:

Use of hyperoxemic reperfusion therapy is considered **investigational and not medically necessary** for all indications.

Rationale

A non-randomized controlled trial by Trabattoni and colleagues published in 2006 compared 27 individuals with acute MI who received HR therapy, and a control group of 24 MI subjects who received standard therapy. The authors reported participants in the HR group showed a significantly shorter time-to-peak creatine kinase release (4.8 ± 2.2 hour [hr], p=0.001), a shorter creatine kinase half-life period (23.4 ± 8.9 hr vs. 30.5 ± 5.8 hr, p=0.006), and a higher rate of complete ST-segment resolution (78% vs. 42%, p=0.01). Additionally, the HR group also demonstrated a significant improvement of mean left ventricular ejection fraction (LVEF; from 44 ± 9% to 55 ± 11%, p<0.001) and wall motion score index (from 1.77 ± 0.2 to 1.39 ± 0.4, p<0.001) at 3 months post-treatment. The small size and non-randomized design of this study weaken the positive findings.

The Acute Myocardial Infarction with Hyperoxemic Therapy (AMIHOT) I study involved 269 subjects assigned to receive either HR or normoxemic (e.g., normal) blood autoreperfusion (O'Neill, 2007). There was no significant difference in the incidence of the primary endpoints between the study groups. However, in the post-hoc analysis, individuals with anterior acute MI who were treated for longer than 6 hours with HR therapy had a greater improvement in regional wall motion, smaller infarct, and improved ST-segment resolution compared with normoxemic controls.

The largest available study was a randomized controlled trial (RCT) conducted by Stone and colleagues (2009). AMIHOT II study involved 301 subjects with anterior ST-segment myocardial infarction (MI) randomized to receive either standard treatment (n=79) or 90 minutes of HR with intracoronary supersaturated oxygen delivery combined with standard treatment (n=222). The authors reported that among the 281 randomized subjects who received SPECT imaging, infarct size (IS) was 26.5% in the control group compared with 20.0% in the HR group (unadjusted p=0.10; adjusted p=0.03). Post-hoc analysis indicated that IS was correlated with LVEF. In participants with LVEF less than 40%, IS was reduced from 33.5% in the control group to 23.5% in the HR group. Such differences were not noted in the group of subjects with LVEF greater than 40%. No significant differences between groups were noted in terms of cardiac biomarkers or ST-segment measurement. At 30 days, the incidence of major cardiac adverse events was not significantly different between treatment and control groups.

David and colleagues (2019) reported the outcomes of a non-randomized, single-arm study (IC-HOT trial) which evaluated the safety of HR selectively delivered to the left main coronary artery (LMCA) for 60 minutes after percutaneous coronary intervention in individuals with anterior ST-elevation MI. HR therapy was administered to the LMCA after stent implantation in 100 participants with anterior STEMI and proximal or mid-LAD occlusion presenting within 6 hours of the onset of symptoms. The primary endpoint was the 30-day composite rate of net adverse clinical events (reinfarction, clinically driven target vessel revascularization, stent thrombosis, severe heart failure, thrombolysis in MI, major/minor bleeding or death) compared to an objective performance goal of 10.7%. Cardiac magnetic resonance imaging was performed at 4 and 30 days to determine IS. SSO2 delivery was successful in 98% of the participants. Net adverse clinical events at 30 days developed in 7.1% of participants (meeting the primary safety endpoint of the study); the authors reported one case of stent thrombosis, one case of severe heart failure and no deaths. The median IS was 24.1% [14.4%, 31.6%] at 4 days and 19.4% [8.8%, 28.9%] at 30 days. The authors concluded that following primary percutaneous coronary intervention in acute anterior STEMI, HR via the LMCA was associated with a favorable early safety profile. Limitations of the study include its non-randomized design, use of a safety endpoint (rather than an outcome reflecting efficacy), use of an unmatched historical cohort population, and modest sample size, among others. The authors acknowledge that "larger randomized trials are warranted to confirm that optimized SSO2 delivery reduces IS and improves prognosis in patients with large anterior STEMI. Post-approval randomized trials planned to further examine the effectiveness of optimized SSO2 delivery."

There are a limited number of peer-reviewed published clinical studies evaluating the safety and efficacy of HR therapy for the treatment of individuals with MI. Two RCTs of moderate size, two non-randomized controlled trials, and one small case series were identified during the search of the peer-reviewed literature. Overall study results indicated that HR resulted in no significant differences in primary outcome measures when compared with controls. Additional well-designed studies with appropriate comparators and long-term results are necessary to establish the clinical utility of HR therapy in individuals with MI.

Background/Overview

HR therapy, also known intracoronary hyperoxemic perfusion (IHP), supersaturated oxygen infusion therapy, superoxygenation therapy, aqueous oxygen (AO) therapy, and SSO2, is designed to lessen the damage to cardiac tissue due to an acute MI. This

procedure involves the use of a device that removes arterial blood from a person, supersaturates it with oxygen to create highly oxygen-enriched blood and then reintroduces the supersaturated blood into the person's affected coronary artery following percutaneous intervention with coronary artery stent placement.

In April 2019, the FDA granted premarket approval (PMA P170027) for the TherOx Downstream® System manufactured by TherOx Inc. of Irvine, CA. Continued FDA approval is contingent upon several factors including but not limited to the submission of annual reports and post-approval study (PAS) reports. The PAS reports must be submitted every six (6) months during the first two (2) years of the study and annually thereafter, unless otherwise specified by FDA (FDA, 2019[b]).

According to the FDA PMA letter, the TherOx Downstream System is:

> Indicated for the preparation and delivery of SuperSaturated Oxygen Therapy (SSO2 Therapy) to targeted ischemic regions perfused by the patient's left anterior descending coronary artery immediately following revascularization by means of percutaneous coronary intervention (PCI) with stenting that has been completed within 6 hours after the onset of anterior acute myocardial infarction (AMI) symptoms caused by a left anterior descending artery infarct lesion (FDA, 2019[b]).

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When Services are Investigational and Not Medically Necessary:
When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

0659T	Transcatheter intracoronary infusion of supersaturated oxygen in conjunction with percutaneous coronary revascularization during acute myocardial infarction, including catheter placement, imaging guidance (eg, fluoroscopy), angiography, and radiologic supervision and interpretation

ICD-10 Procedure

5A0222C	Assistance with cardiac oxygenation, supersaturated

ICD-10 Diagnosis

	All diagnoses

References

Peer Reviewed Publications:

1. David SW, Khan ZA, Patel NC, et al. Evaluation of intracoronary hyperoxemic oxygen therapy in acute anterior myocardial infarction: The IC-HOT study. Catheter Cardiovasc Interv. 2019; 93(5):882-890.
2. Dixon SR, Bartorelli AL, Marcovitz PA, et al. Initial experience with hyperoxemic reperfusion after primary angioplasty for acute myocardial infarction: results of a pilot study utilizing intracoronary aqueous oxygen therapy. J Am Coll Cardiol. 2002; 39(3):387-392.
3. O'Neill WW, Martin JL, Dixon SR, et al: AMIHOT Investigators. Acute Myocardial Infarction with Hyperoxemic Therapy (AMIHOT): a prospective, randomized trial of intracoronary hyperoxemic reperfusion after percutaneous coronary intervention. J Am Coll Cardiol. 2007; 50(5):397-405.
4. Stone GW, Martin JL, de Boer MJ, et al. Effect of supersaturated oxygen delivery on infarct size after percutaneous coronary intervention in acute myocardial infarction. Circ Cardiovasc Interv. 2009; 2(5):366-375.
5. Trabattoni D, Bartorelli AL, Fabbiocchi F, et al. Hyperoxemic perfusion of the left anterior descending coronary artery after primary angioplasty in anterior ST-elevation myocardial infarction. Catheter Cardiovasc Interv. 2006; 67(6):859-865.
6. Warda HM, Bax JJ, Bosch JG, et al. Effect of intracoronary aqueous oxygen on left ventricular remodeling after anterior wall st-elevation acute myocardial infarction. Am J Cardiol 2005; 96(1):22-24.

Government Agency, Medical Society, and Other Authoritative Publications:

1. TherOx. Evaluation of intracoronary hyperoxemic oxygen therapy in anterior acute myocardial infarction patients (IC-HOT). NLM Identifier: NCT02603835. Last updated on September 26, 2017. Available at: https://clinicaltrials.gov/ct2/show/NCT02603835?term=sso2&rank=1. Accessed on March 06, 2023.
2. U.S. Food and Drug Administration (FDA) Center for Devices and Radiological Health. Summary of safety, effectiveness of Data (SSED): U.S. Food and Drug Administration (FDA) Center for Devices and Radiological Health. Summary of safety, effectiveness of Data (SSED): TherOx DownStream System. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170027B.pdf. Accessed on March 06, 2023.
3. U. S. Food and Drug Administration (FDA) Premarket Approval (PMA) database. Therox Downstream System (P170027). Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P170027. Accessed on March 06, 2023.

Document History

Status	Date	Action
Reviewed	05/11/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated References section.
	09/28/2022	Updated Coding section with 10/01/2022 ICD-10-PCS changes; added 5A0222C, removed deleted codes 5A0512C, 5A0522C.
Reviewed	05/12/2022	MPTAC review. Updated References section.
Reviewed	05/13/2021	MPTAC review. Updated Rationale and References sections. Updated Coding section with 07/01/2021 CPT changes; added 0659T replacing 96379 NOC.
Reviewed	05/14/2020	MPTAC review. Updated Rationale and References sections.
Reviewed	06/06/2019	MPTAC review. Updated Rationale and References sections.
Reviewed	07/26/2018	MPTAC review. The document header wording updated from "Current Effective Date" to "Publish Date." Updated References section.

Reviewed	08/03/2017	MPTAC review. Updated Background/Overview and References sections.
Reviewed	08/04/2016	MPTAC review. Updated Reference section. Removed ICD-9 codes from Coding section.
Reviewed	08/06/2015	MPTAC review. Updated Rationale, Background/Overview and Reference sections.
Reviewed	08/14/2014	MPTAC review. Updated Description/Scope, Rationale and Reference sections.
Reviewed	08/08/2013	MPTAC review.
Reviewed	08/09/2012	MPTAC review. Revised Rationale and Reference sections.
Reviewed	08/18/2011	MPTAC review.
Reviewed	08/19/2010	MPTAC review. Updated Rationale and Reference sections.
Reviewed	08/27/2009	MPTAC review.
New	08/28/2008	MPTAC review. Initial document development.

Applicable to Commercial HMO members in California: When a medical policy states a procedure or treatment is investigational, PMGs should not approve or deny the request. Instead, please fax the request to Anthem Blue Cross Grievance and Appeals at fax # 818-234-2767 or 818-234-3824. For questions, call G&A at 1-800-365-0609 and ask to speak with the Investigational Review Nurse.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.