Open Access Research

BMJ Open

Early vasopressor use following traumatic injury: a systematic review

Mathieu Hylands,[1] Augustin Toma,[2] Nicolas Beaudoin,[3] Anne Julie Frenette,[4] Frédérick D'Aragon,[3,5] Émilie Belley-Côté,[2,6] Emmanuel Charbonney,[4] Morten Hylander Møller,[7] Jon Henrik Laake,[8] Per Olav Vandvik,[9] Reed Alexander Siemieniuk,[2] Bram Rochwerg,[2,10] François Lauzier,[11] Robert S Green,[12] Ian Ball,[13] Damon Scales,[14] Srinivas Murthy,[15] Joey S W Kwong,[16] Gordon Guyatt,[2] Sandro Rizoli,[17] Pierre Asfar,[18] François Lamontagne[5,6]

To cite: Hylands M, Toma A, Beaudoin N, *et al*. Early vasopressor use following traumatic injury: a systematic review. *BMJ Open* 2017;**7**:e017559. doi:10.1136/bmjopen-2017-017559

► Prepublication history and additional material for this paper are available online. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2017-017559).

Received 29 April 2017
Revised 31 July 2017
Accepted 14 September 2017

CrossMark

For numbered affiliations see end of article.

Correspondence to
Dr François Lamontagne;
francois.lamontagne@usherbrooke.ca

ABSTRACT

Objectives Current guidelines suggest limiting the use of vasopressors following traumatic injury; however, wide variations in practice exist. Although excessive vasoconstriction may be harmful, these agents may help reduce administration of potentially harmful resuscitation fluids. This systematic review aims to compare early vasopressor use to standard resuscitation in adults with trauma-induced shock.

Design Systematic review.

Data sources We searched MEDLINE, EMBASE, ClinicalTrials.gov and the Central Register of Controlled Trials from inception until October 2016, as well as the proceedings of 10 relevant international conferences from 2005 to 2016.

Eligibility criteria for selecting studies Randomised controlled trials and controlled observational studies that compared the early vasopressor use with standard resuscitation in adults with acute traumatic injury.

Results Of 8001 citations, we retrieved 18 full-text articles and included 6 studies (1 randomised controlled trial and 5 observational studies), including 2 published exclusively in abstract form. Across observational studies, vasopressor use was associated with increased short-term mortality, with unadjusted risk ratios ranging from 2.31 to 7.39. However, the risk of bias was considered high in these observational studies because patients who received vasopressors were systematically sicker than patients treated without vasopressors. One clinical trial (n=78) was too imprecise to yield meaningful results. Two clinical trials are currently ongoing. No study measured long-term quality of life or cognitive function.

Conclusions Existing data on the effects of vasopressors following traumatic injury are of very low quality according to the Grading of Recommendations, Assessment, Development and Evaluation methodology. With emerging evidence of harm associated with aggressive fluid resuscitation and, in selected subgroups of patients, with permissive hypotension, the alternatives to vasopressor therapy are limited. Observational data showing that vasopressors are part of usual care would provide a strong justification for high-quality clinical trials of early vasopressor use during trauma resuscitation.

Trial registration number CRD42016033437.

Strengths and limitations of this study

- This is the first systematic review of early vasopressor use in trauma to incorporate a detailed search strategy, explicit inclusion and exclusion criteria, and duplicate screening, data extraction and risk of bias assessment by independent reviewers.
- This review uses the Grading of Recommendations, Assessment, Development and Evaluation approach to evaluate the overall quality of evidence.
- Conclusions are limited by the number and methodological quality of the available studies.

INTRODUCTION

Rationale

Vasopressors increase arterial pressure primarily by inducing vasoconstriction.[1] In the setting of hypovolaemic shock, they are sometimes used as bridge therapy until an intervention targeting the source of the problem can be implemented.[2] For example, during the early phase of resuscitation following trauma, vasopressors can maintain a minimal perfusion pressure without exposing patients to large volumes of intravenous fluid.[3–7] Early fluid administration, be it from massive transfusions or crystalloid administration, can lead to life-threatening complications such as trauma-induced coagulopathy.[3 8] Permissive hypotension also restricts fluid use, and in patients with haemorrhagic shock following penetrating torso injuries this strategy has been shown to be associated with better survival rates compared with aggressive resuscitative measures.[6] However, the generalisability of these findings to other trauma populations, such as patients with traumatic brain injury (TBI) or following blunt trauma, is unclear.[9] Current guidelines consider TBI as an absolute contraindication to permissive hypotension, as this could risk jeopardising cerebral perfusion.[10]

In spite of this potential role as fluid-sparing adjuncts,[11] vasopressors potentiate vasoconstriction and may therefore worsen peripheral and organ perfusion despite high blood pressure values.[12] Nascent haemostatic clots may also be dislodged if normotension is rapidly achieved in a bleeding patient.[13] Other interventions that increase blood pressure with limited fluid volumes, such as hypertonic saline, have been found to be harmful or to provide no important benefit in low risk of bias randomised controlled trials (RCTs).[14–16] Conversely, vasopressors may be beneficial in populations vulnerable to hypotension, such as victims of TBI in whom hypotension doubles mortality.[9] Thus, while trauma guidelines restrict vasopressor use to cases of severe hypotension refractory to fluid therapy,[10 17 18] the balance between the benefits and harms of vasopressors in trauma is unknown, and clinical equipoise exists. Some studies report that vasopressor use is common in unstable patients with trauma, particularly in the setting of pelvic fractures[19] or TBI.[20] In the latter case, vasopressors are administered to support systemic haemodynamics, and more specifically to ensure adequate cerebral perfusion pressures and avoid secondary neurological insults.[21]

Over 4.8 million trauma fatalities were documented worldwide in 2013 alone.[22] Despite this, no systematic review has focused specifically on the use of vasopressors during the early phase of trauma resuscitation.

Objective

We undertook this systematic review to answer the following question: 'In patients with acute traumatic injury, what is the effect of vasopressor therapy on patient important outcomes?' We hypothesised that, in observational studies, early vasopressor use would be associated with worse outcomes due to prognostic imbalance (clinicians would use vasopressors in sicker patients); in contrast, we hypothesised that vasopressors would not be associated with worse outcomes in RCTs.

This review was performed to inform a guideline that addressed the same topic (https://www.magicapp.org/app#/guideline/1273), as part of the broader WikiRecs project, which aims to provide rapid, evidence-based summaries and recommendations composed as synopses.[23 24]

METHODS

Protocol and registration

The design and reporting of this systematic review (PROSPERO CRD42016033437) follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[25] A detailed protocol is published separately.[26]

Eligibility criteria

We evaluated both clinical trials and controlled observational studies reporting associations between early vasopressor use and clinical outcomes. We define early vasopressor use as occurring during the prehospital or emergency department phase of care or during emergency trauma surgery. Studies that addressed vasopressor use exclusively during the postoperative phase, after arrival to the intensive care unit (ICU) or >24 hours from arrival to the trauma bay were excluded, as were studies with non-controlled designs (eg, case reports and case series). We included studies only if their population of interest consisted of adult victims of acute traumatic injury, either penetrating or blunt. Vasopressors included epinephrine, norepinephrine, phenylephrine, dopamine, ephedrine, vasopressin and vasopressin analogues. We included studies in which the intervention included dobutamine or other primarily inotropic drugs only if these accounted for <10% of the study population. We did not exclude studies based on clinical outcomes reported provided follow-up extended to at least 24 hours. The detailed screening flow chart is presented in online supplementary appendix 1.

Information sources, search strategy and study selection

With the help of a medical librarian, we developed electronic search strategies for the following databases: MEDLINE, EMBASE, the Central Register of Controlled Trials and ClinicalTrials.gov. Our search spanned from each database's inception until 12 October 2016. Terms for circulatory shock and vasopressors were combined and we adapted search strategies to database-specific subject heading and keywords (online supplementary appendix 2). We imposed no restrictions based on language, publication status or methodological quality.

Additionally, we manually reviewed conference proceedings from 10 major scientific meetings in trauma and critical care from 2005 to 2016 to identify additional relevant reports (Society of Critical Care Medicine, European Society of Intensive Care Medicine, International Society of Intensive Care and Emergency Medicine, American Thoracic Society, American Association for the Surgery of Trauma, Eastern Association for the Surgery of Trauma, European Society for Trauma and Emergency Surgery, Shock Society, European Shock Society, and the American College of Chest Physicians). Although the methods of studies published exclusively as abstracts are more challenging to evaluate, we performed an extensive search of conference proceedings in order to minimise the risk of publication bias.[27–29]

Using the Covidence web platform (www.COVIDENCE.org), five reviewers independently screened titles and abstracts in duplicate. For studies that either reviewer felt might be eligible, two reviewers independently screened full text for eligibility. Disagreements were resolved by discussion.

Data collection process

Using prepiloted standardised forms, pairs of reviewers independently extracted data from each included study. We contacted all authors for missing data, including those of studies published as abstracts.

Data items

Data items collected included individual study characteristics and design, inclusion and exclusion criteria, differences in baseline characteristics between intervention groups, type, dosing and timing of vasopressors used, raw data for prespecified clinical outcomes, reported results of adjusted and unadjusted analyses, as well as associated measures of uncertainty, and risk of bias domains.

Quality assessment

Single study risk of bias

We judged risk of bias at the study level using a modified version of the Cochrane Collaboration tool for RCTs.[29] This tool addresses randomisation, allocation concealment, blinding, loss to follow-up, selective outcome reporting and other risks of bias. We used the 'Clinical Advances through Research and Information Technology' group tools to assess risk of bias in observational studies (https://distillercer.com/resources/).[30 31] These tools evaluate the selection of intervention and control groups, the adequacy of assessment of prognostic factors, exposure and clinical outcomes, statistical adjustment and/or matching, follow-up, similarity of cointerventions between groups, and other risks of bias.

Overall quality of evidence

We assessed the overall certainty of absolute effect estimates at the outcome level using the 'Grading of Recommendations Assessment, Development, and Evaluation' (GRADE) approach.[32]

The GRADE system evaluates risk of bias in the body of evidence, consistency of results across studies, precision of effect estimates and publication bias. Indirectness of evidence is also considered, that is, whether or not the population, interventions and outcomes of individual studies correspond to those of interest for our review. Taking these domains into account, GRADE classifies the overall quality of evidence as being either high, moderate, low or very low for each outcome of interest.[32]

Agreement

We calculated a kappa statistic to report agreement between reviewers for full-text inclusion.

Outcomes

For all outcomes, we compared early vasopressor use with standard resuscitation, which may or may not have included vasopressor therapy in patients unresponsive to intravenous fluid resuscitation. We prespecified the following outcomes of interest for the purpose of analysis: short-term mortality at longest follow-up up to 90 days (primary outcome), long-term mortality beyond 90 days, fluid and blood product requirements during the early resuscitation period, requirements for acute (up to 90 days) or chronic (beyond 90 days) renal replacement therapy, duration of renal replacement therapy, duration of mechanical ventilation, incidence of acute kidney injury (as defined by individual study authors), incidence of vasopressor-associated adverse events (new-onset cardiac arrhythmia, digit, limb or skin ischaemia, mesenteric ischaemia and myocardial ischaemia), neurological outcome and long-term quality of life (no restriction on instruments used). Adverse events were documented as defined in individual studies.

Summary measures and synthesis of results

We planned to include the results of clinically homogeneous studies in a random-effects quantitative meta-analysis. However, given the small number of included studies, their varying methodologies and their serious risk of bias, we judged quantitative meta-analysis to be inappropriate and instead report a qualitative summary of each study.[33] Data are presented as reported in individual studies. Additionally, dichotomous data are reported as risk ratios (RR) and continuous data as mean differences (MD), with associated 95% CI, in order to facilitate interpretation.

Additional analyses

We had also planned to conduct a number of subgroup analyses, which are detailed in the study protocol along with associated a priori hypotheses.[26] The small number of studies and their variability in methods precluded subgroup analyses.

RESULTS

Study selection

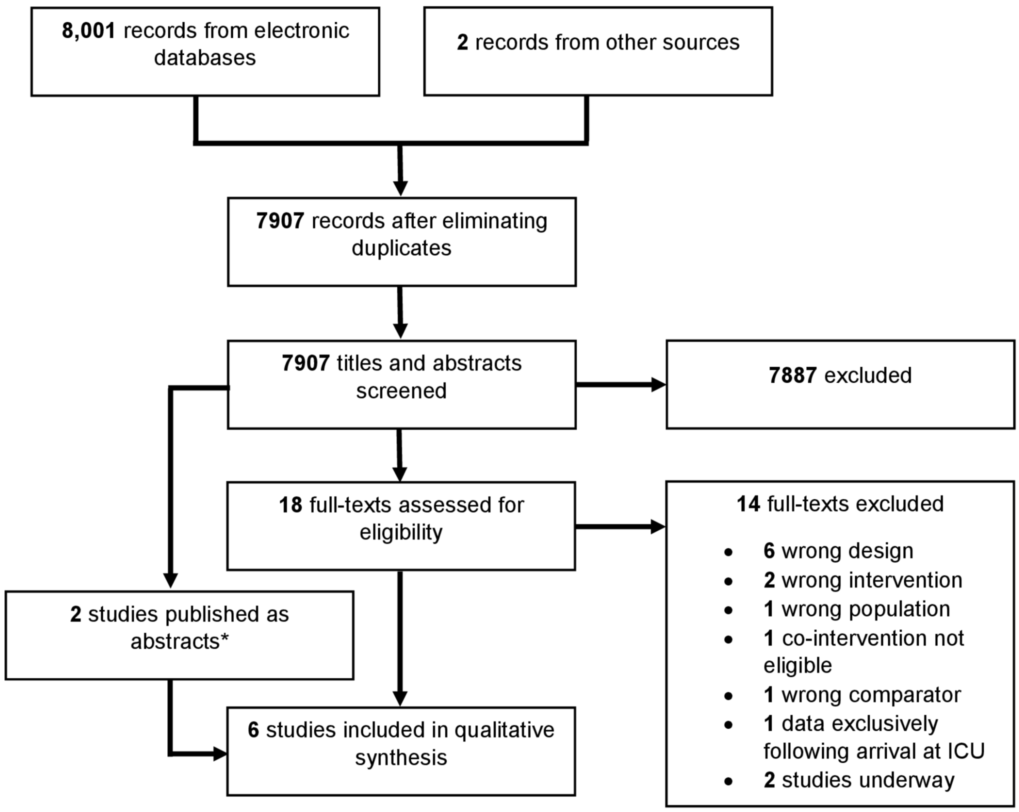
Of 8001 citations, we retrieved 18 full-text articles and included 6 studies (1 RCT, 5 observational studies), including 2 studies published only in abstract form.[34 35] One highly cited observational study on vasopressor use in trauma was excluded because it addressed vasopressor use exclusively after patient arrival in the ICU.[36] We identified two ongoing clinical trials (https://clinicaltrials.gov/show/NCT01611935; https://clinicaltrials.gov/ct2/show/NCT00379522),[37 38] but after contacting study personnel, the investigators preferred not to provide clinical data for this review. A PRISMA flow chart illustrates the selection process (figure 1). Characteristics of eligible studies are detailed in table 1.

Outcomes

Short-term mortality

In the one eligible RCT, Cohn *et al* reported that survival to 30 days assessed by Kaplan-Meier curves was similar between patients receiving low-dose vasopressin infusions versus placebo (p=0.64).[39]

Across all observational studies, early vasopressor use was associated with a statistically significant (p<0.05) increased risk of short-term mortality (range of RR 2.31–7.39; table 2). Sperry *et al* found this association to be significant despite adjusting for an extensive number of covariates (mortality: HR 1.81; 95% CI (1.1 to 2.9)).[40] Van Haren *et al* performed a secondary analysis that excluded patients receiving epinephrine in order to eliminate patients with imminent cardiovascular collapse. Under such conditions, vasopressor use was not independently



*Studies published exclusively as abstracts were assessed for eligibility by contacting individual study investigators for relevant information.

Figure 1 PRISMA flow chart. ICU, intensive care unit; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

associated with increased risk of death (p=0.52).[41] Batistaki *et al* provided only the β coefficient associated with vasopressors in their logistic regression model, which leaves the direction of effect (−2.60) unclear, as it may refer to an association with either survival or mortality.[42] Although we attempted to contact study authors, we did not obtain a reply and were unable to clarify this issue (table 2).

Fluid and blood product requirements

Clinical trial data suggest that both fluid and blood product requirements were lower in patients treated early with vasopressin than in the control group (fluids: 13.2±9.8L vs 16.0±12.8L, p=0.03; blood products: 3.8±5.0L vs 5.4±6.6L, p=0.04). The MDs calculated from the data provided in the study do not yield statistically significant associations between these cointerventions and vasopressor use (fluids: MD −2.80L, 95% CI (−7.83 to 2.23); blood products: MD −1.60L, 95% CI (−4.18 to 0.98)). Study authors report a statistically significant association between vasopressin administration and fluid requirements at 120 hours, but not at the other prespecified time points (1 hour, 6 hours, 24 hours and 48 hours).[39]

In observational studies, fluid and blood product requirements were systematically higher among patients who received vasopressors[34 35 40–42] (table 2).

Mechanical ventilation

Ventilator-free days were similar between groups (MD 2.2 more days; 95% CI (−10.8 to 15.2)) in the clinical trial of early vasopressin administration versus placebo.

Meanwhile, in both observational studies that reported this intervention, mechanical ventilation requirements were higher for patients who received early vasopressors[35 40] (table 2).

Renal replacement therapy

Although not reported in the original publication, Hamada *et al*[35] found no association between vasopressor use and rates of renal replacement therapy (RR 1.36, 95% CI (0.36 to 5.10); personal communication, S Hamada 2016) (table 2).

Risk of bias within studies

The only RCT was blinded (patients and healthcare workers) but 12% of patients (9/78) were lost to follow-up at 30 days. This loss to follow-up could, under an extreme case scenario (all patients lost to follow-up in the intervention group survived while all those in the control group died), reverse the direction of effect.[43] The study was terminated prematurely because of enrolment difficulties, which is a cause for concern where authors report potential benefits of vasopressors (fluid and blood

Table 1 Characteristics of eligible studies

Source (country)	Intervention	Control	Inclusion criteria	Exclusion criteria	Intervention/control (n)	Outcomes assessed	Funding source
Randomised controlled trial							
Cohn *et al*[39] (USA)	Low-dose vasopressin on arrival (4 IU bolus followed by infusion at 2.4 IU/hour over 5 hours)	Normal saline placebo (3 mL bolus followed by infusion at 200 mL/hour over 5 hours)	Acute traumatic injury SBP<90 mm Hg	Presenting >6 hours postinjury Received >4 L fluids since injury Cardiac arrest prior to randomisation Pregnancy Known objection to resuscitation or blood products	38/40	24 hours, 5 days and 30-day mortality Adverse events (any, severe) Incidence of MODS to 30 days Fluid requirements at 1 hour, 6 hours, 24 hours, 48 hours and 120 hours Blood product requirements at 1 hour, 6 hours, 24 hours, 48 hours and 120 hours	NR
Observational studies							
Batistaki *et al*[42] (Greece)	Dopamine or epinephrine use within 24 hours	No dopamine or epinephrine within 24 hours	Multiple trauma Clinical class III or IV haemorrhage	Presenting >4 hours postinjury Spinal or cardiac trauma Chronic illness Pregnancy	22/22	Mortality at 48 hours and 1 month PRBC requirements Days in ICU MOF	NR
Sperry *et al*[40] (USA)	Phenylephrine, norepinephrine, dopamine or vasopressin use within 12 hours	No vasopressor use within 12 hours (includes patients receiving only epinephrine)	Blunt trauma Prehospital or ED hypotension (SBP<90 mm Hg) or elevated base deficit (≥6 mEq/L) Blood transfusion within 12 hours AIS≥2 for any body region except brain	Age>90 years Cervical spine trauma Death within 48 hours	119/802	Ventilator days FFP requirements % with >6 units of PRBC Mortality ICU days Length of stay	NR
Van Haren *et al*[41] (USA)	Epinephrine, phenylephrine, ephedrine, norepinephrine, vasopressin or dobutamine use during emergency trauma surgery	No vasopressor use during emergency trauma surgery	Trauma Require emergency surgery after work-up and resuscitation	Isolated orthopaedic or neurosurgical indication for surgery Minor trauma Admission to ICU or ward before surgery	225/521	Mortality Crystalloid requirements 24 hours and operative PRBC requirements 24 hours and operative FFP requirements	NR

Continued

Table 1 Continued

Source (country)	Intervention	Control	Inclusion criteria	Exclusion criteria	Intervention/control (n)	Outcomes assessed	Funding source
Hamada *et al*[35] (France)	Prehospital norepinephrine	No prehospital norepinephrine	Severe trauma One or more of SBP≤90 mm Hg, transfusion of >4 units PRBC within 6 hours or prehospital vasopressor use	Traumatic brain injury Cardiac arrest on arrival	39/53	Volume expansion Volume of blood products in 24 hours Renal replacement therapy within 90 days Prehospital intubation % requiring mechanical ventilation Duration of mechanical ventilation PRBC requirements Mortality	NR
Gauss *et al*[34] (France)	Prehospital norepinephrine	No prehospital norepinephrine	One or more of transfusion of >4 units PRBC within 24 hours or SBP<90 mm Hg	Refractory circulatory arrest	14/28	Prehospital fluids FFP requirements in 24 hours PRBC requirements in 24 hours Mortality	NR

AIS, Abbreviated Injury Scale; ED, emergency department; FFP, fresh-frozen plasma; ICU, intensive care unit; IU, international units; MOF, multiple organ failure; NR, not reported; PRBC, packed red blood cells; SBP, systolic blood pressure; MODS, multiple organ dysfunction syndrome.

Table 2 Effect of early vasopressor use in observational studies

Studies	Vasopressor	Control	Effect estimate
Unadjusted short-term mortality (longest follow-up ≤90 days)			
Van Haren *et al*[41]	83/225 (37%)	26/521 (5%)	RR 7.39 (4.90 to 11.16)
Hamada *et al*[35]	17/39 (44%)	10/53 (19%)	RR 2.31 (1.19 to 4.48)
Batistaki *et al*[42]	11/22 (50%)	3/22 (14%)	RR 3.67 (1.18 to 11.37)
Sperry *et al*[40]	41/119 (34%)	71/802 (9%)	RR 3.89 (2.79 to 5.43)
Adjusted short-term mortality (longest follow-up ≤90 days)			
Sperry *et al*[40]			HR 1.81 (1.1 to 2.9)*
Fluid received during early resuscitation period			
Van Haren *et al*[41] (operative crystalloids, mL)†	4000 (3500)	3100 (3000)	p<0.01
Hamada *et al*[35] (volume expansion, mL)†	1500 (1000)	1000 (750)	p=0.01
Gauss *et al*[34] (prehospital fluid load, mL)†	1500 (1125)	1000 (940)	p<0.01
Blood product given during early resuscitation period			
PRBC use			
Van Haren *et al*[41] (operative PRBC, mL)†	1250 (2938)	250 (1250)	p<0.01
Hamada *et al*[35] (transfused PRBC, units)†	9.5 (7)	7 (6)	p=0.05
Gauss *et al*[34] (units over first 24 hours)†	6.5 (6)	6 (3)	p=ns
Sperry *et al*[40] (>6 units PRBC)	76/119 (64%)	71/802 (9%)	RR 1.49 (1.28 to 1.75)
Batistaki *et al*[42] (total requirement, units)‡	5.8 (1.9)	5.2 (1.5)	p=0.2
FFP use			
Van Haren *et al*[41] (operative FFP, mL)†	750 (1 750)	0 (750)	p<0.01
Sperry *et al* (mL)[40]	1704±1934	1001±1424	MD 703 (341 to 1064)
Renal replacement therapy use (≤90 days)			
Hamada *et al*[35]	4/39 (10%)	4/53 (8%)	RR 1.36 (0.36 to 5.10)
Duration of mechanical ventilation (days)			
Hamada *et al*[35]	10.8±9.6	5.7±6.2	MD 5.1 (1.7 to 8.5)
Sperry *et al*[40]	15.9±15	9.9±11	MD 6.0 (3.2 to 8.8)

All effect estimates are presented with associated 95% CIs.
Continuous data presented as mean±SD unless otherwise specified.
*Adjusted for age, gender, hospital centre, injury severity score (ISS), presenting Glasgow Coma Score, SBP <90 mm Hg on arrival, comorbidities (medical history of myocardial infarction, heart failure, chronic obstructive pulmonary disease (COPD), cirrhosis, smoking or alcoholism), blood product requirements, biochemical markers of injury (base deficit and pH), hyperglycaemia, requirement for major operative intervention, Acute Physiology and Chronic Health Evaluation (APACHE) II score, use of a pulmonary artery catheter, steroid administration and aggressive crystalloid resuscitation (>16 L over 12 hours).
†Median (IQR).
‡Unclear if reported as mean or median.
FFP, fresh frozen plasma; MD, mean difference; ns, non-significant; PRBC, packed red blood cells; RR, relative risk; SBP, systolic blood pressure.

product requirements) since studies stopped early for benefit are at increased risk of bias.[44] Moreover, fluid and blood product requirements were selectively reported at 120 hours but not at the other prespecified time points. There were also more penetrating injuries (30% vs 16%) and gunshot wounds (26% vs 8%) in the control group than in the early vasopressin group, which introduces a potential baseline prognostic imbalance. We therefore graded this study as 'very serious risk of bias', although this is an uncommon decision when applying the GRADE methodology[45] (table 3).

Significant baseline imbalances between patients treated with and without vasopressors suggest a high risk of selection bias for all included observational studies, where patients treated with vasopressors were systematically more severely injured. In one study,[41] patients receiving vasopressors were less likely to have suffered a penetrating injury (59% vs 73%, p<0.001) but nonetheless had higher injury severity score (ISS) (25 vs 16, p<0.001). Three studies excluded patients who died of circulatory arrest on arrival[34 35] or who did not survive 48 hours postinjury,[40] which introduces a significant risk of survivorship bias. One study excluded patients with TBI,[35] although this population is more likely to receive vasopressors than non-brain-injured patients[20] (table 4).

Table 3 Risk of bias in included randomised controlled trial

	Cohn *et al*[39]
Random sequence generation	Low
Allocation concealment	Unclear (high)
Blinding	Low
Incomplete outcome data (mortality)	High
Incomplete outcome data (other outcomes)	Unclear (low)
Selective outcome reporting (mortality)	Low
Selective outcome reporting (other outcomes)	High
Other risks of bias	High*†

Unclear (low): unclear but judged to be probably low risk of bias.
Unclear (high): unclear but judged to be probably high risk of bias.
*Trial stopped early.
†Significant baseline imbalance between groups.

Synthesis of outcomes across studies

Table 5 presents a GRADE evidence profile summarising the overall quality of clinical trial evidence addressing vasopressor use following trauma. The overall quality of evidence is very low, due to the serious risk of bias and imprecision of effect estimates. We found no clinical trial data pertaining to a number of our prespecified clinical outcomes (long-term mortality, requirement for renal replacement therapy, adverse events (arrhythmia, digit, limb or skin ischaemia, mesenteric ischaemia, myocardial ischaemia and acute kidney injury), long-term neurological function and long-term quality of life).

Agreement

We obtained a kappa statistic of 0.56 (95% CI 0.16 to 0.97) for full-text inclusion.

DISCUSSION

Summary of evidence

This systematic review highlights that the balance between benefits and harms of vasopressor therapy during the early phase of resuscitation following traumatic injury is uncertain. The only RCT addressing the question is drastically underpowered and also has risk of bias concerns.

Table 4 Risk of bias in included observational studies

	Batistaki *et al*[42]	Sperry *et al*[40]	Gauss *et al*[34]*	Hamada *et al*[35]*	Van Haren *et al*[41]
Selection of cohorts	Unclear (high)	Low	Low	Low	Low
Assessment of exposure	Low	Unclear (high)	Low	Unclear (high)	Low
Absence of outcome at start of study (mortality)	Low	Low	Low	Low	Low
Absence of outcome at start of study (other outcomes)	Low	Low	Low	Low	Low
Matching or statistical adjustment (unadjusted mortality)	High	High	High	High	High
Matching or statistical adjustment (adjusted mortality)	High	Unclear (high)	High	N/A	Unclear (high)
Matching or statistical adjustment (other outcomes)	High	High	High	High	High
Assessment of prognostic factors	Unclear (high)	Unclear (high)	Unclear (high)	Unclear (high)	Unclear (high)
Assessment of outcome (mortality)	Low	Low	Low	Unclear (high)	Low
Assessment of outcome (other outcomes)	Low	Low	Low	Unclear (high)	Low
Follow-up (mortality)	Unclear (low)	Unclear (low)	Unclear (low)	Unclear (low)	Unclear (low)
Follow-up (other outcomes)	Unclear (low)	Unclear (low)	Unclear (low)	Unclear (low)	Unclear (low)
Similarity of cointerventions	Unclear (high)	High	Unclear (high)	High	High
Other risks of bias	High†	High†‡	High†	High†	High†

Unclear (low): unclear but judged to be probably low risk of bias.
Unclear (high): unclear but judged to be probably high risk of bias.
*We contacted the investigators of studies published exclusively as abstracts in order to perform risk of bias assessments.
†Important baseline imbalance between groups.
‡Survival bias (early deaths excluded).
N/A, not applicable.

Table 5 GRADE evidence profile of randomised controlled trials: effect of early vasopressor use on mortality following traumatic injury

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (n) (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With standard resuscitation	With early vasopressor use	Relative effect (95% CI)	Risk with standard resuscitation	Risk different with early vasopressor use
Short-term mortality											
78 (1 RCT)	Very serious *†	Not serious	Not serious	Very serious‡§	None	⊕◯◯◯ VERY LOW	11/40 (27.5%)	13/38 (34.2%)	RR 1.24 (0.64 to 2.43)	275 per 1000	66 more per 1000 (99 fewer to 393 more)
Fluid requirements											
78 (1 RCT)	Very serious*¶	Not serious	Not serious	Serious‡	None	⊕◯◯◯ VERY LOW	41	37	–	The mean of fluid requirements (first 120 hours) was 0 L.	MD 2.8 L lower (7.83 lower to 2.23 higher)
Blood product requirements											
78 (1 RCT)	Very serious*¶	Not serious	Not serious	Serious‡	None	⊕◯◯◯ VERY LOW	41	37	–	The mean of blood product requirements (first 120 hours) was 0 L.	MD 1.6 L lower (4.18 lower to 0.98 higher)
Blood product requirements (% requiring massive transfusion)											
62 (1 RCT)	Serious*	Not serious	Not serious	Very serious‡§	None	⊕◯◯◯ VERY LOW	22/36 (61.1%)	12/26 (46.2%)	RR 0.76 (0.47 to 1.23)	611 per 1000	147 fewer per 1000 (324 fewer to 141 more)
Mechanical ventilation (VFDs)											
78 (1 RCT)	Serious*	Not serious	Not serious	Very serious‡	None	⊕◯◯◯ VERY LOW	40	38	–	The mean of VFDs was 0 VFD.	MD 2.2 VFDs higher (10.83 lower to 15.23 higher)

*Imbalance between baseline prognostic variables.
†Significant loss to follow-up.
‡Does not rule out either benefit or harm.
§Very small number of events.
¶Study terminated early (24% anticipated sample size).
GRADE, Grading of Recommendations, Assessment, Development and Evaluation; MD, mean difference; RCT, randomised controlled trial; RR, risk ratio; VFD, ventilator-free day.

In the observational studies, vasopressor use was associated with worse outcomes. These results are at very high risk of bias because of prognostic imbalance and selection bias. The associations reported in these studies may be entirely attributable to confounding.

In light of the paucity of trustworthy evidence regarding the effects of vasopressor therapy in trauma, physicians charged with the care of patients with trauma face a clinical conundrum: for a majority of patients, no therapy seems safe. Permissive hypotension, beneficial for patients who sustained penetrating torso injuries,[6] is potentially harmful for patients who have suffered a TBI, in whom hypotension is associated with increased mortality.[9] The safety of this approach is also questionable outside densely populated urban centres where tertiary trauma care is rapidly available. In the landmark study by Bickell *et al*, the reported transport time was <15 min, which is not achievable in areas far from tertiary trauma centres.[46] The alternative, fluid therapy, reportedly increases the risk of bleeding,[6] coagulopathy,[3 8] compartment syndrome[47] and surgical complications.[4] In this context, vasopressors are used in 6%–30% of patients with trauma in some centres, despite recommendations to limit their use.[41 48] A recent survey of European trauma care providers concluded that vasopressor use was frequent, but controversial (76% respondents (171/225) agreed with vasopressor use).[49] This provides a strong rationale for clinical trials of vasopressors during the early resuscitation phase of trauma victims.

Currently, the degree of uncertainty precludes any recommendation regarding vasopressor use in trauma (https://www.magicapp.org/app#/guideline/1273). Two clinical trials currently underway[37 38] may provide useful insights on this question. However, they have not been designed a priori to capture long-term neurological or quality of life-related outcomes. It is conceivable that interventions that decrease blood loss and improve short-term survival may worsen brain injury in vulnerable subgroups, such as the elderly and victims of TBIs. Furthermore, the vasopressor choice of agent, as well as its dosing and timing of administration, has yet to be defined if this intervention is found to be beneficial.

Strengths and limitations

The strengths of this review include the use of the GRADE approach to assess the overall quality of evidence. We performed a comprehensive review including non-published literature. This review answers a clear question that focuses on a specific clinical scenario, which is the early phase of trauma care. In an effort to isolate the effects of vasopressors administered during active haemorrhage, we excluded studies that reported vasopressor administration following a patient's arrival to the ICU.

No standardised definition exists for what constitutes early trauma care, and others may define it differently and thus chose different eligibility criteria. The heterogeneous and sparse data limit our ability to draw firm conclusions; we were unable to pool estimates across study types and found very low certainty evidence.

CONCLUSIONS

This systematic review highlights the lack of reliable data on patient important outcomes to inform the use of vasopressors in the early phases of trauma resuscitation. Further rigorous randomised trials are needed to define the role of vasopressors in this clinical setting.

Author affiliations
[1]Department of Surgery, Université de Sherbrooke, Sherbrooke, Québec, Canada
[2]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada
[3]Department of Anaesthesiology, Université de Sherbrooke, Sherbrooke, Québec, Canada
[4]Centre de recherche de l'Hôpital du Sacré-Coeur de Montréal, Université de Montréal, Montréal, Québec, Canada
[5]Centre de recherche du CHU de Sherbrooke, Sherbrooke, Québec, Canada
[6]Department of Medicine, Université de Sherbrooke, Sherbrooke, Canada
[7]Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
[8]Department of Anaesthesiology, Oslo University Hospital, Rikshospitalet Medical Centre, Oslo, Norway
[9]Norwegian Knowledge Centre for the Health Services, Oslo, Norway
[10]Department of Medicine, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada
[11]Centre de Recherche du CHU de Québec, Université Laval, Québec, Canada
[12]Department of Emergency Medicine and Critical Care Medicine, Dalhousie University, Halifax, Canada
[13]Department of Emergency Medicine and Critical Care Medicine, Queen's University, Kingston, Canada
[14]Department of Critical Care Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada
[15]Department of Pediatrics and Critical Care Medicine, University of British Columbia, Vancouver, British Columbia, Canada
[16]Center for Evidence-Based and Translational Medicine, Wuhan University, Wuhan, Hubei Province, China
[17]Department of Trauma and Acute Care Surgery, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada
[18]Centre Hospitalier Universitaire d'Angers, Angers, Pays de la Loire, France

Contributors MH and FLam drafted the study protocol, designed data collection forms, performed statistical analyses and drafted the study manuscript. MH, AT, NB, A-JF and JSWK screened titles and abstracts, full-text articles and conference proceedings, as well as performed data collection and risk of bias assessments. FLam, FDA, EB-C, EC, MH, JHL, POV, RAS, BR, FLau, RSG, IB, DS, SM, GG, SR, PA and FLam critically reviewed the study design, the published protocol and the final manuscript. All authors have read and approved the final version of the manuscript.

Funding This work was supported by the Department of Surgery of the Centre Hospitalier Universitaire de Sherbrooke, grant numbers FRChir-1524 and FRChir-1403.

Competing interests SR has been a paid member of a scientific advisory board for CSL Behring, outside the present study. All other authors declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All relevant data for this study are available as an online supplementary appendix.

REFERENCES

1. Hollenberg SM. Vasoactive drugs in circulatory shock. *Am J Respir Crit Care Med* 2011;183:847–55.
2. Dünser M, Hjortrup PB, Pettilä V. Vasopressors in shock: are we meeting our target and do we really understand what we are aiming at? *Intensive Care Med* 2016;42:1176–8.
3. Maegele M, Lefering R, Yucel N, *et al*. Early coagulopathy in multiple injury: an analysis from the German Trauma Registry on 8724 patients. *Injury* 2007;38:298–304.
4. Schnüriger B, Inaba K, Wu T, *et al*. Crystalloids after primary colon resection and anastomosis at initial trauma laparotomy: excessive volumes are associated with anastomotic leakage. *J Trauma* 2011;70:603–10.
5. Beloncle F, Meziani F, Lerolle N, *et al*. Does vasopressor therapy have an indication in hemorrhagic shock? *Ann Intensive Care* 2013;3:13.
6. Bickell WH, Wall MJ, Pepe PE, *et al*. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med* 1994;331:1105–9.
7. Morrison CA, Carrick MM, Norman MA, *et al*. Hypotensive resuscitation strategy reduces transfusion requirements and severe postoperative coagulopathy in trauma patients with hemorrhagic shock: preliminary results of a randomized controlled trial. *J Trauma* 2011;70:652–63.
8. David JS, Voiglio EJ, Cesareo E, *et al*. Prehospital parameters can help to predict coagulopathy and massive transfusion in trauma patients. *Vox Sang* 2017;112:557–66.
9. Chesnut RM, Marshall LF, Klauber MR, *et al*. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma* 1993;34:216–22.
10. Rossaint R, Bouillon B, Cerny V, *et al*. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. *Crit Care* 2016;20:1.
11. Beloncle F, Meziani F, Lerolle N, *et al*. Does vasopressor therapy have an indication in hemorrhagic shock? *Ann Intensive Care* 2013;3:13–16.
12. Bellomo R, Wan L, May C. Vasoactive drugs and acute kidney injury. *Crit Care Med* 2008;36:S179–S186.
13. Dutton RP, Mackenzie CF, Scalea TM. Hypotensive resuscitation during active hemorrhage: impact on in-hospital mortality. *J Trauma* 2002;52:1141–6.
14. Bulger EM, May S, Kerby JD, *et al*. Out-of-hospital hypertonic resuscitation after traumatic hypovolemic shock: a randomized, placebo controlled trial. *Ann Surg* 2011;253:431.
15. Bulger EM, May S, Brasel KJ, *et al*. Out-of-hospital hypertonic resuscitation following severe traumatic brain injury: a randomized controlled trial. *JAMA* 2010;304:1455–64.
16. Cooper DJ, Myles PS, McDermott FT, *et al*. Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: a randomized controlled trial. *JAMA* 2004;291:1350–7.
17. *ATLS Advanced Trauma Life Support for doctors - student course manual*. Ninth Edition: American College of Surgeons, 2012.
18. Spahn DR, Bouillon B, Cerny V, *et al*. Management of bleeding and coagulopathy following major trauma: an updated European guideline. *Crit Care* 2013;17:R76.
19. Fangio P, Asehnoune K, Edouard A, *et al*. Early embolization and vasopressor administration for management of life-threatening hemorrhage from pelvic fracture. *J Trauma* 2005;58:978–84.
20. Hylands M, Godbout M-P, Lamontagne F. 1177: Vasopressor use following traumatic injury- a single- center historical cohort study. *Crit Care Med* 2015;43:296.
21. Carney N, Totten AM, O'Reilly C, *et al*. Guidelines for the management of severe traumatic brain injury. *Neurosurgery* 2017;80:6–15.
22. Haagsma JA, Graetz N, Bolliger I, *et al*. The global burden of injury: incidence, mortality, disability-adjusted life years and time trends from the Global Burden of Disease study 2013. *Inj Prev* 2016;22:3–18.
23. Siemieniuk RAC, Guyatt GH. The next frontier in critical care guidelines: rapid and trustworthy recommendations. *Can J Anaesth*. In Press. 2017;64:689–92.
24. Siemieniuk RA, Agoritsas T, Macdonald H, *et al*. Introduction to BMJ Rapid Recommendations. *BMJ* 2016;354:i5191.
25. Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
26. Hylands M, Toma A, Beaudoin N, *et al*. Vasopressor use following traumatic injury: protocol for a systematic review. *BMJ Open* 2017;7:e014166.
27. Guyatt GH, Oxman AD, Montori V, *et al*. GRADE guidelines: 5. Rating the quality of evidence-publication bias. *J Clin Epidemiol* 2011;64:1277–82.
28. Eden J, Levit L, Berg A, *et al*. *Finding What Works in Health Care: Standards for Systematic Reviews*. Washington, DC: The National Academies Press, 2011.
29. Higgins JPT, Green S. The Cochrane Collaboration, 2011. Cochrane handbook for systematic reviews of interventions Version 5.1. 0, 2014. updated March 2011. www.cochrane-handbook.org
30. Tool to assess risk of bias in case-control studies. https://distillercer.com/wp-content/uploads/2014/02/Tool-to-Assess-Risk-of-Bias-in-Case-Control-Studies-Aug-21_2011.doc
31. Tool to assess risk of bias in cohort studies. https://distillercer.com/wp-content/uploads/2014/02/Tool-to-Assess-Risk-of-Bias-in-Cohort-Studies.doc
32. Guyatt GH, Oxman AD, Vist GE, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
33. Borenstein LHL, Higgins JPT, Rothstein HR. When Does it Make Sense to Perform a Meta-Analysis? *Introduction to Meta-Analysis*: John Wiley & Sons, Ltd, 2009.
34. Gauss T, Hamada S, Duchateau F, *et al*. Prehospital use of norepinephrine does not reduce total amount of prehospital fluid in hemorrhagic shock. *Intensive care medicine*. Spring, New York, USA: Springer, 2011:S151.
35. Hamada S, Gauss T, Harrois A, *et al*. Prehospital control of systolic arterial pressure in haemorrhagic shock. *Intensive care medicine*. Spring, New York, USA: Springer, 2012:S26.
36. Plurad DS, Talving P, Lam L, *et al*. Early vasopressor use in critical injury is associated with mortality independent from volume status. *J Trauma* 2011;71:565–72.
37. Sims CA. AVERT shock: Arginine Vasopressin during the Early Resuscitation of Traumatic shock, 2012. https://clinicaltrials.gov/show/NCT01611935
38. Lienhart HG, Wenzel V, Braun J, *et al*. [Vasopressin for therapy of persistent traumatic hemorrhagic shock: The VITRIS.at study]. *Anaesthesist* 2007;56:145–8.
39. Cohn SM, McCarthy J, Stewart RM, *et al*. Impact of low-dose vasopressin on trauma outcome: prospective randomized study. *World J Surg* 2011;35:430–9.
40. Sperry JL, Minei JP, Frankel HL, *et al*. Early use of vasopressors after injury: caution before constriction. *J Trauma* 2008;64:9–14.
41. Van Haren RM, Thorson CM, Valle EJ, *et al*. Vasopressor use during emergency trauma surgery. *Am Surg* 2014;80:472–8.
42. Batistaki C, Kostopanagiotou G, Myrianthefs P, *et al*. Effect of exogenous catecholamines on tumor necrosis factor alpha, interleukin-6, interleukin-10 and beta-endorphin levels following severe trauma. *Vascul Pharmacol* 2008;48:85–91.
43. Akl EA, Briel M, You JJ, *et al*. Potential impact on estimated treatment effects of information lost to follow-up in randomised controlled trials (LOST-IT): systematic review. *BMJ* 2012;344:e2809.
44. Guyatt GH, Briel M, Glasziou P, *et al*. Problems of stopping trials early. *BMJ* 2012;344:e3863.
45. Guyatt GH, Oxman AD, Vist G, *et al*. GRADE guidelines: 4. Rating the quality of evidence-study limitations (risk of bias). *J Clin Epidemiol* 2011;64:407–15.
46. Sollid S, Munch-Ellingsen J, Gilbert M, *et al*. Pre- and inter-hospital transport of severely head-injured patients in rural Northern Norway. *J Neurotrauma* 2003;20:309–14.
47. Madigan MC, Kemp CD, Johnson JC, *et al*. Secondary abdominal compartment syndrome after severe extremity injury: are early, *aggressive fluid resuscitation strategies to blame? J Trauma* 2008;64:280–5.
48. Collier B, Dossett L, Mann M, *et al*. Vasopressin use is associated with death in acute trauma patients with shock. *J Crit Care* 2010;25:173.e9–14.
49. Hamada SR, Gauss T, Pann J, *et al*. European trauma guideline compliance assessment: the ETRAUSS study. *Crit Care* 2015;19:1.