SYSTEMATIC REVIEW

REVISED Vasoactive agents in acute mesenteric ischaemia in critical care. A systematic review [version 2; peer review: 1 approved, 2 approved with reservations]

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v2 **First published:** 08 Jun 2021, **10**:453
https://doi.org/10.12688/f1000research.52782.1
Latest published: 06 Sep 2021, **10**:453
https://doi.org/10.12688/f1000research.52782.2

Abstract

Background: Acute mesenteric ischaemia (AMI) is a surgical emergency which has an associated high mortality. The mainstay of active treatment includes early surgical intervention, with resection of non-viable bowel, and revascularisation of the ischaemic bowel where possible. Due to the physiological insult of AMI however, perioperative care often involves critical care and the use of vasoactive agents to optimise end organ perfusion. A number of these vasoactive agents are currently available with varied mechanism of action and effects on splanchnic blood flow. However, specific guidance on which is the optimal vasoactive drug to use in these settings is limited. This systematic review aimed to evaluate the current evidence comparing vasoactive drugs in AMI.

Methods: A systematic search of Ovid Medline, Ovid Embase, Cochrane CENTRAL and the Cochrane Database of Systematic Review was performed on the 5th of November 2020 to identify randomised clinical trials comparing different vasoactive agents in AMI on outcomes including mortality. The search was performed through the Royal College of Surgeons of England (RCSEng) search support library. Results were analysed using the Rayyan platform, and independently screened by four investigators.

Results: 614 distinct papers were identified. After screening, there were no randomised clinical trials meeting the inclusion criteria.

Conclusions: This review identifies a gap in literature, and therefore recommends an investigation into current practice and clinician preference in relation to vasoactive agents in AMI. Multicentre randomised controlled trials comparing these medications on clinical outcomes will therefore be required to address this question.

Open Peer Review

Reviewer Status ? ✓ ?

	Invited Reviewers		
	1	**2**	**3**
version 2 (revision) 06 Sep 2021		✓ report	
version 1 08 Jun 2021	? report	? report	? report

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Any reports and responses or comments on the article can be found at the end of the article.

Keywords
Acute Mesenteric Ischaemia, AMI, Critical Care, General Surgery, vasoactives, vasopressors, infarction, ischaemic, perioperative care, splanchnic blood flow, noradrenaline, levosimendan, dobutamine, dopexamine, dopamine, milronone, systematic review, DELPHI, OVID, MEDLINE, EMBASE, COCHRANE, CDSR, Aberdeen, Grampian, Human,

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Author roles: Brennan CA: Formal Analysis, Investigation, Methodology, Project Administration, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Osei-Bonsu P**: Formal Analysis, Investigation, Methodology, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **McClenaghan RE**: Formal Analysis, Methodology, Writing – Original Draft Preparation; **Nassar A**: Data Curation, Formal Analysis, Resources, Software, Visualization; **Forget P**: Conceptualization, Formal Analysis, Project Administration, Supervision, Validation; **Kaye C**: Conceptualization, Supervision, Validation; **Ramsay G**: Conceptualization, Funding Acquisition, Supervision, Validation

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

How to cite this article: Brennan CA, Osei-Bonsu P, McClenaghan RE *et al.* **Vasoactive agents in acute mesenteric ischaemia in critical care. A systematic review [version 2; peer review: 1 approved, 2 approved with reservations]** F1000Research 2021, **10**:453 https://doi.org/10.12688/f1000research.52782.2

First published: 08 Jun 2021, **10**:453 https://doi.org/10.12688/f1000research.52782.1

REVISED **Amendments from Version 1**

This revised addition takes into consideration specific points made by our esteemed peer reviewers.

We have clarified specific points throughout the paper that appeared unclear. This included going into more detail with the specific reasoning for paper exclusion, which was not initially included. This was clarified in the methods, results, and discussion sections. We also clarified the reasoning for not further analysing case reports, instead focusing on RCT's. With this point, we have added a statement to the conclusion expressing the potential for further analysis within this dataset. We have also clarified syntax in relation to the aim of the paper – to investigate the treatment of mesenteric ischaemia, rather than vasoactive agents as a cause for ischaemia. We have provided additional references in the discussion in relation to this.

Any further responses from the reviewers can be found at the end of the article

Introduction

Acute mesenteric ischaemia (AMI) is a time- critical surgical emergency,[1] where early diagnosis and management can prevent bowel infarction, multiorgan failure and death.[2–4] It is defined as a sudden inadequacy of arterial supply or venous drainage to the bowel, leading to ischemia and cellular damage, with or without necrosis.[5,6] AMI has an estimated incidence of ~1:1000 hospital admissions.[1,4,7–9]

A number of pathophysiological mechanisms can lead to mesenteric ischaemia.[4] "Occlusive" mesenteric ischaemia is due to arterial or venous thrombosis or embolism. "Non-occlusive" is due to acute circulatory failure, usually in the critically unwell patient.[10,11] Non-occlusive mesenteric ischaemia (NOMI) can also occur in the setting of critical illness secondary to the use of vasoactive drugs because of splanchnic vasoconstriction.[5] Each of these processes cause a gut-derived systemic inflammatory response syndrome (SIRS) or mesenteric ischaemic necrosis, leading to severe metabolic derangement and culminating in multiple organ dysfunction requiring critical care intervention.[12,13]

Early imaging with computerised tomography (with arterial and portal venous phase)[6] is important for diagnosis and instigating a timely management plan. The optimal management of AMI depends on the underlying pathophysiology and whether the affected bowel is ischaemic or infarcted. Treatment of AMI focuses on reperfusion and/or resection of non-viable bowel.[14] As in any critically unwell patient, adequate resuscitation of haemodynamic parameters is important to optimise end-organ perfusion and prevent the development of multiorgan failure.

Given the extent of sepsis response, AMI management usually requires critical care support. Vasoactive drugs are often required in this setting to optimise haemodynamic status, with the aim of improving supply to the end organs as well as optimising the perfusion of blood to the adjacent intestine segments to the area of ischaemia.[15] However, the choice of vasoactive agents is unclear for patients with AMI. This is a result of the various mechanism of action of these medications and differing levels of associated splanchnic vasoconstriction. Some agents, such as noradrenaline and adrenaline, can be effective in improving systemic vascular resistance and thus, maintain the perfusion pressure to the brain and heart. However, they can also be associated with profound splanchnic vasoconstriction which could exacerbate bowel ischaemia by precipitating NOMI.[1,16] Other drugs are perceived to have less of an effect on splanchnic vasculature and could theoretically improve perfusion to the primary area of pathology but may impact on perfusion pressure for other organs.

The mortality rate is variable but often high, especially when detected late or accompanied by metabolic derangement.[4,7] This variability in mortality may be secondary to differences in local practice[5,17,18] and between clinicians. It may also reflect the lack of evidence-based guidelines available for these conditions.[19–23] Vasoactive agents vary in their mechanisms of action, and balance of vasoconstriction, inotropy, and splanchnic vascular dilatation. It is not known whether one may be more beneficial than others in the setting of AMI. This primary aim of this systematic review is to evaluate the current evidence comparing mortality outcomes for vasoactive drugs in AMI. Our PROSPERO summary is illustrated in Figure 1.

Methods

Protocol and registration

This review has been prepared in line with the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) statement. The protocol for this systematic review was developed and registered to PROSPERO prior to the analysis of search results (CRD42020212291, 11/11/2020).

Study Objectives

Search title	The use of vasoactive agents in acute mesenteric ischemia in critical care: a systematic review
Research question	Is there a difference in mortality associated with different vasoactive agents in Acute Mesenteric Ischemia?
Population	Any adult with Acute Mesenteric Ischemia
Intervention(s)	Dopexamine, Dopamine, Dobutamine, Levosimendan
Comparators	No vasoactive agents, any other vasoactive agent(s)
Primary Outcome	Mortality
Secondary Outcome(s)	Survival, remaining length of small bowel, time to anastomosis, length of critical care stay, length of in hospital stay, other
Exclusion criteria	Paediatric populations, non-human trials
Search Databases	Ovid medline, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews

Figure 1. Summary of study objectives.

Eligibility criteria

This systematic review aims to identify randomised clinical trials (RCTs) comparing mortality rates associated with different vasoactive agents in AMI. The target population were any patients with AMI admitted into a critical care environment. Vasoactive drugs included were noradrenaline, adrenaline, dopexamine, dobutamine, dopamine, levosimendan, vasopressin, ephedrine or phenylephrine. Comparators were either no vasoactive drug or any other vasoactive drug. The primary outcome was mortality. Secondary outcomes were survival, length of preserved bowel, time to anastomosis, length of critical care admission, and overall length of hospital stay. All published works were searched regardless of date of publication or language.

Information sources

Searched sources were Ovid Medline, EMBASE, Cochrane CENTRAL and the Cochrane Database of Systematic Review.

Search strategy

The literature search was conducted by the library department of the Royal College of Surgeons of England. The Patient, Intervention, Control and Outcome (PICO) framework was used and is outlined in Figure 1. Electronic databases of Ovid Medline, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews (CDSR) were searched for relevant studies. The search was completed on the 5th of November 2020 and included all relevant studies since 1946 including non-English studies and case reports. Search strategies included certain drugs, such as noradrenaline, adrenaline, dopexamine, dobutamine, dopamine, levosimendan, vasopressin, ephedrine or phenylephrine were specified. However, freedom of the searchers to add more terms if required was allowed. A combination of keywords and controlled vocabulary was adapted for each database. Search strategies are outlined in Figures 2, 3 and 4.

Selection process

Studies were screened for relevant phrases of inclusion, where papers were identified as randomised control trials, performed on non-animal subjects, on the subject relating to the usage of vasoactive drugs in AMI. Papers were screened by four reviewers (CB, PO, EM, PF) independently. The process was facilitated using the Rayyan Platform, allowing for independent and anonymous review and analysis of searched literature. Any discrepancies underwent further review until a consensus was reached.

Data collection process

Data was collected from the reports identified by the literature search using the Rayyan platform. This platform facilitated independent and anonymous collection of data.

Data items

The Data items we sought were the following: the country of study, the study design, the intervention type (vasoactive medication), pathology and surgery (if any) subtype, the study size, the follow-up-time, the remaining length of small bowel, time to anastomosis, length of critical care stay, length of in hospital stay.

Database: Ovid MEDLINE(R) ALL <1946 to November 03 2020>		Results per line:	Number of results:
Date:	05/11/2020		
1	Mesenteric Ischemia/	1094	**225**
2	((mesenter* or bowel* or small intestin*) adj6 isch?emi*).ti,ab,kw,kf.	6887	
3	or/1-2	7262	
4	Critical Care/ or Critical Illness/	77049	
5	((care* or therap* or ill*) adj6 (critical* or intensive* or acute*)).ti,ab,kw,kf.	333190	
6	(ICU or IC or ITU or CC or CCU or acute*).ti,ab,kw,kf.	1413077	
7	or/4-6	1594818	
8	3 and 7	2715	
9	Pharmaceutical Preparations/	54108	
10	(pharmaceutic* or drug* or substance* or medicin* or medicat* or agent* or agonist* or antagonist* or peptid* or receptor* or infus* or dose* or dosage* or intravenous*).ti,ab,kw,kf.	6239984	
11	Dopamine/ or Dopamine Agents/ or Dopamine Agonists/ or Dopamine Antagonists/ or Dobutamine/ or Simendan/	94894	
12	(dopamine or hydroxytyramine or dobutamin* or dobucor or dobuject or simendan or levosimendan or dextrosimendan or simadax or dopexamine or dopacard speywood).ti,ab,kw,kf.	137038	
13	Vasoactive Intestinal Peptide/ or Vasodilation/ or Vasodilator Agents/ or Vasoconstriction/ or Vasoconstrictor Agents/	112502	
14	(vasoactiv* or vasodilat* or vasocontrict* or vasorelaxa* or vasopress* or vasointestinal or inotrop*).ti,ab,kw,kf.	160008	
15	Epinephrine/ or Metaraminol/ or Phenylephrine/ or Ephedrine/ or Norepinephrine/ or Milrinone/ or Isoproterenol/	157883	
16	(adrenaline or noreadrenaline or metaraminol or metaradrin* or aramine or araminol or hydroxyphenylpropanolamine or phenylephrine or metaoxedrin or metasympatol or mezaton or neo synephrine or neo-synephrine or ephedrine or sal phedrine or sal-phedrine or salphedrine or epinephrine or epifrin or epitrate or lyophrin or norepinephrine or milrinone or corotrop* or primacor or primacor or isoprenaline or isoproterenol or euspiran or isadrin* or isuprel or izadrin or norisodrine or novodrin).ti,ab,kw,kf.	147993	
17	or/9-16	6475040	
18	8 and 17	533	
19	limit 18 to "all adult (19 plus years)"	225	

Figure 2. Search strategy – Medline.

Database:	Embase <1974 to 2020 Week 44>	Results per line:	Number of results:
Date:	05/11/2020		
1	mesenteric ischemia/	2615	**556**
2	((mesenter* or bowel* or small intestin*) adj6 isch?emi*).ti,ab,kw.	9997	
3	or/1-2	10712	
4	intensive care/ or critical illness/	149722	
5	((care* or therap* or ill*) adj6 (critical* or intensive* or acute*)).ti,ab,kw.	487982	
6	(ICU or IC or ITU or CC or CCU or acute*).ti,ab,kw.	1956193	
7	or/4-6	2222695	
8	3 and 7	4327	
9	drug/	39114	
10	(pharmaceutic* or drug* or substance* or medicin* or medicat* or agent* or agonist* or antagonist* or peptid* or receptor* or infus* or dose* or dosage* or intravenous*).ti,ab,kw.	8259213	
11	dopamine/ or dobutamine/ or simendan/ or dopexamine/	134112	
12	(dopamine or hydroxytyramine or dobutamin* or dobucor or dobuject or simendan or levosimendan or dextrosimendan or simadax or dopexamine or dopacard speywood).ti,ab,kw.	177754	
13	vasoactive intestinal polypeptide/ or vasodilatation/ or vasodilator agent/ or vasoconstriction/ or vasoconstrictor agent/	136474	
14	(vasoactiv* or vasodilat* or vasocontrict* or vasorelaxa* or vasopress* or vasointestinal or inotrop*).ti,ab,kw.	210125	
15	epinephrine/ or metaraminol/ or phenylephrine/ or ephedrine/ or noradrenalin/ or milrinone/ or isoprenaline/	221420	
16	(adrenaline or noreadrenaline or metaraminol or metaradrin* or aramine or araminol or hydroxyphenylpropanolamine or phenylephrine or metaoxedrin or metasympatol or mezaton or neo synephrine or neo-synephrine or ephedrine or sal phedrine or sal-phedrine or salphedrine or epinephrine or epifrin or epitrate or lyophrin or norepinephrine or milrinone or corotrop* or primacor or primacor or isoprenaline or isoproterenol or euspiran or isadrin* or isuprel or izadrin or norisodrine or novodrin).ti,ab,kw.	174613	
17	or/9-16	8556994	
18	8 and 17	1150	
19	limit 18 to (adult <18 to 64 years> or aged <65+ years>)	556	

Figure 3. Search strategy – EMBASE.

Database:	Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews (CDSR)	Results per line:	Number of results:
Date:	05/11/2020		
#1	[mh ^"Mesenteric Ischemia"]	5	**CENTRAL: 47** **CDSR: 0**
#2	((mesenter* OR bowel* OR small NEXT intestin*) NEAR/6 (isch?emi*)):ti,ab,kw	160	
#3	{OR #1-#2}	160	
#4	([mh ^"Critical Care"] OR [mh ^"Critical Illness"])	3712	
#5	((care* OR therap* OR ill*) NEAR/6 (critical* OR intensive* OR acute*)):ti,ab,kw	53228	
#6	(ICU OR IC OR ITU OR CC OR CCU OR acute*):ti,ab,kw	164589	
#7	{OR #4-#6}	184400	
#8	(#3 AND #7)	88	
#9	[mh ^"Pharmaceutical Preparations"]	196	
#10	(pharmaceutic* OR drug* OR substance* OR medicin* OR medicat* OR agent* OR agonist* OR antagonist* OR peptid* OR receptor* OR infus* OR dose* OR dosage* OR intravenous*):ti,ab,kw	888890	
#11	([mh ^Dopamine] OR [mh ^"Dopamine Agents"] OR [mh ^"Dopamine Agonists"] OR [mh ^"Dopamine Antagonists"] OR [mh ^Dobutamine] OR [mh ^Simendan])	3016	
#12	(dopamine OR hydroxytyramine OR dobutamin* OR dobucor OR dobuject OR simendan OR levosimendan OR dextrosimendan OR simadax OR dopexamine OR dopacard NEXT speywood):ti,ab,kw	9306	
#13	([mh ^"Vasoactive Intestinal Peptide"] OR [mh ^Vasodilation] OR [mh ^"Vasodilator Agents"] OR [mh ^Vasoconstriction] OR [mh ^"Vasoconstrictor Agents"])	7501	
#14	(vasoactiv* OR vasodilat* OR vasocontrict* OR vasorelaxa* OR vasopress* OR vasointestinal OR inotrop*):ti,ab,kw	19915	
#15	([mh ^Epinephrine] OR [mh ^Metaraminol] OR [mh ^Phenylephrine] OR [mh ^Ephedrine] OR [mh ^Norepinephrine] OR [mh ^Milrinone] OR [mh ^Isoproterenol])	7189	

Figure 4. Search strategy - Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR).

#16	(adrenaline OR noreadrenaline OR metaraminol OR metaradrin* OR aramine OR araminol OR hydroxyphenylpropanolamine OR phenylephrine OR metaoxedrin OR metasympatol OR mezaton OR neo NEXT synephrine OR ephedrine OR sal NEXT phedrine OR salphedrine OR epinephrine OR epifrin OR epitrate OR lyophrin OR norepinephrine OR milrinone OR corotrop* OR primacor OR primacor OR isoprenaline OR isoproterenol OR euspiran OR isadrin* OR isuprel OR izadrin OR norisodrine OR novodrin):ti,ab,kw	18402	
#17	{OR #9-#16}	894953	
#18	(#8 AND #17)	50	
#19	([mh Child] OR [mh Infant] OR [mh Pediatrics])	73550	
#20	(p*diatric* OR child* OR baby OR babies OR infant* OR toddler* OR neo NEXT nat* OR neonat* OR newborn* OR new NEXT born* OR preschool* OR pre NEXT school* OR preadolescen* OR pre NEXT adolescen* OR preteen* OR pre NEXT teen* OR teenage* OR teen NEXT age* OR pubescen* OR pre NEXT pubescen* OR juvenile*):ti,ab,kw	205787	
#21	{OR #19-#20}	205793	
#22	(#18 NOT #20)	47	

Figure 4. *(continued)*

Risk of bias in individual studies
The reviewers were to assess selected studies using the Grading of Recommendations Assessment, Development and Evaluation (short GRADE) system. GRADE assesses study limitations/risk of bias, inconsistency, indirectness, impreciseness and publication bias. These criteria would have been applied on a study-by-study basis and an outcome level by two reviewers and where there was inconsistency, a third reviewer would assess and provide an outcome. We planned to perform a meta-analysis if the reported results permitted.

Data synthesis
In the case of a negative search without any eligible randomised controlled trials, the plan was to discuss the existing evidence regarding the problem (AMI) and how the intervention might work (use of vasoactive drugs).

Meta-bias(es)
The methods were to be reviewed externally to identify possible sources of potential bias.

Confidence in cumulative evidence
Strength was to be assessed using GRADE tools.

Results
This systematic review aimed to identify randomised control trials comparing mortality rates in relation to the use of different vasoactive drugs in AMI. Ovid Medline, EMBASE, Cochrane CENTRAL and the Cochrane Database of Systematic Review were systematically searched as outlined in Figures 1-4.

The initial search identified a total of 700 articles. After screening for duplicates, 614 articles remained and were reviewed for eligibility. Of these articles, 563 were not randomised control trials and thus immediately excluded. A further 22 trails were excluded as they were in animal studies. The remaining 29 RCT's were reviewed, and their subject of focus in all cases was not related to mesenteric ischaemia. Thus, there were no eligible studies identified addressing the specific study question. Reasons for exclusion included: non-randomised controlled trials and studies, non-human trials, and studies which bore no semblance to the question of interest. In view of this, no quantitative analysis was performed. The PRISMA flowchart is outlined in Figure 5.

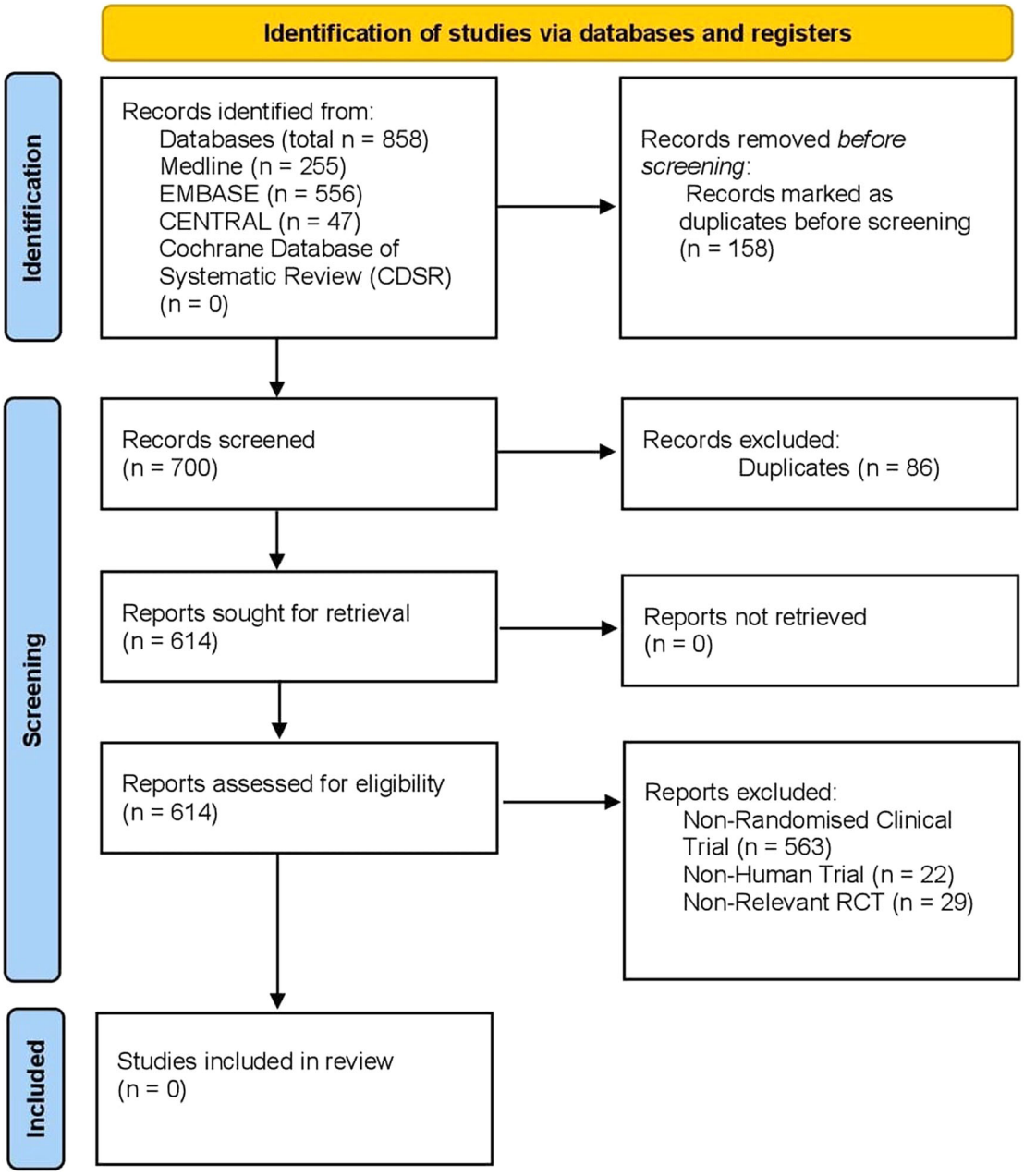

Figure 5. PRISMA flowchart.

Discussion

There is significant variation in the management of AMI, and this may reflect regional variations in mortality associated with this condition. The recent ACPGBI guidance[24] on Emergency General Surgery highlighted the relative paucity of research in this field. However, a synthesis of specific aspects of AMI management, such as the choice of vasoactive medications and its influence on mortality was beyond its remit.

This systemic review aimed to ask that question and assessed the previous publications available. It is of interest that this work failed to identify any studies comparing the use of these drugs in AMI against outcomes. Although the focus of this paper is evaluating choice of vasoactive support and not comparing risk of associated ischaemia with agents, it worth considering both conditions pathophysiology's for the evaluation of the most promising agent for a future RCT. Of the 29 excluded RCT's, only 3 were studies comparing vasoactive agents. Although comparative studies, their subject base was

deemed too different to be included for our subject matter. Hajjar et al compared vasopressin and noradrenaline in vasoplegic shock after cardiac surgery.[25] Given the different physiological mechanism of shock, it is difficult to use this comparison for mesenteric ischaemia. Liu et al compared terlipressin and noradrenaline in septic shock, but identified no difference.[26] Laterre et al compared serlipressin with placebo in another context of septic shock, and found no difference.[27] Overall the comparative studies identified did not shed light on the optimal choice for mesenteric ischaemia.

In patients who present with symptoms, clinical findings or imaging suggestive of mesenteric arterial ischaemia, resuscitative measures including the avoidance of systemic hypoxia and intravenous fluids are crucial first steps to optimising blood pressure and end organ perfusion.[6] Broad spectrum intravenous antibiotics should also be administered promptly due to the potential for bacterial complications in view of the breach of the mucosal barrier.[6] Of the small cohort of patients deemed suitable, urgent revascularisation should be pursued to re-perfuse the ischaemic gut through liaison with the interventional radiologists and vascular surgeons. Most patients who are admitted to critical care units will require vasoactive drugs to optimise their blood pressure and cardiovascular status. However, the ideal drug which gives an appropriate increase in systemic arterial pressure without causing a decrease in or compromise of splanchnic perfusion remains to be elicited and the literature on this question is absent.

Catecholamines

Noradrenaline and adrenaline

In the context of AMI, splanchnic blood flow would seem a salient factor. Pharmacologically, noradrenaline is an endogenous catecholamine which primary has a direct alpha-1 effect, although there is a small degree of β-1 adrenergic agonism. It increases systemic vascular resistance (SVR), increasing afterload;- and causes venoconstriction increasing preload. It is weakly a positive inotrope through its β-1 effect. Some studies suggest that noradrenaline reduces hepato-splanchnic blood flow in septic and non-septic patients.[28,29] Similarly, adrenaline, a sympathomimetic, was found to have a reductive effect on splanchnic blood flow.[30]

Dopamine and dopexamine

Dopamine is a catecholamine, a precursor to noradrenaline, and mediates inotropy via dopamine receptors and vasoconstriction via the alpha-adrenergic pathway. It shows a dose dependent change in action; causing splanchnic dilatation at low doses while increasing SVR at higher doses. Meier-Hellmann *et al.*[31] reported an increase in hepato-splanchnic blood flow in septic patients given dopamine although Neviere and colleagues[32] reported a decrease in gut mucosal perfusion. Maynard *et al.*[33] suggested that dopexamine, a dopamine analogue which has vasodilatory effects, may improve gut microcirculation in septic shock; although subsequent investigators did not confirm these beneficial effects.

Dobutamine

Dobutamine, a synthetic catecholamine is a β1-selective adrenoceptor agonist which is utilised clinically as a positive inotrope in the treatment of acute heart failure and cardiogenic shock. Creteur and colleagues[34] determined that a dobutamine infusion did improve both splanchnic oxygenation in septic animals and in septic patients. However, Bomberg *et al.*[35] suggest that in pigs, dobutamine may improve arteriovenous shunting, but conversely may reduce jejunal mucosal perfusion.

Non-catecholamines

Vasopressin

One observational cohort study found that vasopressin, a potent non-catecholamine vasoconstrictor which acts on vasopressin receptors, improved small bowel perfusion and mortality in patients with non-occlusive mesenteric ischaemia (NOMI) who had undergone cardiopulmonary bypass for elective cardiac surgery.[13] However, no further assessment of outcome in AMI appears to have been assessed.

Levosimendan and milrinone

Levosimendan is an inotrope which improves contractility by sensitizing cardiac muscle to calcium. It also produces vasodilation by opening ATP-sensitive K+ channels in vascular smooth muscle, although this is not yet demonstrated in the splanchnic circulation.

An experimental study on hypoxic, stressed new-born piglets showed milrinone, a phosphodiesterase inhibitor which produces an inotropic effect and vascular dilation, improves mesenteric perfusion.[36]

There is thus some basic scientific experimental data available on the effects of some vasoactive agents on the splanchnic circulation. However, there are a number of limitations to this, and none have been extrapolated into clinical trials investigating vasoactive medication in AMI, against other agents. In relation to our study question, most of the experimental data focuses on patients in a shocked state as a result of sepsis, or in elective settings such as planned cardiac surgery, rather than in AMI. None of the studies report any clear data in relation to mortality or morbidity, length of hospital or critical care stay associated with any vasoactive agents.

There may be a role for dobutamine, levosimendan, milrinone, dopamine or vasopressin or other vasoactive agents in improving splanchnic perfusion in mesenteric ischaemia, but further, more extensive, patient-based study is required to elucidate these theories and their clinical significance in relation to patient survival and morbidity.

Limitations

This study did not identify any qualifying randomised controlled trials in relation to the study question and therefore did not produce a quantitative analysis.

It should be considered why no randomised controlled trials have occurred in this field thus far. The acute presentation and potential early requirement for vasoactive support, coupled with initial uncertainty of diagnosis, may make comparative studies more difficult to perform.

Conclusions

This systematic review has identified a gap in literature and research relating to the choice of vasoactive agent in AMI. There are therefore actions we would recommend to aid identifying best practice for this condition. The results of this study would suggest that it is important to investigate current practice and clinician preference. The first step to this would therefore be a Delphi Study which is currently underway and can be found via this link: **https://is.gd/vasoactive_agents_AMI**. Following the survey is an optionable Delphi process.

RCTs where comparison of outcomes with different vasoactive agents is analysed could ultimately improve the care of the critically ill patient with mesenteric ischaemia and remains absent from any work relating to AMI.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Reporting guidelines

Harvard Dataverse. PRISMA checklist and Review Data for: Vasoactive agents in acute mesenteric ischaemia in critical care. A systematic review. DOI: https://doi.org/10.7910/DVN/2GN0BS.[37]

Acknowledgements

With thanks to **Helen Fulbright**, PhD, MA, PGDip LIS, BA (Hons), MCLIP, **Information Specialist**, Royal College of Surgeons of England Library and Archives Team, for conducting the literature searches.

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PubMed Abstract | Publisher Full Text | Free Full Text

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Open Peer Review

Current Peer Review Status: ? ✓ ?

Version 2

Reviewer Report 22 September 2021

https://doi.org/10.5256/f1000research.58870.r93548

✓ **Norman Galbraith**
[1] University Department of Surgery, Glasgow Royal Infirmary, Glasgow, UK
[2] University of Glasgow, Glasgow, UK
[3] NHS Scotland, Glasgow, UK

Thank you for having the opportunity to look at this manuscript again, and for the authors incorporating some of the suggested changes.

Most systematic reviews will not have multiple main tables in the article for separate search criteria and the article would be more aesthetic and readable to an audience of they were compressed into one table or better supplemental, but I will leave that to the editors discretion.

In one response to a comment from a prior review, there was a suggestion of merit of another review looking at non RCT studies. I would suggest that this subject probably doesn't need multiple separate reviews and that component would be best placed here. However, the aim is clear not to include non RCT studies and this beyond the scope of this review.

This article achieves the aim of highlighting a gap in the literature and paves the way for future research in an interesting and understudied subject.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: General surgery, colorectal surgery, Inflammatory response, macrophage/monocyte function

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 29 June 2021

https://doi.org/10.5256/f1000research.56103.r87010

?

Xavier Wittebole
Department of Critical Care Medicine, Clinique Universitaire St Luc, Université Catholique de Louvain, Brussels, Belgium

GENERAL COMMENTS:

The authors performed a systematic review to assess the role of vasopressors in acute mesenteric ischemia (AMI). From 614 papers, they could not find any randomized controlled trial and conclude "*Multicenter randomized controlled trials comparing these medications on clinical outcomes will therefore be required to address this question*." They further discuss the effects of some of these vasoactive agents.

SPECIFIC COMMENTS:

- The authors distinguish 2 different mechanisms that may explain AMI and propose vasopressors would be responsible for non-occlusive MI (NOMI). However, in NOMI, it is difficult to assess the exact role of vasopressors versus the cause for which the vasopressors are used. For instance, the microcirculatory changes observed in sepsis may also explain some ischemic lesions without any effect of vasopressors per se. This could be briefly discussed.

- The authors should also better clarify the fact they searched for the best vasopressor therapy in AMI versus the medication that would be responsible for the development of AMI.

- A recent meta-analysis (Belletti *et al.* 2020[1]) assessed the effects of continuous epinephrine infusion on survival in critical care patients. In this MA, a secondary endpoint evaluated the development of bowel ischemia. This study might be a source of other papers that could be assessed for this present study.

- It might be of interest the authors check some large trials on vasopressors (vasopressin and the Vasst study; selepressin and the SepsisAct study; angiotensin II and the Athos-3 study; etc). By evaluating the side effects in those trials (mesenteric ischemia), the authors could already provide a beginning of answer to the question raised. While out of the scope of this study, this might however be of interest.

- When discussing the various vasoactive drugs, I would propose the authors classify them as "mostly vasopressors" (nor-adrenalin, etc) and "mostly inotropes" dobutamine, etc) and "mixed action" (epinephrine, etc).

- Some vasopressors are not discussed. (terlipressin, selepressin, angiotensin II).

MINOR COMMENTS:

- I personally found the abstract's background too long.
- Figures 2, 3 and 4 could be provided in a supplementary appendix.
- The authors could also remind the reader that CT scan has a low sensitivity to diagnose trans-mural ischemia (see for instance Verdot *et al.* (2021[2])).
- In the Eligibility Criteria paragraph, the authors propose various secondary outcomes including "length of critical care admission". I would propose to write "ICU length of stay".

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Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Critical Care Medicine, Sepsis

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 21 June 2021

https://doi.org/10.5256/f1000research.56103.r87013

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Norman Galbraith
[1] University Department of Surgery, Glasgow Royal Infirmary, Glasgow, UK
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[3] NHS Scotland, Glasgow, UK

This is a systematic review of which vasoactive therapeutics are best in patients with acute mesenteric ischaemia. This is a clinically important and under-researched condition with a poor evidence base. I applaud the authors for raising pursuing this topic and this article is an important step to highlight the lack of evidence, despite being so common, in a systematic way. The article is well written and understandable. Methodologically, it follows the PRISMA steps of a systematic review.

Some suggestions I have are:

1. It wasn't entirely clear to me whether this study was to determine which agents were optimum in part of the treatment of acute mesenteric ischaemia (i.e. occlusive), or which agent was a potential cause of acute mesenteric ischaemia in the already critically unwell patient with another primary diagnosis e.g. sepsis. I would suggest clarifying this when stating the aim/hypothesis at the end of the introduction, or in the methods section (and potentially in the "Research question" section of Figure 1 by including the phrase "the treatment of" or "prevention of").

2. As a clinically important, common but well known to be under-researched area, it is maybe not surprising there are no RCT's in this subject. Did the authors consider widening their search to include non-randomised prospective studies, or observational/retrospective studies where we might expect some evidence to lie? If not, due to the likely biased nature of some of these weaker type of studies, I would suggest the authors state/justify why they have not included this body of evidence in their study. Alternatively, if the authors have searched this or have some data of observational studies, adding this as a table or supplementary table would strengthen the paper.

3. Having the exact search strategy included is appreciated and makes the study more reproducible, however, I would suggest putting all of these tables to the supplementary section.

4. To further the strength of the methodology, demonstrating that the "grey literature" has been searched to check for additional evidence/publication bias would be helpful. Some articles now use the OpenGrey platform to do this.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: General surgery, colorectal surgery, Inflammatory response, macrophage/monocyte function

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 24 Aug 2021

Christopher Brennan, NHS Grampian, Aberdeen, UK

- *It wasn't entirely clear to me whether this study was to determine which agents were optimum in part of the treatment of acute mesenteric ischaemia (i.e. occlusive), or which agent was a potential cause of acute mesenteric ischaemia in the already critically unwell patient with another primary diagnosis e.g. sepsis. I would suggest clarifying this when stating the aim/hypothesis at the end of the introduction, or in the methods section (and potentially in the "Research question" section of Figure 1 by including the phrase "the treatment of" or "prevention of").*
- **Response:** Our review intends to look at vasoactive choice in treatment of mesenteric ischaemia, as opposed to risk of causing ischaemia. Although ischaemia as side effect of vasoactive agents was not considered here, it is of interest to consider both for the pathophysiology and for the evaluation of the most promising agent for a future RCT. We have clarified this in the aims section of the introduction.

- *As a clinically important, common but well known to be under-researched area, it is maybe not surprising there are no RCT's in this subject. Did the authors consider widening their search to include non-randomised prospective studies, or observational/retrospective studies where we might expect some evidence to lie? If not, due to the likely biased nature of some of these weaker type of studies, I would suggest the authors state/justify why they have not included this body of evidence in their study. Alternatively, if the authors have searched this or have some data of observational studies, adding this as a table or supplementary table would strengthen the paper.*
- **Response:** Many thanks for your comment. For the purpose of this review, only RCT's were considered. A further review in the future with our search protocol, analysing case reports, would likely be of merit. Our review highlights the lack of RCT's on the subject matter, which can be used to prompt further analysis of data. We have added a statement to the conclusion.

- *Having the exact search strategy included is appreciated and makes the study more reproducible, however, I would suggest putting all of these tables to the supplementary section.*
- **Response:** Many thanks. The structure of this systematic review is as per the publishers guidelines.

- *To further the strength of the methodology, demonstrating that the "grey literature" has been searched to check for additional evidence/publication bias would be helpful. Some articles now use the OpenGrey platform to do this.*
- **Response:** Many thanks for your comment. However, we have not performed a grey literature search as we wish to assess if there is any direct comparison published, in the form of RCT between different vaso-active agents in this setting.

Competing Interests: Nil

Reviewer Report 14 June 2021

https://doi.org/10.5256/f1000research.56103.r87014

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Nick Heywood
East Lancashire Hospitals NHS Trust, East Lancashire, UK

I would like to thank the authors for the opportunity to review this paper "Review of Vasoactive agents in acute mesenteric ischaemia in critical care. A systematic review." This is indeed an area where there is paucity of research and this paper certainly demonstrates that. I do however have the following points which should be addressed before acceptance for indexing in Pub Med.

- The authors state that their aim in the introduction is: "*This primary aim of this systematic review is to evaluate the current evidence comparing mortality outcomes for vasoactive drugs in AMI",* however in the results section they state that *"This systematic review aimed to identify randomised control trials comparing mortality rates in relation to the use of different vasoactive drugs in AMI."* The authors state in the abstract results section that there is no randomised controlled trial, and this is the only result. The authors included non-randomised trials including case reports in their search, yet there is no comment on the results, nor any narrative as to the types of study out of the 614 returned in the search. There should be a descriptive in the result section as to the numbers of each types of study, i.e. number of case reports (including number of patients in these case reports), number of observational studies etc.

- The Methods section is very detailed and could be easily replicated. I commend the authors

for their thorough search of the all the relevant articles.

- With regards to the findings, they do indeed make this study difficult to write in a manuscript and the authors need to be clear about searching for rCTs vs case inclusion of case reports. For example, if the authors were not interested in case reports, why were they not excluded early in the study. It may be that they wanted to ensure no studies were missed, but this should be discussed in the paper.

- The findings, or lack thereof, makes the discussion limited. Upon reading the discussion, it felt like reading a review article rather than the discussion section of a systematic review. I understand that the authors need to write the discussion, but much of this does not seem relevant to the discussion section of this type of article. It feels more at place in an introduction or a separate article regarding the choices of treatments for this disease process.

- The authors should focus on discussing the types of papers that were found in the review, what types of studies they found and their limitations. The should also discuss why some of the 29 non-relevant RCTs were indeed non-relevant. Although the authors touch upon this in the introduction, they may wish to focus the discussion on the difficulties associated with undertaking this type of study and why there may be lack of data. A degree of speculation is needed here, but would be more relevant than the pharmacology of vasoactive drugs, for which should not really be included in the discussion section.

Overall, I agree that this message is very important and certainly supports future work, that I am glad to see is being developed, however, this paper needs more work before acceptance for indexing in PubMed

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Partly

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: My areas of expertise include general surgery with specific interest in collaborative research, colorectal sruegry and in particular pelvic floor disorders and cancer

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 24 Aug 2021

Christopher Brennan, NHS Grampian, Aberdeen, UK

- *The authors state that their aim in the introduction is: "This primary aim of this systematic review is to evaluate the current evidence comparing mortality outcomes for vasoactive drugs in AMI", however in the results section they state that "This systematic review aimed to identify randomised control trials comparing mortality rates in relation to the use of different vasoactive drugs in AMI." The authors state in the abstract results section that there is no randomised controlled trial, and this is the only result. The authors included non-randomised trials including case reports in their search, yet there is no comment on the results, nor any narrative as to the types of study out of the 614 returned in the search. There should be a descriptive in the result section as to the numbers of each types of study, i.e. number of case reports (including number of patients in these case reports), number of observational studies etc. Our primary interest in undertaking this work was to assess whether there was capacity for a randomised clinical trial to be developed comparing different vasoactive agents in this field. Thus, for this systematic review only RCT's were considered for inclusion.*
- **Response:** The search protocol identified many non-RCT's, which were excluded at an early stage and not further analysed. The further RCT's were excluded for being entirely unrelated, or trials not performed in humans. We have edited the results section to clarify this. We have also added a descriptor in the results section highlighting the breakdown of results, and reasons for exclusion.

- *The Methods section is very detailed and could be easily replicated. I commend the authors for their thorough search of the all the relevant articles.*
- **Response:** We thank the reviewer for their commendation.

- *With regards to the findings, they do indeed make this study difficult to write in a manuscript and the authors need to be clear about searching for rCTs vs case inclusion of case reports. For example, if the authors were not interested in case reports, why were they not excluded early in the study. It may be that they wanted to ensure no studies were missed, but this should be discussed in the paper. Case reports were identified in the initial search protocol and thus acknowledged. However as we were specifically interested in RCT's, these were excluded.*
- **Response:** As the reviewer suggests, we did not want to miss any studies and this is why we did not remove case reports initially. This fact has been further highlighted in the methods section.

- *The findings, or lack thereof, makes the discussion limited. Upon reading the discussion, it felt like reading a review article rather than the discussion section of a systematic review. I understand that the authors need to write the discussion, but much of this does not seem relevant to the discussion section of this type of article. It feels more at place in an introduction or a separate article regarding the choices of treatments for this disease process.*
- **Response:** Given the results of our systematic review we felt that discussion around the broader topic would be of benefit to provide context to the relevance of our review. Due to the review only specifically looking for RCT's, further analysis of the

case reports identified was not performed. This is an area of research that, with our search strategy freely available, could be performed in the future. We have added this statement to the conclusion section.

- *The authors should focus on discussing the types of papers that were found in the review, what types of studies they found and their limitations. The should also discuss why some of the 29 non-relevant RCTs were indeed non-relevant. Although the authors touch upon this in the introduction, they may wish to focus the discussion on the difficulties associated with undertaking this type of study and why there may be lack of data. A degree of speculation is needed here, but would be more relevant than the pharmacology of vasoactive drugs, for which should not really be included in the discussion section.*
- **Response:** Of the 29 human non-relevant RCT's, none were on the subject of mesenteric ischaemia, or vasoactive support. We have specifically clarified this point in the discussion section.

Competing Interests: Nil.