

Metaraminol and Noradrenaline in Septic Shock: A Retrospective Comparison

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Abstract

Introduction

Vasopressor use is an important facet of septic shock management, in order to maintain hemodynamic targets and end organ perfusion. Traditionally, Noradrenaline has been the 'gold standard' drug of choice for septic shock. Metaraminol is an alternative vasopressor that has been used for septic shock. However, there has been minimal research in comparing the two drugs in septic patients, particularly with regards to total time spent on infusion.

Objectives

To compare total time spent on either Metaraminol or Noradrenaline infusion by septic shock patients, whilst adjusting for baseline severity of illness. Secondary outcomes included incidence of mechanical ventilation and new requirement of renal replacement therapy, and mortality.

Methods

A retrospective medical records review was undertaken, looking at all septic shock patients admitted to ICU in 2019, who received either Metaraminol or Noradrenaline. Data extracted from eRIC (the ICU database) included total time spent on infusion, APACHE III scores, incidence of mechanical ventilation, incidence of renal replacement therapy, and mortality.

Results

Our review yielded 174 patients who were eligible for further statistical analysis (63 in Metaraminol group, and 111 in the Noradrenaline group). The mean duration of infusion in the Metaraminol group was 1655 minutes, and 2663 minutes in the Noradrenaline group. The mean APACHE III Scores were 62 in the Metaraminol group and 77 in the Noradrenaline group. A one-way ANCOVA test found that there was a statistically significant [$F(1, 171)=4.511, p=0.035$] reduction in time spent on Metaraminol infusion, compared with Noradrenaline, after adjusting for baseline severity of illness by way of APACHE III Score.

Conclusion

Our study found a statistically significant reduction in time spent on a Metaraminol infusion compared with Noradrenaline by septic shock patients, after controlling for severity of illness. However, due to its retrospective study design, we were unable to account for bias and confounders, such as antibiotic and fluid administration, or clinician preference for one drug over the other. Nevertheless, our study adds to the paucity of literature comparing Metaraminol to Noradrenaline, and paves the way for future randomized trials comparing the two drugs in septic shock.

Introduction

Sepsis accounts for a significant burden of disease, with worldwide cases up to 50 million a year, including 11 million deaths (1). Left untreated, sepsis can rapidly lead to multi-organ failure and death, due to a dysregulated host immune response to infection. Current resuscitation guidelines include early broad spectrum antibiotic administration and infection source control, along with aggressive fluid resuscitation to avoid developing septic shock. For those in shock, vasopressors are recommended to maintain organ perfusion and avoid progression to multi-organ failure and death (2).

The most common vasopressor used in septic shock is Noradrenaline (2, 13), a catecholamine with predominant α_1 activity, and β_1 to a lesser extent (3). Metaraminol is a pure α_1 agonist, but indirectly leads to endogenous Noradrenaline release (3). Both increase peripheral vascular resistance and mean arterial pressure, thereby improving organ perfusion. Several studies have looked at Noradrenaline in septic shock, however similar research on Metaraminol is scarce (4–7).

Metaraminol has been used for septic shock since the 1960s (11), but despite this, there is a paucity of high level research on its use in sepsis, particularly in comparison with Noradrenaline. Existing research includes anecdotal case reports and small observational studies, but none comparing Metaraminol directly with Noradrenaline. Both agents are used around the world for septic shock, with the choice of agent depending largely on clinician preference or institutional policy (3).

This study aims to investigate the association between choice of vasopressor (Metaraminol or Noradrenaline) and total duration of vasopressor support (in minutes), in septic shock patients. Secondary outcomes include incidence of mechanical ventilation and new requirement of renal replacement therapy (RRT), surrogate markers of end organ perfusion. Other secondary markers include total ICU length of stay (LOS), and mortality.

Methods

Study design

Approval was granted by the Northern Sydney Local Health District Human Research Ethics Committee (2021/PID00874) for a single centre retrospective medical records review.

Setting and participants

Patients were retrospectively recruited from a quaternary metropolitan Australian ICU's database (eRIC). A list was compiled of patients admitted to the ICU in 2019, along with their ANZICS diagnosis codes, age, gender, source of admission, as well as relevant data relating to primary and secondary outcomes (e.g. receiving either Metaraminol or Noradrenaline, requiring mechanical ventilation or renal replacement therapy).

The ANZICS diagnosis codes were analysed for specific keywords relating to infection, such as 'sepsis', 'pneumonia', 'abscess'. Patients were enrolled based on these keywords, indicating infection from any

source. A table of the ANZICS diagnosis codes which were used to capture and enrol patients is attached as Appendix 1. Patients under the age of 18 were excluded.

Outcomes

The primary outcome was total time spent on either a Metaraminol or Noradrenaline infusion. Secondary outcomes included ICU LOS, mortality, and incidence of mechanical ventilation and renal replacement therapy.

Confounders and bias

Due to a retrospective study design, it was not possible to control for confounders. Vasopressor support is only one facet of sepsis management, with adequate fluid resuscitation, appropriate antibiotic therapy and source control, and (in some cases) metabolic resuscitation via administration of steroids, all contributing to halting disease progression. Data on these variables (such as timing of antibiotics, amount of fluids given, and/or steroid administration) was not readily available for extraction and analysis from eRIC.

Inherent bias may be present in the study due to clinician preference for one particular vasopressor over the other. Traditionally, the 'sicker' septic patients received Noradrenaline, whilst Metaraminol has been used as bridging until a central line can be placed. The reasoning behind vasopressor choice was not readily available from the eRIC database, and therefore could not be used to rationalise bias over one or the other drug.

Statistical analysis

Statistical analysis was performed using the one-way ANCOVA test to compare Metaraminol and Noradrenaline infusion times, whilst controlling for illness severity via the APACHE III scores. This particular test was chosen as it would allow us to compare the effect of a categorical variable (choice of vasopressor) on a continuous variable (time spent on infusion), whilst controlling for another continuous variable (APACHE III score as a surrogate for severity of illness). Using this test, we were able to directly compare Metaraminol with Noradrenaline, whilst controlling for baseline severity of illness.

Results

Review of the eRIC database for 2019 yielded 3767 patients. 251 patients received Metaraminol or Noradrenaline (or both), and had an ANZICS admission diagnosis code which included 'sepsis, infection, abscess' or system specific diagnosis of infection (e.g. cholangitis, cellulitis, pneumonia). Of these patients, 75 patients received both Metaraminol and Noradrenaline during their ICU admission, and therefore removed from analysis. The remaining 176 patients were included in the analysis as per the inclusion criteria; over 18 years of age and requiring either Metaraminol or Noradrenaline for septic shock. 64 of these patients received Metaraminol and 112 received Noradrenaline.

One outlier was removed from each group. In the Noradrenaline group, one patient received Noradrenaline for only one minute, without ongoing infusion of either Noradrenaline or Metaraminol. After a review of the patient's record, it was deemed that they in fact did not receive any vasopressor, and were not septic. In the Metaraminol group, one patient received Metaraminol for 12802 minutes (the longest duration in the Metaraminol group). On review of the patient's record, it was noted that the patient had chronic asymptomatic hypotension, with a negative septic screen. It was deemed that the patient's hypotension was physiological, rather than secondary to sepsis.

This left 63 patients in the Metaraminol group and 111 patients in the Noradrenaline group, who underwent statistical analysis.

The one-way ANCOVA test found that there was a statistically significant [$F(1, 171) = 4.511, p = 0.035$] reduction in time spent on Metaraminol infusion than Noradrenaline, after accounting for illness severity. The large sample size allowed for analysis of a non-normal distribution of data, and Levene's Test showed equal variance between the groups. As we were comparing only two groups, post-hoc analyses were not required.

Table 1
Patient baseline and demographic characteristics

Characteristic	Metaraminol (n = 63)	Noradrenaline (n = 111)
Median Age (years)	71 (18–91)	65 (18–91)
Number female (%)	27 (43%)	54 (49%)
Mean APACHE III Score	62 (27–94)	77 (29–176)
Outcomes		
Mean duration of infusion (min)	1655 (51-8169)	2663 (26-21892)
Mean Length of Stay (hour)	80 (9-244)	135 (2-609)
Ventilated	9 (14%)	31 (28%)
CRRT	0 (0%)	5 (4%)
Both	0 (0%)	11 (10%)
Died in ICU	3 (5%)	13 (12%)
Died in Hospital	2 (3%)	3 (3%)
Source		
Uncoded	22 (35%)	52 (47%)
Endocarditis	0 (0%)	3 (3%)
Respiratory	21 (33%)	20 (18%)
Gastrointestinal	11 (17%)	22 (20%)
Urinary	4 (6%)	8 (7%)
Gynaecological	2 (3%)	0 (0%)
Soft tissue	3 (5%)	6 (5%)

Discussion

This study was a retrospective records review of septic shock patients admitted to a single metropolitan ICU in 2019. We found that despite a higher mean APACHE III score and higher incidence of mechanical ventilation and RRT in the Noradrenaline group, there was a statistically significant reduction (after adjusting for severity of illness) in time spent on vasopressor in patients receiving Metaraminol, as opposed to those receiving Noradrenaline.

There have been previous studies comparing various inotropes/vasopressors, including Noradrenaline, Adrenaline, and Vasopressin, but only very few that included Metaraminol (3–8). This is the first study till date as far as the authors are aware, that directly compares Metaraminol to Noradrenaline in septic shock.

There were several drawbacks to this study. Due to its retrospective design, there was lack of control over confounders and variables. We could not feasibly collect data on confounders to duration of vasopressor support, such as fluid resuscitation, timing of antibiotics and/or source control, and provision of steroids for septic shock. These factors may have had an impact on the total duration of vasopressor support. The sample size for this study was relatively small, as it only included patients from one calendar year (2019). There were also double the number of patients in the Noradrenaline group as opposed to Metaraminol. This may have been due to clinical preference, as Noradrenaline is currently considered the 'gold standard' inotropic support in shock. Using the APACHE III score as a marker of illness severity may exclude other causes of sickness not calculated by the score. Therefore, there may have been sicker patients in the Noradrenaline group despite adjusting for the APACHE III scores, as evidenced by the higher incidence of ventilation and renal replacement. This could provide a reasoning as to why patients in the Noradrenaline group spent longer on an infusion, than those on Metaraminol. Seventy-five patients received both Metaraminol and Noradrenaline. These patients were excluded from the final analysis, as it was impossible to compare outcomes due to the use of both drugs. It is also difficult to speculate the cause for this, without review of each individual patient's record.

Conclusion

Despite its drawbacks, our study is the first of its kind (to our knowledge) to compare Metaraminol and Noradrenaline use in septic shock, and found that there was a statistically significant reduction in time spent on Metaraminol than Noradrenaline, in this cohort of patients. There is not enough evidence to postulate causations, but it is hypothesis generating, paving the way for future research in this area. Currently, there is scarce evidence in current literature comparing both drugs in septic shock, and certainly no randomised trials. Future randomised trials with sound methodology designed to control for bias and confounders are warranted based on these results.

Declarations

Ethics approval

Approval was granted by the Northern Sydney Local Health District Human Research Ethics Committee (2021/PID00874) for a single centre retrospective medical records review.

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

AK conceived the research question and conducted literature review, data and statistical analysis, and manuscript write up. AD and MG assisted with draft revisions and editing, suggestions, and advice. All authors read and approved the final manuscript.

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Figures

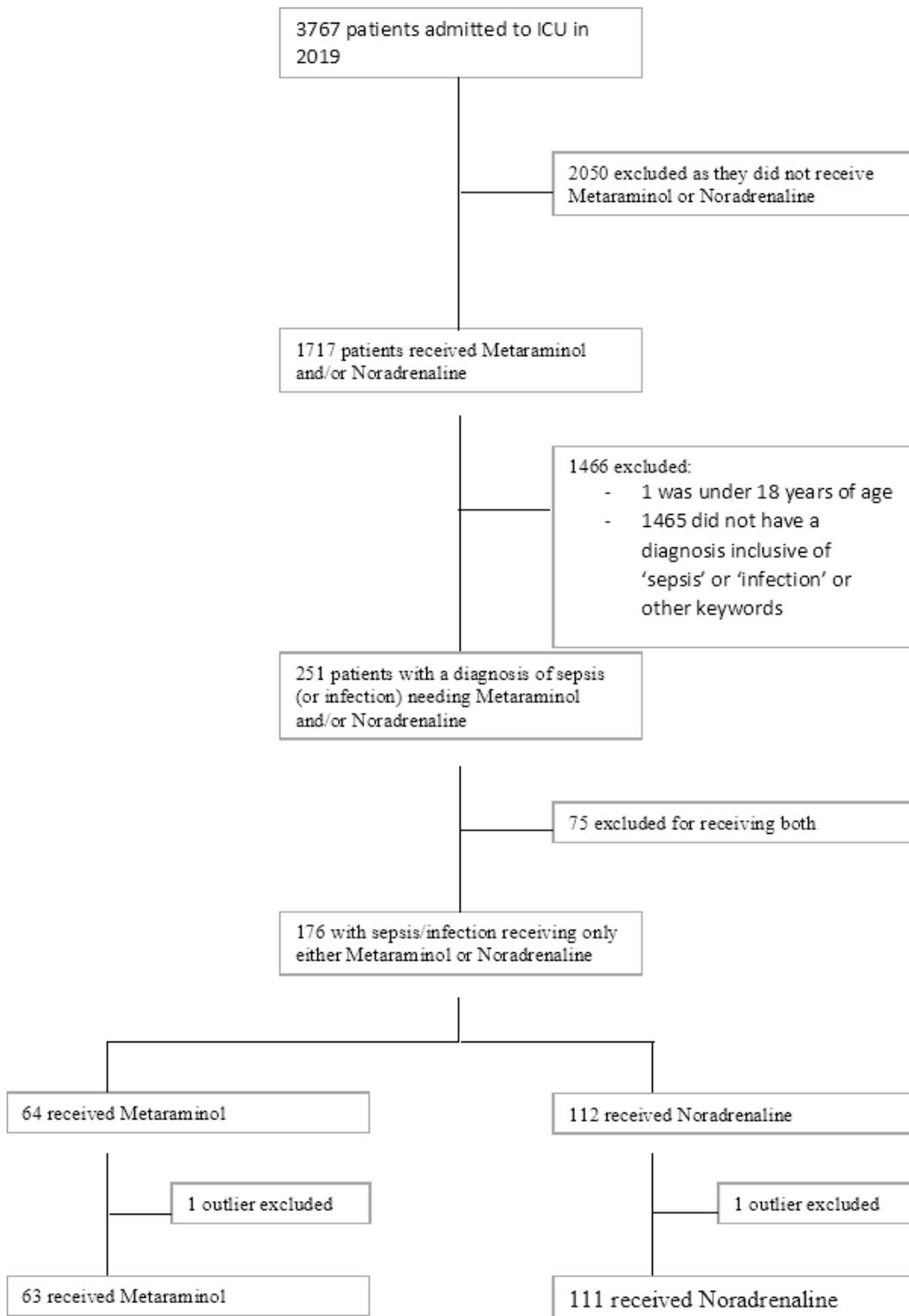


Figure 1

Patient recruitment

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Appendix.docx](#)