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Midodrine therapy for vasopressor dependent shock in the intensive care unit: a protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Intensive care unit (ICU) lengths of stay are modified by ongoing need for haemodynamic support in critically ill patients. This is most commonly provided by intravenous vasopressor therapy. Midodrine has been used as an oral agent for haemodynamic support in patients with orthostatic hypotension or cirrhosis. However, its efficacy in treating shock in the ICU, particularly for patients weaning from intravenous vasopressors, remains uncertain. The objective of this systematic review is to determine the efficacy of midodrine in vasopressor dependent shock.

Methods and analysis We will search Ovid MEDLINE, Ovid Embase, CINAHL and Cochrane Library for observational trials and randomised controlled trials evaluating midodrine in critically ill patients from inception to 21 April 2022. We will also review unpublished data and relevant conference abstracts. Outcomes will include ICU length of stay, duration of intravenous vasopressor support, ICU mortality, hospital mortality, hospital length of stay and rates of ICU readmission. Data will be analysed in aggregate, where appropriate. We will evaluate risk of bias using the modified Cochrane tool and certainty of evidence using Grading of Recommendations, Assessment, Development and Evaluations methodology. We will perform trial sequential analysis for the outcome of ICU length of stay.

Ethics and dissemination Ethics approval is not required as primary data will not be collected. Findings of this review will be disseminated through peer-related publication and will inform future clinical trials.

PROSPERO registration number CRD42021260375.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Strengths of our review include the inclusion of the MIDAS trial, preplanned subgroup analysis of different shock aetiologies, patients with cirrhosis and acute kidney injury, broad inclusion criteria; planned sequential trial analysis and usage of Grading of Recommendations, Assessment, Development and Evaluations to assess certainty of evidence.

⇒ Several important limitations remain. First, lack of standardisation of midodrine dosing protocols which may not always be in keeping with product monographs and difficulties in aggregate data analysis. We will ensure that we are transparent with reporting drug dosing protocols for our studies and ensure that aggregate study analysis only involves similar dosing protocols.

⇒ Studies have previously included differing aetiologies of shock, and this may lead to a heterogeneous patient population. We have addressed by including a priori subgroups to evaluate the effectiveness of midodrine for shock across subsets of shock and based on pre-existing patient characteristics.

⇒ Finally, while there are many trials that previously evaluated midodrine for intravenous vasopressor dependent shock, results are conflicting. This has led to uncertainty regarding midodrine use in undifferentiated shock in the intensive care unit. Our sequential trial analysis will provide the necessary methodology for better control of type I and type II errors than traditional meta-analysis and reduce spurious conclusions from previously conducted studies.

BACKGROUND

Shock is a common reason for intensive care unit (ICU) admission which often requires intravenous vasopressor support.[1–3] Vasopressor agents such as norepinephrine, vasopressin and epinephrine are recommended in septic shock.[4–6] However, as patients recover from their critical illness and require less other physiological support, the use of intravenous vasopressors may be their only indications for ongoing ICU admission. This may prolong their ICU length of stay (LoS) and lead to ICU capacity strain. To date, there are no clear guidelines on starting adjuvant oral therapies for either help managing

vasopressor use early in critical illness or to help wean off vasopressor therapy in the resolving phases of shock. These resolving phases can include hypotension with no signs of tissue hypoperfusion or end organ damage. Establishing an effective oral adjunctive therapy could reduce the need for invasive haemodynamic monitoring in titrating intravenous vasopressors and could liberate these patients earlier from the ICU.

Midodrine is an oral alpha agonist that is currently indicated in patients with orthostatic hypotension, intradialytic hypotension and blood pressure management in cirrhosis and hepatorenal syndrome.[7–12] Prior work has assessed midodrine efficacy in critically ill patients with mixed results. Earlier trials have demonstrated reduced duration of intravenous vasopressor therapy and a decreased ICU LoS with midodrine therapy.[13 14] However, these data are not supported by more recent studies.[15] One of most recent trial investigating the use of midodrine in critically ill patients, the MIDAS study, found no difference between placebo and midodrine groups in intravenous vasopressor duration or ICU LoS.[16] However, this study had several important limitations including small size and prolonged recruitment period, which may reflect a participant selection bias and being underpowered to detect a significant difference between groups. Further, more recently published randomised controlled trials (RCTs) have found results that conflict with the MIDAS trial, further questioning the role of midodrine for vasopressor dependent hypotension.[17–19] While a recently published meta-analysis examining the role of midodrine in resolving shock did not find any difference in intravenous vasopressor duration, ICU or hospital lengths of stay or mortality, the review did not provide any subgroup analysis or use Grading of Recommendations, Assessment, Development and Evaluations (GRADE) recommendations or trial sequential analysis (TSA) methods.[20] Further, it was conducted prior to the publication of most recent evidence.

Objectives

Accordingly, we aim to conduct a systematic review and meta-analysis on the use of midodrine for intravenous vasopressor dependent shock in the ICU. We hypothesise that the use of midodrine in critically ill patients will lead to decreased ICU LoS and decreased duration of intravenous vasopressors. We will plan to conduct subgroup analysis on select patient populations that have traditionally benefitted from this therapy, including those patients with cirrhosis and acute kidney injury (AKI), and will perform TSA for the outcome of ICU LoS.

METHODS

Patient and public involvement

No patient or public were involved in this systematic review and meta-analysis.

Study design

We will perform a systematic review of observational and randomised controlled studies. Meta-analysis will be performed on observational and randomised controlled studies separately, as appropriate.

Study registration

In accordance with Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA) guidelines, this systematic review is registered with the International Prospective Register of Systematic Reviews (CRD42021260375; 16 July 2021).

Data source and search methods

A search strategy was developed in consultation with a research librarian and independently peer-reviewed by a second librarian (online supplemental appendix 1).[21] We will search the following electronic databases: Ovid MEDLINE, Ovid Embase, CINAHL and Cochrane Library (via Wiley) from inception until 21 April 2022. We will combine search terms related to shock (ie, hypotension requiring vasopressors), vasopressors (ie, norepinephrine, epinephrine, vasopressin, phenylephrine), intensive care (ie, involving any ICU setting) and midodrine.

Additional search sources: we will search unpublished literature through trial registry platforms (ClinicalTrials.gov) and Google Scholar. We will also search for meeting abstracts from the past 2 years, where available, using Conference Proceedings Citation Index (Clarivate Analytics) and by handsearching published proceedings from the following associations: Society of Critical Care Medicine, European Society of Intensive Care Medicine, International Symposium of Intensive and Emergency Medicine. We will export search results into Covidence (www.covidence.org).

Eligibility criteria

We will include studies if they meet the following eligibility criteria: (1) include patients with vasopressor dependent shock, (2) are performed in the intensive care (ie, intended to refer to patients admitted to an ICU setting capable of providing vasopressor therapy), (3) evaluate oral midodrine therapy as compared with placebo or usual care and (4) evaluate one of our outcomes of interest. We will include both adult and paediatric studies, all dosing regimens and titration protocols for midodrine, and aetiologies of vasopressor dependent hypotension. We will only include observational studies and RCTs; we will review previous systematic reviews, narrative reviews and meta-analyses to ensure we have captured all relevant studies. We will also review relevant conference abstracts and proceedings.

Outcome measures

Outcomes will include: (1) ICU total LoS; (2) duration of intravenous vasopressor therapy, (3) hospital LoS, (4) ICU mortality, (5) hospital mortality, (6) rates and duration of physiological support, (7) rates of ICU readmission and (8) clinically important adverse events (ie, bradycardia, uncontrolled hypertension, cardiac ischaemia, bowel and limb ischaemia.)

Where possible, this will be determined from decision of ICU discharge and will include total time from ICU admission. Physiological support will include: (A) rate of invasive mechanical ventilation (IMV), (B) duration of IMV, (C) rate of non-invasive ventilation (NIV), (D) duration of NIV, (E) rate of renal replacement therapy (RRT) and (F) duration of RRT). Adverse events will include: (1) bradycardia, (2) hypertension, (3) cardiac ischaemia and (4) bowel and limb ischaemia.

Screening and data extraction

We will identify eligible studies in a two staged process. In the first phase, at least two investigators will independently review the titles and abstracts of all retrieved citations. Disagreements will be resolved through discussion by the two assessors, then adjudicated by a third author as needed. In the second phase, the same two reviewers will screen full texts for eligibility using a predeveloped tool. We will resolve any disagreements in this second stage using discussion and third-party adjudication if needed. We will capture reasons for exclusion at this second stage and produce a PRISMA flow chart demonstrating the screening process.

We will extract data in duplicate and independently using standardised data abstraction forms. We will extract the following specific variables: patient characteristics, age, sex, type of ICU, aetiology of shock, number of patients, study inclusion and exclusion criteria and geographical location. We will also capture the type, dose and duration of intravenous vasopressors, any cointervention used (ie, steroids use; type and amount of intravenous fluids) in either the intervention or comparator groups, and outcome data.

Risk of bias assessment

We will assess risk of bias using the modified Cochrane tool for RCTs (https://www.evidencepartners.com/resources/methodological-resources/tool-to-assess-risk-of-bias-in-randomized-controlled-trials-distillersr). We will use GRADE framework to evaluate certainty in pooled outcome data based on risk of bias, imprecision, inconsistency, indirectness and publication bias. Based on these domains, certainty will be assessed between very low, low, moderate and high.

Data analysis

Continuous data will be presented means and SD, or medians and IQR, and compared (where appropriate) using a t-test or Wilcoxon's rank sum test. Categorical variables and proportions will be compared using the Pearson's χ^2 or Fischer's exact tests as appropriate. We will summarise the eligible studies in terms of point estimates or proportions, with p values or 95% CIs, where appropriate.

We will perform meta-analyses using RevMan V.5.4 software (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration 2014). Outcomes of interest will include lengths of ICU and hospital stays, ICU and hospital mortality and duration of intravenous vasopressor use. We will use the method of DerSimonian and Laird to pool effect sizes for each outcome under a random-effects model for all outcomes of interest.[22] Study weights will be calculated using the inverse variance method. We will present the results as relative risk (RR) with 95% CIs for dichotomous outcomes[23] and mean difference for continuous outcomes. We will assess heterogeneity using the I^2 statistic, the χ^2 test for homogeneity ($p<0.1$ for significance of substantial heterogeneity), and visual inspection of the forest plots. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. We will assess for publication bias using Begg's funnel plots if there are 10 or more studies per outcome.

Trial sequential analysis

We will conduct TSA using a random effects model for ICU LoS and duration of intravenous vasopressor therapy. TSA allows for a power calculation to assess whether optimal information size (ie, events) has been reached which subsequently may inform assessments of precision in pooled point estimates. It is a tool for quantifying the statistical reliability of data in the cumulative meta-analysis adjusting significance levels for sparse data and repetitive testing on accumulating data.[24] For the TSA, we will use a statistical significance level of 5%, a power of 80% and an RR reduction of 10% to represent a clinically important difference. We will use a model variance-based heterogeneity correction and perform analysis using TSA V.0.9.5.10 beta software (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigs Hospitalet, Copenhagen, Denmark).[24]

Subgroup analyses

Where a sufficient number of trials are available (ie, greater than three studies), we will conduct the following prespecified subgroup pooled analyses (hypothesised direction of effect in parentheses):

- Septic shock versus non-septic shock (hypothesis: septic shock would have improved outcomes with midodrine, compared with non-septic shock).
- Surgical versus non-surgical patients (hypothesis: surgical patients will have improved outcomes with midodrine, compared with non-surgical patients).
- Cirrhotic versus non-cirrhotic patient shock (hypothesis: cirrhotic would have improved outcomes with midodrine, compared with non-cirrhotic shock).
- AKI versus non-AKI patients (hypothesis: non-AKI would have improved outcomes with midodrine, compared with AKI patients).
- Age greater or less than 65 years (hypothesis: younger patients will have improved outcomes with midodrine compared with those older than 65 years).

If subgroups effects are credible, we will present the outcomes separately for each subgroup. We will use ICEMAN tool to assess credibility.[25]

DISCUSSION

ICU admission is typically required for either monitoring or physiologic support. When haemodynamic support is required, intravenous vasopressors are the mainstay in treatment of septic and other forms of shock. Norepinephrine has been accepted to be the first choice in treatment of septic shock, according to the latest Surviving Sepsis Campaign.[4] Second-line treatments include vasopressin and epinephrine. However, intravenous vasopressor therapy typically requires central-line insertion and maintenance to minimise complications.[26] Ongoing need of intravenous vasopressor therapy necessitates ongoing ICU admission, which may be prolonged in slow to recover shock. Oral agents have been proposed to be an option to shorten duration of intravenous vasopressor therapy and decrease ICU LoS. Midodrine is one such agent and has been previously studied.[13–16 20 27–30]

There have been several previous trials evaluating midodrine as an intravenous vasopressor sparing agent. While there have been previous reviews of these studies, a major limitation has been the lack of large, prospective, RCTs evaluating midodrine in critically ill patients. Recently, there have been several RCTs that have evaluated the use of midodrine as an adjunctive therapy to intravenous vasopressor dependent hypotension.[16–19] The MIDAS trial randomised 136 undifferentiated hypotensive patients to either midodrine or placebo evaluating the median time from study drug initiation until discontinuation of intravenous vasopressors. The study investigators determined that there was no significant difference between groups. While there exist several methodological concerns with this study (ie, no change with baseline blood pressure in either group; no details regarding fluid management; only three sites from two countries; sample size calculation based on only small study data; lack of requirements of other organ supports; and 7-year recruitment period indicating potential selection bias), it is the largest RCT evaluating the effects of midodrine for critically ill patients and will be important to include in any future review.[16] More recently, there have been smaller published RCTs that have shown conflicting results.[17–19] Adly *et al* evaluated the use of midodrine in 60 patients with septic shock and clinical stability on low-dose intravenous vasopressors for at least 24 hours and determined that midodrine was associated with significantly shortened duration of intravenous vasopressor support and significant decreased mortality. However, this study was not blinded and was small in size, thus limiting its validity.[17] Ahmed *et al* evaluated midodrine specifically for the use of blood pressure support in 90 patients with neurogenic shock and also determined that the use of midodrine was associated with decreased duration of intravenous vasopressor support and decreased ICU LoS. Again, however, this study was unblinded and of small sample size, which also limits its validity.[18] Finally, the MAVERIC study, a pilot open-label RCT of 62 patients on low-dose intravenous vasopressor therapy, determined that adjunctive midodrine, while safe to use, was not associated with any physiological or clinical efficacy.[19] While previous systematic reviews have included the MIDAS study, there has been no review or meta-analysis conducted to date that has included the most recently published RCTs. Further, previous studies have not included any a priori subgroup analysis and our review will be evaluating the use of midodrine specifically in patients with known cirrhosis as well as with AKI. We do appreciate that while many potential subgroup analyses have been predetermined, these may not all be possible to conduct due to limited sufficient trials and patient numbers. Finally, we will be conducting a sequential trial analysis in order to evaluate the evidence of midodrine as it relates to ICU lengths of stay and adjust thresholds for significance if insufficient sample size is reached in our identified RCTs in our meta-analysis.

Our systematic review and meta-analysis aim to evaluate the role of midodrine in the treatment of vasopressor dependent shock in the ICU. This, along with our planned subgroup analyses, will inform on the optimal use of midodrine for critically ill patients. We anticipate our systematic review will inform future RCTs and eventual evidence-based clinical practice guidelines on the optimal circumstances to initiate midodrine therapy in the ICU.

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