REVIEW ARTICLE

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Intraluminal oxygen mitigates acute mesenteric ischaemia: a systematic review of methods and outcomes in animal studies

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Abstract

Background: Acute Mesenteric Ischaemic (AMI) is a rare condition with significant morbidity and mortality. Many causes of AMI exist, which usually begin with mucosal injury. Onset is insiduous and there is frequent diagnostic delay. Current treatments can only control established injury and prevent propagation, hence new interventions are needed. The prevention and treatment of AMI by intraluminal delivery of oxygen has yet to be investigated in the clinical setting. This article aims to systemically review experimental studies investigating this novel therapy.

Methods: Following the PRISMA guidelines, searches of PubMed and Ovid MEDLINE databases were performed up to June 2022. Two independent investigators extracted the data.

Results: There were 20 experimental studies, 16 of which used an occlusive ischaemia reperfusion model. Six different formulations were used to deliver intraluminal oxygen, with perflurocarbon being the most common. Studies consistently showed local and systemic benefits. Intraluminal oxygen therapy improved histological severity of mucosal injury in all studies when oxygen was delivered during the ischaemia phase, but could cause harm if given during the reperfusion phase. Improvement was also demonstrated in endpoints assessing intestinal function, biomarkers of intestinal damage, measures of systemic physiological derangement and mortality.

Conclusion: Intraluminal oxygenation appears to be an effective treatment for AMI. There remain significant questions regarding optimal timing and delivery formulation before clinical translation of this treatment strategy.

Background

Acute hypoxic injury to the intestine occurs when intestinal oxygen demand outstrips mesenteric blood supply and defines acute mesenteric ischaemia (AMI).[1] It is a rare (incidence 0.09%–0.2%) but important condition with mortality consistently reported over 50%.[2] AMI encompasses occlusive arterial, venous and non-occlusive subtypes. Non-occlusive mesenteric ischaemia (NOMI) is a subtype of AMI occurring most commonly in critical illness with shock. Vascular tone in the mesenteric circulation increases, and blood is shunted away from the intestine to organs more immediately critical to sustaining life.[3] Despite increasing oxygen extraction, inadequate supply results in ischaemia starting at the intestinal mucosa.[4] This ischaemia can be exacerbated by feeding (increasing metabolic demand) and the use of non-selective vasopressors (decreasing intestinal blood flow).[1,5] Subclinical and overt ischaemia contributes to the development of gut dysfunction,[6] enteral feeding intolerance,[7] and when severe to intestinal infarction, perforation and peritonitis.[1]

Diagnosis of AMI is challenging, as the presenting symptoms and signs are non-specific, and there are no perfect biomarkers.[8] CT angiography is valuable, and identifies vessel occlusion or local complications requiring surgical intervention.[9] Treatment depends on the aetiology,

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but common principles include restoration of blood supply and surgical control of ischaemic complications. Treatment of occlusive AMI may require pharmacologic, endovascular or open revascularisation, while treatment for non-occlusive AMI is limited to the treatment of the underlying disease. Intra-arterial vasodilator treatment has shown some promise in reversing mesenteric vasospasm but is not yet the standard of care.[10] Local complications such as intestinal infarction require surgical resection, but treatment is often too late to prevent the systemic inflammatory response. Given the central role of intestinal damage in propelling multiorgan failure, treatments that mitigate intestinal ischaemia could significantly improve the care of critically ill patients.[11]

A promising experimental approach to the treatment of AMI is the delivery of oxygen to the intestinal lumen. Intraluminal oxygen treatment has been assessed in the preclinical setting[12–31] but to our knowledge has not entered clinical practice. This study aimed to systematically review the available evidence regarding the safety and outcomes of intraluminal oxygen therapy to prevent or treat AMI.

Methods

Study identification

Following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines (Fig. 1), a systematic review of the literature was conducted to evaluate the current evidence (1/1/1946–8/5/2022) from studies investigating intraluminal methods of oxygenation to prevent or treat mesenteric ischaemia.

A formal electronic search of the Ovid MEDLINE and PubMed databases was carried out using the following search strategy:

(1) Therap* OR Protect* OR Effect* OR Affect* OR "Therapeutic" [MeSH] AND
(2) Intestin* OR "Intestinal mucosa*" OR "GI tract" OR "Digestive tract" OR "Small intestine" OR "Large intestine" OR colon* OR Bowel OR Gastrointestin* OR Mesenter* OR Splanchnic OR "Intestines" [MeSH] OR "Gastrointestinal Tract" [MeSH] OR Mucosa* OR "mucous membrane" [MeSH] AND
(3) Ischemi* OR Ischaemi* OR Necrosis OR Necrotic OR Infarction OR Hypoperfusion OR Malperfusion OR "Ischemia/reperfusion Injury" OR "I/R Injury" OR "Ischemia reperfusion injury" OR "Mesenteric ischemia" OR "Intestinal Ischemia" OR "Bowel ischemia" OR "Splanchnic Ischemia" OR "Colonic ischemia" OR "Intestinal malperfusion" OR "Bowel malperfusion" OR "Mesenteric infarction" OR "Bowel Infarction" OR "Bowel Necrosis" OR "Mesenteric hypoperfusion" OR "Acute intestinal vascular failure" OR NOMI OR "Mesenteric ischemia/reperfusion injury" OR "Mesenteric vascular occlusion"[MeSH] OR "Mesenteric Ischemia"[MeSH] OR "Reperfusion Injury"[MeSH] AND

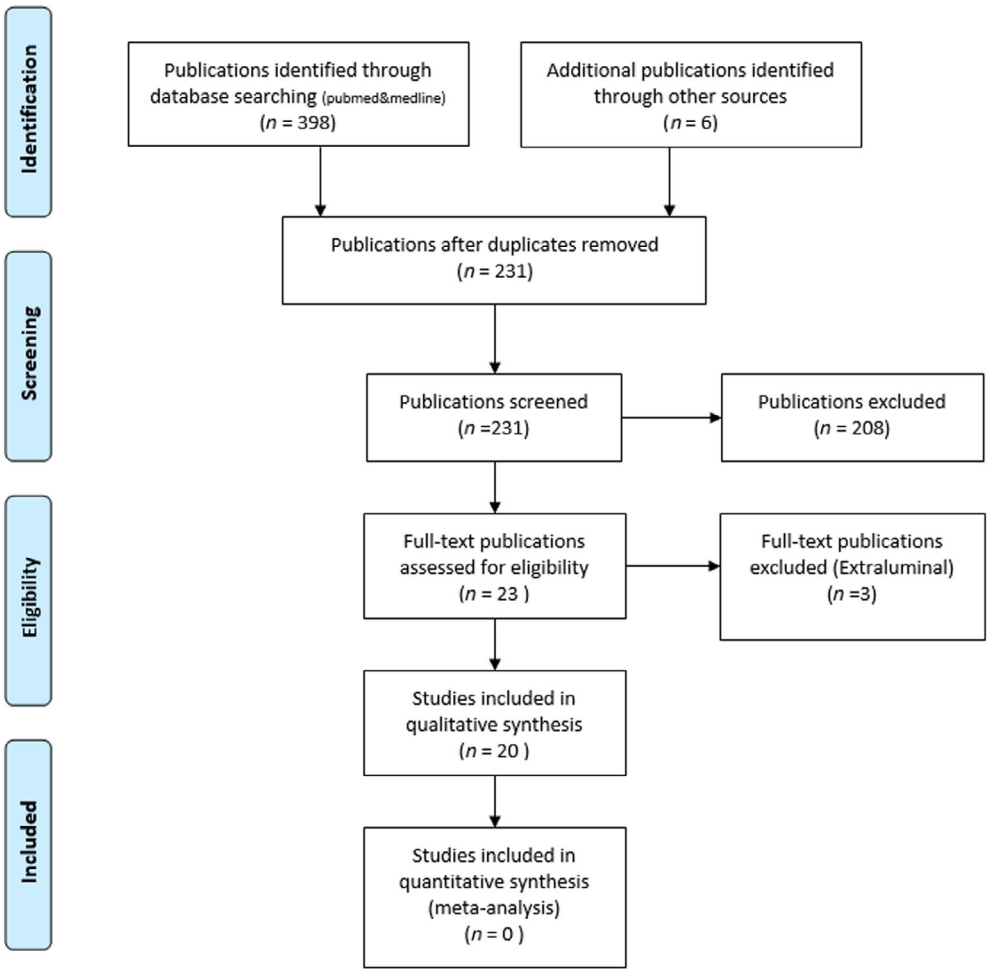

Fig. 1. PRISMA diagram.

Table 1 Summary of included studies

Author (Reference)	Animal Model of Ischaemia	I/R duration	Timing of oxygen delivery	O^2 Formulation Comparison Formulation	Delivery technique	Endpoints	Effect of luminal O^2 on endpoints (*statistical significance)
Ahren (1973)[12]	Cat Partial SMA Occlusion	I: 2.5-3 h + R: 1 h	During ischaemia	Oxygenated Saline Nitrogenated Saline	Infused into isolated segments	1. Histology 2. Macroscopic changes	1. ⇩ damage 2. Improved colour
Shute (1976)[13]	Rat SMA occlusion	I: 2 h	During 30-120 min of ischaemia	Gaseous O^2 No treatment or gaseous N^2	Injected into intestinal lumen	1. Histology 2. Macroscopic changes 3. RR 4. Mortality	1. ⇩ damage 2. Improved colour 3. ⇩ Rise in RR * 4. ⇩ mortality at 48 h (39% versus 89%) *
Robinson (1977)[14]	Rats Mesenteric vessel occlusion	I: 0.25 h	Rinsed with solution prior to ischaemia	Oxygenated Krebs Bicarbonate buffer Nitrogenated Krebs Bicarbonate buffer	Infused into isolated segments	1. Phenylalanine absorption (functional assessment)	1. ⇧ function *.
Shute (1977)[15]	Mice SMA occlusion	I: 2 h	During 30-120 min of ischaemia	Gaseous O^2 No treatment	Injected into intestinal lumen	1. Mortality	1. ⇩ mortality at 48 h (23% versus 69%) *
Moore (1980)[16]	Ponies Mesenteric vessel occlusion	(a) I: 1.5 h, R: 2 h (b) I: 50 min, R: 2 h	At reperfusion	Gaseous Oxygen No treatment	Infused through tubing to lumen	1. Gross observation 2. Histology	1. Preserved colour and peristalsis 2. ⇩ damage
Baba (1981)[17]	Rats, guinea pigs or dogs SMA ligation	SMA occlusion 2 h	During ischaemia	PFC-O^2 (FC-43 and FDA) No treatment or saline	Infused into lumen	1. Histology 2. pO2, pCO2, BE, pH	1. ⇩ damage 2. ⇧ pO2, pH and ⇩ in BE, pCO2 in afferent blood.
Hajjar (1983)[18]	Rats Mesenteric vessel occlusion	I 0.25 h	At reperfusion	O^2 Krebs Bicarbonate buffer solution N^2 Krebs Bicarbonate buffer solution	Infused into lumen	1. Mucosal Leucine influx (gut barrier assessment)	1. ⇩ Leucine influx
Falk (1985)[19]	Cats Induced E coli sepsis	Septic shock for 2.5 h	During shock	Saline-O^2 Saline- N^2	Infused into lumen	1. Histology	1. ⇩ damage
Ricci (1985)[20]	Rats SMA (group A) or SMA + SMV occlusion (group B)	I: 7 h SMA occlusion (A) I: 3 h SMA + SMV occlusion (B)	During ischaemia	PFC-O^2 (FC-47) and gaseous O^2 PFC-N^2 or gaseous N^2	Infused into lumen through cannula	1. Mortality 2. Histology	Group A: 1. ⇩ mortality * 2. ⇩ damage Group B: No significant difference
Oldham (1987)[21]	Rats Distal mesenteric occlusion (no reperfusion)	I: 0.5 h–4 h	During ischaemia	PFC-O^2 (FC-43) Saline-O^2	Injected into lumen	1. Histology	1. ⇩ damage with PFC-O^2 *
Matin (1991)[22]	Dogs Haemorrhagic shock	I: 4 h + R: 1 h	Given during ischaemia when mucosal pH dropped to pH < 7.24	PFC-O^2 PFC- N^2	Infused into stomach through duodenotomy	1.Gastric Histology 2. Macroscopic changes 3. O^2 saturation of mucosa 4. Hb saturation of mucosa 5. Gastric mucosal pH	1. ⇩ damage * 2. ⇩ damage * 3. ⇧ O^2 saturation* 4. ⇧ Hb saturation 5. ⇩ fall in pH *

Table 1 Continued

Author (Reference)	Animal Model of Ischaemia	I/R duration	Timing of oxygen delivery	O^2 Formulation Comparison Formulation	Delivery technique	Endpoints	Effect of luminal O^2 on endpoints (*statistical significance)
Salzman (1993)[23]	Pigs SMA occlusion	I: 2 h + R: 2.5 h	During ischaemia and reperfusion	Oxygenated Ringer's Lactate Nitrogenated Ringer's Lactate	Infused into lumen through tubing	1. Intestinal permeability 2. Mucosal ATP and hypoxanthine content 4. Histology	1.⇩ permeability 2. Normalized ATP 3. ⇩ rise in Hypoxanthine 4. ⇩ damage
Horne (1994)[24]	Ponies Distal Mesenteric artery + vein or vein alone occlusion	I: 3 h, R: 1 h	During reperfusion	Gaseous-O^2 No treatment	Infused into lumen	1. Histology	1. No difference
O'Donnell (1997)[25]	Rats SMA occlusion	I: 1 hr. + R: 2 hr	(i) During ischaemia (ii) During reperfusion	PFC -O^2 (Perflubron®) No treatment	Continuous luminal infusion through afferent and efferent tubing	1. Histology 2. Mucosal enzyme activity	1. (i) ⇩damage*, (ii) ⇧damage* 2. ⇧ mucosal enzyme activity *
Rossman (1997)[26]	Rats SMA occlusion	I: 1 h, R: 2 h	(i) During reperfusion (ii) During ischaemia	PFC-O^2 (Imagent®) No treatment	Intraluminal infusion via tubing through enterostomy	1. Histology 2. Serum ROS 3. Lung LPO	1. (i) ⇩damage*, (ii) ⇧damage* 2. (i) and (ii) ⇩ ROS formation * 3. (i) and (ii) *⇩ LPO formation
Papadimitriou (2004)[27]	Rabbits SMA or SMV or both	I: 8 h	Throughout ischaemia	PFC-O^2 (F-Decalin) PFC (Non-oxygenated)	Intraluminal infusion through catheter placed at distal duodenum via gastrostomy	1. Histology 2. Serum LDH, SGOT, SGPT, CPK	1. ⇩ damage 2. ⇩ rise in LDH*, SGOT, SGPT, CPK*
Gao (2005)[28]	Rabbits SMA occlusion	I 1 h+ R: 2 h	(i) Throughout ischaemia (rate 10 mL/kg/h) (ii) Throughout ischaemia, (rate 20 mL/kg/h)	Hyper-oxygenated 5% glucose solution No treatment	Intraluminal infusion	1. Histology 2. Mitochondrial respiratory function 3. Intestinal mucosal ATP content 4. Intestinal Oxygen Extraction	(i) For infusion at 20 mL/kg/h: 1. ⇩damage* 2. ⇧ function* 3.⇧ ATP content* 4. ⇧ oxygen extraction * (ii) No differences seen at 10 mL/kg/h
Papadimitriou (2007)[29]	Rabbits SMA or SMV or SMA + SMV occlusion	I: 8 h	Throughout ischaemia	PFC-O^2 (F-Decalin) PFC (Non-oxygenated)	Intraluminal infusion through catheter placed at distal duodenum via gastrostomy	1. Arterial Blood samples 2. Physiological Markers: BE, RR, pCO2, pO2, HR, SBP	1. ⇩ acid–base derangement* 2. ⇩ physiological derangement *

Table 1 Continued

Author (Reference)	Animal Model of Ischaemia	I/R duration	Timing of oxygen delivery	O^2 Formulation Comparison Formulation	Delivery technique	Endpoints	Effect of luminal O^2 on endpoints (*statistical significance)
Ntinas (2010)[30]	Rabbits SMA occlusion	I: 2 h + R: 1 h	(i) 30 min pre- ischaemia until the end (ii) 30 min before reperfusion until the end	PFC-O^2 (Perfluoron®) No treatment	Intraluminal infusion through catheter placed at distal duodenum via gastrostomy	1. Enteric MDA 2. D-Lactate 3. Histology	1. (i) ⇩ MDA throughout *, (ii) ⇩ MDA only during reperfusion* 2. (i) ⇩ D-Lactate*, (ii) no difference until 180 min of reperfusion 3. (i) and (ii) ⇩ damage after 120 min*
Ntinas (2011)[31]	Rabbits SMA occlusion	I: 2 h + R: 1 h	(i) 30 min pre- ischaemia until the end (ii) 30 min before reperfusion until the end	PFC-O^2 (Perfluoron®)	Intraluminal infusion through catheter placed at distal duodenum via gastrostomy	1. Mucosal disaccharidase activity 2. Serum CPK 3. Histology	1. (i) and (ii) ⇧ disaccharidase activity* 2. (i) and (ii) ⇩ in CPK after 120 min 3. (i) and (ii) ⇩damage

Abbreviations: BE, base excess; CPK, creatinine phosphokinase; FC 43, perfluorotributylamine; FDA, fluorosol DA; h, hours; HR, heart rate; I, ischaemia; LDH, lactate dehydrogenase; LPO, lipid peroxides; MDA, malondialdehyde; PFC/PFC-O^2, perfluorocarbon/oxygenated perfluorocarbon; R, reperfusion; ROS, reactive oxygen species; RR, respiratory rate; SBP, systolic blood pressure; SGOT and SGPT, liver enzymes now known as aspartate aminotransferase (AST) and aminotransferase (ALT) respectively; SMA, superior mesenteric artery; SMV, superior mesenteric vein.

(4) Intraluminal OR transluminal OR Luminal* OR mural OR transmural OR intramural AND
(5) Oxygen* OR Ventilation OR "Perfusion" [MeSH]

A further manual search of the reference list of eligible papers was performed to identify additional relevant articles.

Selection criteria

Articles that met the following inclusion criteria were included: (1) reporting on a form of hypoxic or ischaemic injury to the gastrointestinal tract, (2) tested oxygen-based intraluminal intervention, and (3) written in English. Studies that reported non-oxygen-based interventions were excluded. Similar studies that looked at oxygenation of the gut via non-intraluminal routes, such as intraperitoneal routes, were also excluded.

Data extraction

Two investigators (DJ and AL) independently extracted and tabulated the data using predesigned data collection forms. The extracted data included study identification, publication year, duration of the experiment, method of oxygenation, method of ischaemia, endpoints, outcome and risk of bias data. Data within selected studies describing alternative treatments or diseases was excluded.

Quality assessment

The quality of the included studies was evaluated using the systematic review centre for laboratory animal experimentation (SYRCLE) risk of bias[32] tool detailed in Table 2. It determines the quality of a study based on 10 different domains: allocation sequence, baseline characteristics, blinded allocations, random housing of animals, blinded investigators/caregivers, random outcome assessment, completeness of outcome data, selective outcome reporting and all other sources of possible bias. The different domains were categorized as 'no', 'yes', 'unclear' or 'unsuitable'. Two investigators independently reviewed all the studies to assess the risk of bias; any disagreement was adjudicated by a third investigator (SP).

Results

Study identification

A total of 398 relevant publications were identified and screened. Of these, 23 were evaluated for eligibility, and 20 were included in the systematic review. The main reasons for exclusion are shown in the PRISMA flow chart (Fig. 1).

Study characteristics

The 20 studies are listed chronologically in Table 1. All studies were on animal subjects. Rats ($n = 8$),[13,14,17,18,20,21,25,26] rabbits ($n = 5$),[27–31] cats ($n = 2$),[12,19] ponies ($n = 2$),[16,24] dogs ($n = 2$),[17,22] guinea pigs ($n = 2$),[17,22] pigs ($n = 1$)[23] and horses ($n = 1$)[24] were among the animals used. The model of intestinal ischaemia used included superior mesenteric artery (SMA) occlusion ($n = 13$),[12,13,15,17,20,23,25–31] superior mesenteric vein (SMV) occlusion ($n = 3$),[24,27,29] SMA and SMV occlusion ($n = 6$),[14,18,20,24,27,29]

Table 2 SYRCLE risk of bias assessment

	1. Allocation sequence generated?	2. Similar groups at baseline?	3. Blinded allocations?	4. Animals randomly housed?	5. Investigators blinded from intervention?	6. Random Outcome assessments?	7. Blinded Outcome assessment?	8. Incomplete data adequately addressed?	9. Study free from selective outcome reporting?	10. Other Sources of bias?
Ahren (1973)[12]	Yes	Yes	N/A	N/A	N/A	Yes	Yes	No	Yes	No
Shute (1976)[13]	No	Yes	N/A	No	No	N/A	No	Yes	Yes	No
Robinson (1977)[14]	No	No	N/A	N/A	N/A	N/A	N/A	No	Yes	No
Shute (1977)[15]	No	Yes	N/A	No	No	N/A	N/A	Yes	Yes	No
Moore (1980)[16]	No	No	N/A	N/A	N/A	N/A	No	No	Yes	No
Baba (1981)[17]	No	No	N/A	N/A	N/A	No	No	No	Yes	Vague description of methods and results
Hajjar (1983)[18]	No	Yes	N/A	N/A	N/A	N/A	N/A	No	Yes	No
Falk (1985)[19]	N/A	Yes	N/A	N/A	N/A	N/A	No	No	Yes	Not a RCT
Ricci (1985)[20]	No	Yes	N/A	N/A	No	N/A	N/A	Yes	Yes	No
Oldham (1987)[21]	No	Yes	N/A	N/A	No	Yes	Yes	No	Yes	No
Matin (1991)[22]	Yes	Yes	N/A	N/A	N/A	N/A	No	Yes	Yes	No
Salzman (1993)[23]	Yes	Yes	N/A	N/A	N/A	N/A	No	Yes	Yes	No
Horne (1994)[24]	Yes	Yes	Yes	N/A	No	No	Yes	Yes	Yes	No
O'Donnell (1997)[25]	No	Yes	N/A	N/A	N/A	N/A	Yes	Yes	Yes	No
Rossman (1997)[26]	No	Yes	N/A	N/A	No	Yes	Yes	No	Yes	No sample size given
Papadimitriou (2004)[27]	No	Yes	N/A	N/A	No	No	Yes	Yes	Yes	No
Gao (2005)[28]	Yes	Yes	N/A	N/A	N/A	N/A	Yes	Yes	Yes	No
Papadimitriou (2007)[29]	No	Yes	N/A	No	N/A	N/A	N/A	Yes	Yes	No
Ntinas A (2010)[30]	Yes	Yes	No	N/A	N/A	N/A	Yes	Yes	Yes	No
Ntinas (2011)[31]	Yes	Yes	N/A	N/A	N/A	N/A	No	No	Yes	No

The significance of color indicate Red = No, Green = Yes.

septicaemia/hypotension ($n = 2$),[19,22] and unspecified ($n = 2$).[16,21] In addition, several studies used distal mesenteric vessel occlusion to render isolated segments of the intestine ischaemic.[14,16,18,21]

Oxygen delivery formulation

Six different formulations were used to deliver oxygen to the lumen of the intestine: perfluorocarbon (PFC) ($n = 10$),[17,20–22,25–27,29–31] oxygen gas ($n = 5$),[13,15,16,20,24] saline (n = 4)[12,17,19,21] Krebs buffer ($n = 2$),[14,18] 5% dextrose ($n = 2$)[14,28] and Ringer's lactate ($n = 1$).[23]

Formulation delivery technique

Studies delivered oxygenated formulation the intestinal lumen via direct injections[13,14,21] or catheter infusions.[20,22,23,27,29–31] Other studies failed to accurately describe the delivery rate, location, and technique (Table 1). All studies used a laparotomy to access the small bowel rather than naso-enteric or trans-anal delivery.

Preparation of oxygenated formulation

Only 10 papers[20–22,25–31] described the method of creating the oxygenated solutions. The primary technique of oxygenating the formulation was bubbling 100% oxygen through the medium ($n = 9$),[20–22,25–27,29–31] followed by bubbling through a mixture of ozone and oxygen ($n = 1$).[28] The remaining papers failed to describe these experimental protocols.

Outcome assessment

A range of different endpoints (or combination of endpoints) were used in the 20 studies, including histology of the intestinal mucosa ($n = 16$),[12,13,16,17,19–28,30,31] biochemistry ($n = 9$),[17,22,23,26–31] mucosal function ($n = 6$),[14,18,23,25,28,31] macroscopic appearance of the intestine ($n = 4$),[12,16,22,24,28] mortality ($n = 3$)[13,15,20] and physiological parameters (i.e. respiratory rate, heart rate, systolic blood pressure) ($n = 2$).[13,29] Histology, the most common primary outcome measure, was assessed using light or scanning electron microscopy. Subjective description of tissue architecture was common,[12,13,17,19,20,23,24,27,31] though many used scoring systems to categorize the severity of damage.[21,22,25,26,28,30] The description of the length and location of the intestine submitted for assessment was generally limited (Table 1).

The overall effect of intraluminal oxygenation

All studies reporting intraluminal oxygenation administered during the ischaemic period demonstrated protection against intestinal damage (Table 1). However, three papers showed that administering intraluminal perfluorocarbon-oxygen (PFC—O^2) during the reperfusion phase could exacerbate mucosal injury.[24–26] No studies investigated the optimal oxygen content or rate of administration for treating AMI.

Effect of the oxygen delivery formulation

It was impossible to determine which of the six formulations provided the best delivery of oxygen as only two studies compared the performance of different formulations. Ricci *et al.* showed similar benefits for PFC—O^2 and gaseous O^2, while Oldham *et al.* demonstrated that PFC—O^2 reduced mucosal injury to a greater extent than oxygenated saline but did not include a control group.[20,21]

Effect of the timing of oxygen delivery

The studies administered oxygen at three different time points: pre-ischaemia,[30,31] during ischaemia,[12,13,15,17,19–22,26,27,29] during reperfusion[16,18,26] or a combination of the three.[23–25,30,31] No studies investigated pre-ischaemia oxygenation alone. The most significant benefit was when oxygen was administered during the

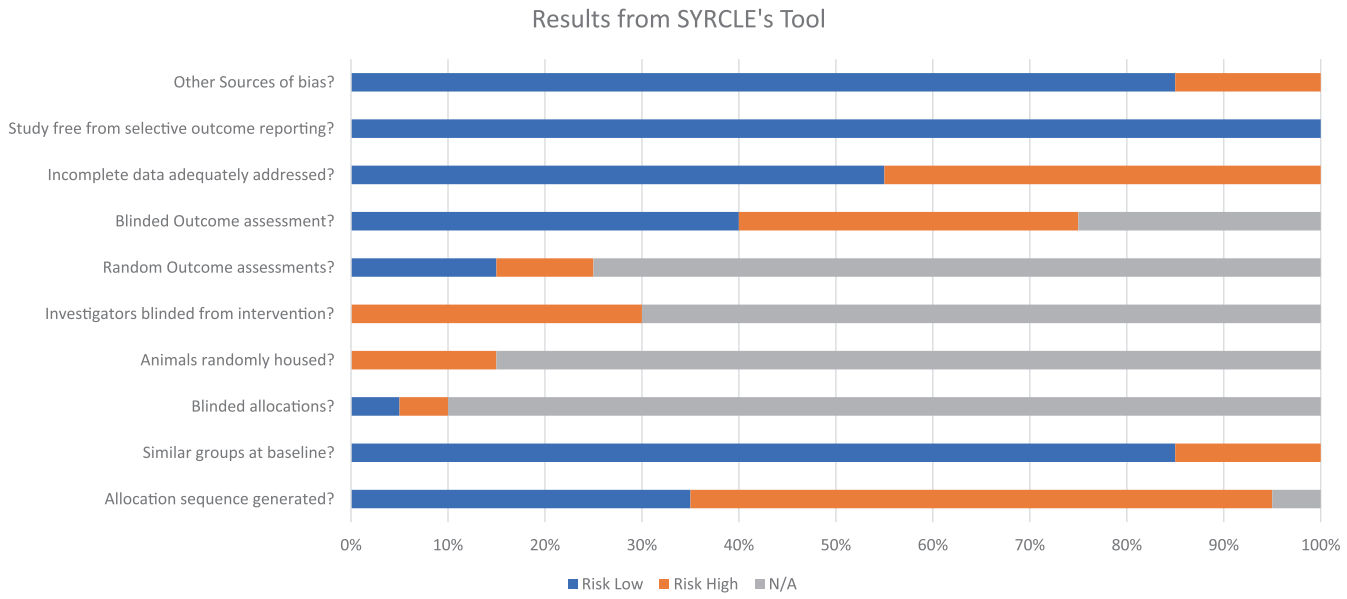

Fig. 2. SYRCLE risk of bias assessment.

period of ischaemia. Intraluminal oxygen therapy potentially worsened outcomes when delivered during reperfusion alone.[24–26]

Quality assessment and risk of bias

The SYRCLE risk of bias tool was applied to all the studies in Figure 2. No average score was given as no domain could be weighted equally. Seventeen studies had similar study groups at baseline. The majority were interventional studies, so only two could be assessed for blinded allocations into groups. Eight of 10 studies had blinded outcome assessment, and none had selective reporting of outcomes.

Discussion

This is the first systematic review reporting evidence from experimental studies of intraluminal oxygenation treating acute mesenteric ischaemia (AMI). All 20 included studies were animal studies, and the majority used an occlusive model of AMI. Oxygen was delivered to the intestinal lumen via six different formulations. Notably, studies uniformly reported a protective effect of intraluminal oxygenation when administered during the ischaemia phase but highlighted the potential for harm if oxygen was administered only during the reperfusion phase. The therapeutic effect was most commonly assessed by comparing the histological severity of intestinal damage.

Investigators used a variety of other outcomes to demonstrate effectiveness, including biomarkers of intestinal damage, assessment of intestinal barrier or absorptive function, local metabolic activity and systemic physiological parameters (Table 1). This data indicates that intraluminal oxygen can effectively mitigate local and systemic complications of AMI. There is, therefore, broad scope for clinical translation of this treatment. When applied in critical illness, intraluminal oxygen therapy could protect the gut from NOMI, where clinicians have little option other than supportive care. Mitigation of gut injury in this setting may limit the generation of toxic mesenteric lymph and offer a novel option for the prevention of multiorgan failure.[11] Other potential clinical settings include the treatment of necrotising enterocolitis, as a bridge to arterial re-vascularisation and post-operatively to support intestinal anastomotic healing. Surprisingly, no clinical studies have been published exploring the intraluminal oxygen treatment of AMI.

An important finding was the possible harm from intraluminal oxygenation therapy administered solely during the reperfusion phase.[24–26] This may account for hesitancy in clinical translation. The potential for hyperoxia to cause harm is well described in critical care conditions, including acute myocardial infarction and adult respiratory distress syndrome.[33] Contributing factors include hyperoxia-induced vasoconstriction and reactive oxygen species formation.[33] In contrast, oxygenation commenced during the ischaemic phase and carried through reperfusion did not appear to cause harm, suggesting that if the damage can be prevented during ischaemia then reperfusion injury is reduced.[25,30,31]

Perfluorocarbon (PFC) was the most common medium used to deliver oxygen. More recently, PFC has been in clinical use to stabilize microbubbles.[34] Microbubbles are microscopic (1–100 μm in diameter) spheres comprising a gas-filled core within a shell.[35] They have an established role as an intravenous contrast agent in diagnostic ultrasonography.[34] More recent work has uncovered a range of therapeutic applications, including drug or gas delivery through intravenous infusion.[36] Oxygen-loaded microbubbles could offer a novel medium for oxygen delivery to the intestinal lumen. Microbubbles would offer excellent oxygen delivery due to their high gas-carrying capacity, biological compatibility and efficient oxygen release. The application of ultrasound waves can further enhance delivery.[36] Animal studies have shown promising safety and efficacy in treating systemic hypoxia through intraperitoneal and intravenous infusion of oxygen microbubbles.[37,38] Oxygen microbubbles also appear capable of gas exchange when delivered into the gut lumen.[39,40] To our knowledge, the ability of oxygen microbubbles to treat intestinal ischaemia has not been studied.

The intraluminal route offers the most direct application of therapies to the gut, enhancing the therapeutic window at its intended target. Another possible benefit of delivering intraluminal therapy is irrigation of the ischaemic luminal environment. This effect was demonstrated independent of oxygen with Kreb's buffered solution.[18] When the same solution was oxygenated, the ensuing protective effects were even more significant, suggesting an additive effect of intraluminal irrigation and oxygenation.[18] It should be noted that irrigation (rather than oxygenation) may have enhanced the effectiveness of other therapies reviewed in this article. The intraluminal route also offers the potential for co-delivery of other gut-directed therapies, such as nutrition or metabolic fuels, including butyrate.[41,42] It is essential to recognize limits to intraluminal delivery, including the need for intestinal tract continuity, preserved peristalsis and the risks of excessive distension.

This review has several important limitations. First, the low quality of the studies demonstrated by the risk of bias tool (Fig. 2) meant that a formal meta-analysis was not possible. To some extent, the low quality can be explained by the intent of earlier studies, which aimed to explore the pathophysiology of AMI rather than assess treatment options.[12,19] We note that the promising findings of this systematic review need to be confirmed in robustly designed studies of adequate power. Secondly, heterogeneity in the included studies, including the animal species used, the various models of intestinal ischaemia, the dose or formulation of delivered oxygen and the different endpoints, makes it impossible to make direct comparisons. In addition, few studies delivered formulation to the intestinal lumen through a clinically applicable technique. Importantly this proves the therapeutic concept, but further work is needed to investigate treatment delivery in this setting before translation. Finally, most studies initiated intraluminal oxygen delivery at the same time that intestinal ischaemia was induced. This standardizes experimental protocol but is less applicable in practice where the onset of ischaemia may be insidious and not readily appreciable.

Conclusion

This is the first systematic review of the evidence for intraluminal oxygen treatment of AMI. There was a demonstrable benefit in the vast majority of studies, both locally and systemically. An important

finding was that intraluminal oxygen treatment delivered only during the reperfusion phase can exacerbate intestinal injury. Before clinical translation can begin, essential research questions must be answered. Promising oxygen-carrying media must be compared to find the optimal delivery formulation. This should consider adaptations to traverse the gastroduodenal environment and allow naso-enteric delivery. Once established, safety and efficacy need to be assessed in specific and translatable models of intestinal ischaemia. With further work, intraluminal oxygen therapy has the potential to improve outcomes in patients with acute mesenteric ischaemia.

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Conflict of interests

None declared.

Author contributions

Daniel Joh: Formal analysis; investigation; writing – original draft. **Mathew Morreau:** Formal analysis; writing – original draft; writing – review and editing. **Angela Lee:** Data curation; investigation; writing – original draft. **Sayali Pendharkar:** Data curation; supervision; writing – review and editing. **Bruce Stokes:** Writing – review and editing. **Roger Warren:** Writing – review and editing. **Anthony JR Hickey:** Conceptualization; supervision; writing – review and editing. **Anthony Phillips:** Conceptualization; supervision; writing – review and editing. **John A Windsor:** Conceptualization; supervision; writing – review and editing.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Data S1: Formal Search Strategy IlOT Supplementary.
Data S2: PRISMA_2020_checklist_ ILOT_Morreau.