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Effect of early adjunctive vasopressin initiation for septic shock patients: a target trial emulation

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Abstract

Background In septic shock, the optimal timing of adjunctive vasopressin initiation shock is unknown. We aimed to assess the effect of its early initiation for patients with septic shock.

Methods We conducted a multicenter target trial emulation to estimate the intensive care unit (ICU) mortality effect of early (≤ 6 h) adjunctive vasopressin compared with usual care. Eligible patients had septic shock diagnosed within 6 h of ICU admission. The primary outcome of this study was 30-day ICU mortality. Subgroup analyses were conducted to test the interaction of early vasopressin start with peak norepinephrine-equivalent dose (NED) at 6 h, APACHE score, peak lactate at 6 h and invasive mechanical ventilation. Secondary outcomes were the impact of delayed vasopressin introduction on 30-day ICU mortality and effect of NED at vasopressin start on 30-day ICU mortality. We used the parametric g-formula to emulate a target trial.

Results Overall, 3,105 patients fulfilled the inclusion criteria. Mean age was 62 years and mean APACHE III score was 83. In the first six hours of vasopressor therapy, 1,864 (60%) patients were invasively ventilated. Estimated 30-day ICU mortality was 19.34% (95%CI, 17.0 to 21.68) in the no vasopressin group and 18.45% (95%CI, 16.26 to 20.63) in the early vasopressin group; relative risk 0.95 (95%CI, 0.93 to 0.98). The estimated 30-day ICU mortality effect of starting vasopressin was particularly strong at lower norepinephrine doses (< 0.25 $\mu g.kg^{-1}.min^{-1}$) and significant at lower norepinephrine doses than recommended by the Surviving Sepsis Campaign Guidelines. Vasopressin administration progressively increased over the study period, from 35.2% (95%CI, 30.0 to 40.5) in 2015 to 45.1% (95%CI, 40.7 to 49.6) in 2021 (ß = + 1.3% per year; 95%CI, + 0.46 to + 2.16, $p = 0.011$). Patients had progressively lower norepinephrine equivalent dose (ß = − 0.05 $\mu g.kg^{-1}.min^{-1}$ per year; 95%CI, − 0.09 to − 0.002, $p = 0.038$) and lower total SOFA score (ß = − 0.1 point per year; 95%CI, − 0.18 to − 0.07, $p < 0.001$) at vasopressin start.

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Conclusions In this emulation of a hypothetical target trial, patients with septic shock benefited from early vasopressin administration. These findings can help design prospective randomised-control trials of early adjunctive vasopressin use in septic shock.

Keywords Vasopressin, Sepsis, Shock, Hypotension, Vasodilation, Critical care

Introduction

There is increasing interest in catecholamine-sparing vasopressor strategies in the management of septic shock [1, 2]. The Surviving Sepsis Campaign guidelines currently recommend norepinephrine as the first-line agent for this condition, with a weak recommendation for commencing adjunctive vasopressin when the dose of norepinephrine base is in the range of 0.25–0.5 μg.$kg^{-1}.min^{-1}$ [3]. Thus, clinicians may regard vasopressin as a 'rescue' therapy rather than an essential component of a multimodal vasopressor strategy. Furthermore, current sepsis guidelines do not recommend a timing threshold for vasopressin initiation despite randomized and observational data suggesting that timing may be an important consideration [4–9].

An individual patient data meta-analysis of four randomized controlled trials of vasopressin in septic shock suggested potential benefit when vasopressin is commenced in less severe shock states (i.e., lower lactate levels, lower norepinephrine dose), and in the absence of established acute kidney injury [10]. Earlier initiation of adjunctive vasopressin in patients with less severe shock, therefore, warrants further investigation.

Accordingly, we conducted a target trial emulation using a large, multicentre database to estimate the effect of early vasopressin initiation on mortality in septic shock patients. We aimed to test the primary hypothesis that early (≤6 h) vasopressin initiation would be associated with lower hospital mortality compared with no vasopressin adjunction. Our secondary hypothesis was that late (>6 h) vasopressin therapy would be associated with worse outcomes.

Methods

Study design

We conducted a target trial emulation (TTE) of early vasopressin in septic shock patients. We used routinely collected electronic medical record clinical data from twelve intensive care units (ICU) in Queensland, Australia. The study sites comprised five tertiary, three outer metropolitan, and four regional ICUs and included most of Queensland's state-wide ICU capacity.

Population

We included all adult ICU patients (≥18 years) admitted with a diagnosis of septic shock within the first six hours of admission. We excluded patients transferred from another ICU or were admitted solely for palliative care or organ donation. In addition, we excluded patients who commenced vasopressin within the first hour of ICU admission. We reasoned that such patients might have had vasopressin started before or within the first hour of ICU admission, introducing uncertainty about the real start time.

Intervention

Patients were assigned by TTE to treatment groups if they met eligibility criteria in the first six hours of ICU admission. In the primary analysis, patients in the treatment group commenced adjunctive vasopressin within six hours of septic shock. Patients in the control group did not commence adjunctive vasopressin at all. In secondary analyses, vasopressin was started either at a prespecified time or norepinephrine-equivalent dose (NED) threshold.

Definitions

The norepinephrine formulation used in all centres was norepinephrine tartrate [11, 12]. Vasopressors other than vasopressin were converted to norepinephrine-equivalent doses according to previously published conversion tables [13–15]. Sepsis and septic shock were defined according to the Sepsis-3 consensus definition using previously published methodology [16, 17].

Outcomes

The primary outcome of this study was to assess the impact of early timing (≤6 h since septic shock) of vasopressin initiation on 30-day ICU mortality. Subgroup analyses were conducted to test the interaction of vasopressin start within 6 h of ICU admission with peak NED at 6 h, APACHE score, peak lactate at 6 h and invasive mechanical ventilation. Secondary outcomes were the impact of delayed vasopressin introduction on 30-day ICU mortality, effect of NED at vasopressin start on 30-day ICU mortality. Exploratory outcomes were changes in vasopressin administration over the study

period (prevalence of prescription, NED at vasopressin start, total SOFA score at vasopressin start and time from ICU admission to vasopressin start).

Statistical analysis

Baseline characteristics are reported as absolute values with percentages for categorical variables or medians with the interquartile interval for quantitative variables. Annual proportion with a 95% confidence interval was calculated out of the yearly number of included ICU admissions. Changes in annual incidence were performed by testing its interaction with time via linear regression. To quantify the causal effect of early vasopressin start on 30-day ICU mortality, we used a target trial emulation protocol (electronic supplementary material, ESM, Table S1) and the parametric g-formula [18–21]. This method allows for the reliable estimation of the risk of outcomes under sustained interventions (analogous to a per-protocol analysis in a randomized controlled trial), adjusted for both pre-and post-baseline prognostic factors, which themselves might be influenced by preceding treatments (ESM, Figs. S1–S3). This framework has demonstrated high stability and the ability to obtain precise adjustment in various situations [22–25]. Briefly, during g-modelling, parametric regression models are fitted to estimate the complete joint distribution of the outcome and time-varying covariates given previous treatment and covariate history (ESM, Table S2) and tested for fit with estimation of usual care (Fig. S3). This joint distribution is then used in Monte Carlo simulations to estimate the risk of the outcome if all patients have had early vasopressin initiation and to compare such risk with the observed risk under an intervention that never allows for vasopressin initiation. In addition, nonparametric bootstrapping with 500 resamples was used to estimate 95% confidence intervals (CIs). The results are reported as absolute risk, risk differences and risk ratios with 95% CIs. Statistical analyses were performed using R version 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria) [26] with the packages 'dplyr'[27], 'ggplot2'[28], 'ggpubr' [29], 'gtsummary' [30], 'mice' [31] and 'gfoRmula' [32]. Sensitivity analyses, description of how missing data were handled, details on missing data patterns and number of patients available in each time interval before g-computation are described in detail in the Online Data Supplement (ESM, Table S3, Figs. S4–S5).

Data access and storage

We obtained hospital administrative data and intensive care data from the clinical information systems eCritical MetaVisionTM (iMDsoft, Boston, MA, USA) and the Australia and New Zealand Intensive Care Society (ANZICS) Centre for Outcome and Resource Evaluation (CORE) Adult Patient Database (APD). The data were stored in a password-protected file in a non-identifiable format.

Results

Baseline characteristics

Within the 7-year study period, there were 74,851 unique admissions to the twelve study ICUs. Within this population, 3,105 patients presented with septic shock within six hours of ICU admission and were eligible for the target trial (Supplemental Fig. S6). Their baseline characteristics are presented in Table 1. The majority of patients were male (60%), with a mean age of 62 years and a mean APACHE III score of 83. Approximately half were admitted from the emergency department and one-third from the ward. Among patients admitted from the emergency department, the median length of stay before ICU admission was 5 h (2.5 – 7.8). In the first six hours of vasopressor therapy, 1,864 (60%) patients were invasively ventilated, and 109 (3.5%) received renal replacement therapy. The maximum NED was 0.15 (0.06 – 0.28) $\mu g.kg^{-1}.min^{-1}$, and the mean peak lactate was 4.5 ± 3.2 $mmol.L^{-1}$. Vasopressin was initiated in 1,209 (39%) patients and started at a mean time of 5.6 ± 7.1 h from vasopressor start. Median NED at vasopressin initiation was 0.25 $\mu g.kg^{-1}.min^{-1}$ (0.15 – 0.39).

Primary analysis—vasopressin start within 6 h of septic shock

As shown in Fig. 1, in 3,105 patients analysed in the target trial emulation, the estimated 30-day ICU mortality was 19.34% (95% CI, 17.0 to 21.68) in the no vasopressin group and 18.45% (95% CI, 16.26 to 20.63) in the early vasopressin start within 6 h group; relative risk 0.95 (95% CI, 0.93 to 0.98).

As shown in Fig. 2, there was a time effect when comparing an approach that never allowed vasopressin use (Supplemental Figs. S7–S9) with vasopressin start within 6 h showing the lowest relative risk for mortality.

Subgroup and threshold analysis

As shown in Fig. 3, vasopressin start within 6 h of septic shock diagnosis was associated with a decreased likelihood of 30-day ICU mortality in all sub-groups explored. As shown in in Fig. 4 and Figs. S10–S11, the estimated 30-day ICU mortality effect of starting vasopressin at lower doses of norepinephrine was stronger.

Exploratory analyses

As shown in Fig. 5, vasopressin administration progressively increased over the study period, from 35.2 (95% CI, 30.0 to 40.5) in 2015 to 45.1 (95% CI, 40.7

Table 1 Baseline characteristics and intervention of eligible cohort

Variable	N = 3,105
Demographic	
Age (years), Mean ± SD	62 ± 16
Sex female, n (%)	1,230 (40)
Body mass index (kg.m^{-2}), Mean ± SD	30 ± 9
Admission	
ICU admission source, n (%)	
Emergency department	1,433 (46)
Operating Theatre	505 (16)
Other hospital	237 (7.6)
Ward	877 (28)
Comorbidities	
Chronic respiratory disease, n (%)	146 (4.7)
Chronic cardiovascular disease, n (%)	98 (3.2)
Chronic liver disease, n (%)	177 (5.7)
Diabetes, n (%)	112 (3.6)
Chronic immunosuppression, n (%)	543 (17)
Hemopathy, n (%)	221 (7.1)
Metastatic cancer, n (%)	100 (3.2)
Prognosis scores	
APACHE III score, Mean ± SD	83 ± 29
APACHE III risk of death (%), Mean ± SD	40 ± 27
SOFA score, Mean ± SD	7.0 ± 3.1
Time of randomization (0 h to 6 h)	
Maximum noradrenaline equivalent dose (µg.kg^{-1}.min^{-1}) at 6 h, Median (Q1–Q3)	0.15 (0.06–0.28)
Invasive ventilation at 6 h, n (%)	1,864 (60)
CRRT at 6 h, n (%)	109 (3.5)
Peak lactate at 6 h, mmol.L^{-1}, Mean ± SD	4.5 ± 3.2
Nadir pH at 6 h, Mean ± SD	7.23 ± 0.14
Peak serum creatinine at 6 h, µmol.L^{-1}, Median (Q1–Q3)	142 (94—222)
Peak white cell count at 6 h, 10^9.L^{-1}, Mean ± SD	17 ± 14
Day of vasopressor start (0 h to 24 h)	
Invasive ventilation at 24 h, n (%)	1,920 (62)
CRRT at 24 h, n (%)	317 (10)
Maximum noradrenaline dose (µg.kg^{-1}.min^{-1}) at 24 h, Median (Q1–Q3)	0.17 (0.07–0.32)
Peak lactate at 24 h, mmol.L^{-1}, Mean ± SD	5.0 ± 3.6
Nadir pH at 24 h, Mean ± SD	7.23 ± 0.14
Peak serum creatinine at 24 h, µmol.L^{-1}, Mean ± SD	194 ± 156
Peak white cell count at 24 h, 10^9.L^{-1}, Mean ± SD	19 ± 14
Hydrocortisone, n (%)	1,545 (50)
Type of vasopressor	
Noradrenaline, n (%)	3,013 (97)
Adrenaline, n (%)	676 (22)
Vasopressin, n (%)	1,209 (39)
Noradrenaline equivalent dose at vasopressin start (µg.kg^{-1}.min^{-1}), Median (Q1–Q3)	0.25 (0.15–0.39)
Time from vasopressor start to vasopressin start (hrs), Mean ± SD	5.6 ± 7.1
Dopamine, n (%)	76 (2.4)
Metaraminol, n (%)	767 (25)
Dobutamine, n (%)	256 (8.2)
Milrinone, n (%)	89 (2.9)

Continuous values are presented as mean ± SD or median (Q1–Q3), categorical variables are presented as n (%)

ICU, intensive care unit; APACHE, acute physiology and chronic health evaluation, SOFA, sequential organ failure assessment; CRRT, continuous renal replacement therapy

to 49.6) in 2021 (ß = +1.3% per year; 95% CI, +0.46 to +2.16, $p = 0.011$). Patients had progressively lower NED (ß = −0.05 µg.kg^{-1}.min^{-1} per year; 95% CI, −0.09 to −0.002, $p = 0.038$) and lower total SOFA score (ß = −0.1 point per year; 95% CI, −0.18 to −0.07, $p < 0.001$) at vasopressin start.

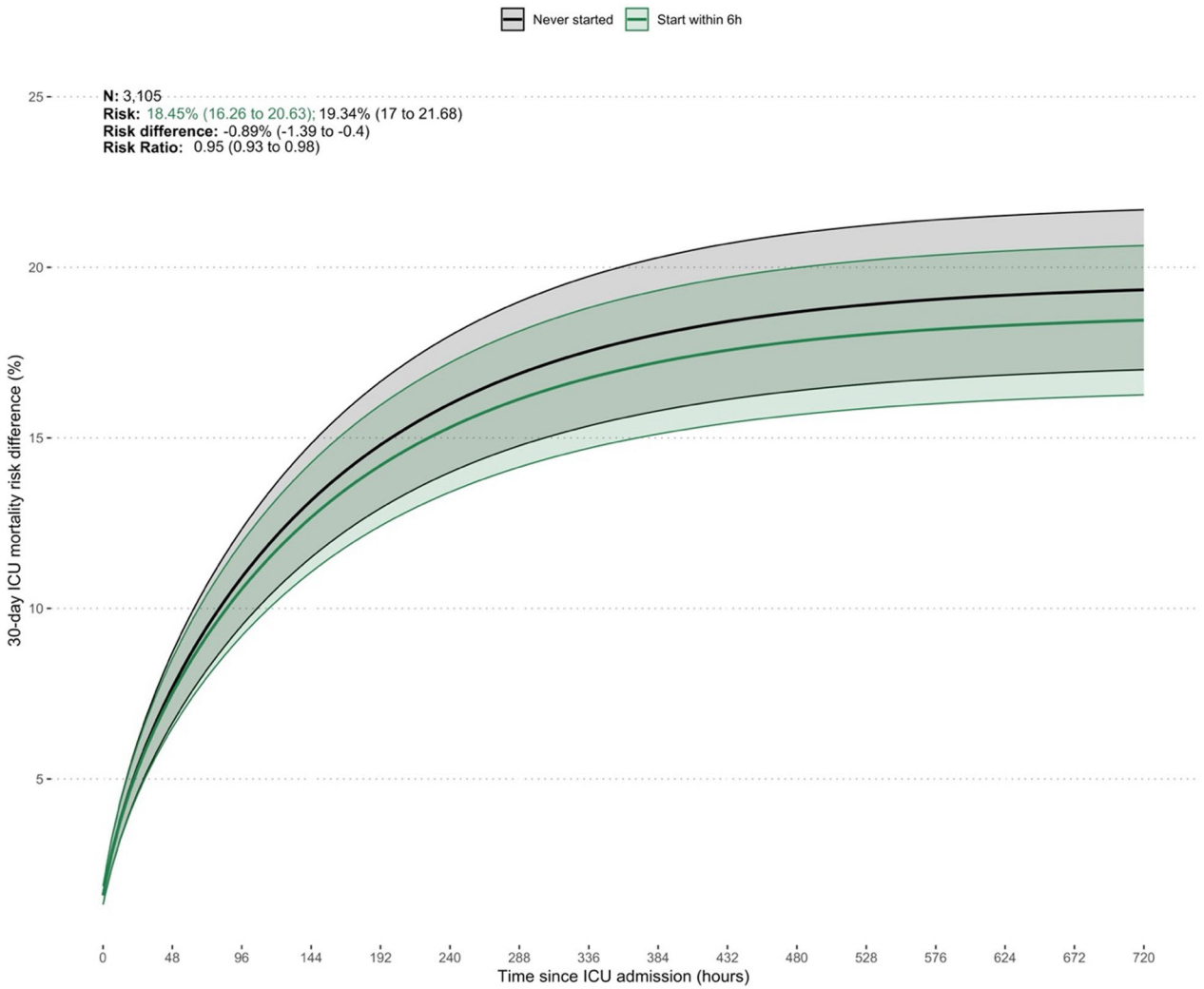

Fig. 1 Estimated 30-day potential drug-induced mortality risk under a treatment strategy that allows to start vasopressin in the first 6 h versus an intervention that never allows for vasopressin start

Intervention	N	Intervention risk (%)	Control risk (%)	Relative risk (95% CI)
Start within 6h vs. Never started	3105	18.45	19.34	0.95 (0.93 to 0.98)
Start after 12h vs. Never started	3105	18.61	19.34	0.96 (0.94 to 0.98)
Start after 18h vs. Never started	3105	18.76	19.34	0.97 (0.95 to 0.99)
Start after 24h vs. Never started	3105	18.86	19.34	0.98 (0.96 to 0.99)
Start after 48h vs. Never started	3105	19.08	19.34	0.99 (0.98 to 0.99)

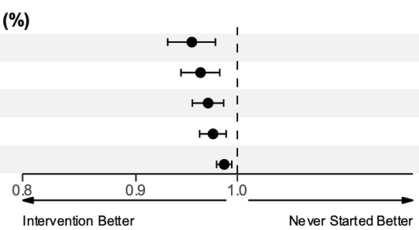

Fig. 2 Forest plot of risk difference of 30-day ICU mortality for each of the interventions tested against an intervention that never allows for vasopressin start

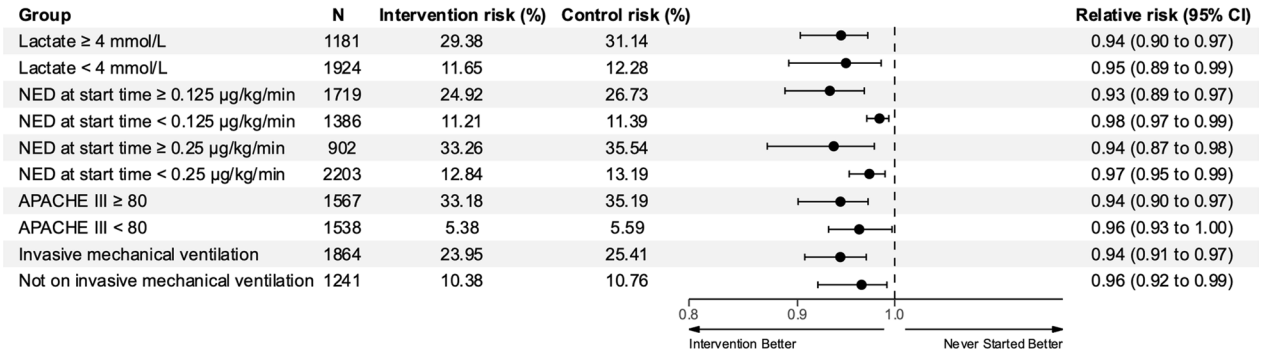

Fig. 3 Forest plot of risk difference of 30-day ICU mortality for each of the interventions that allows to start vasopressin in the first 6 h versus an intervention that never allows for vasopressin start according to subgroups

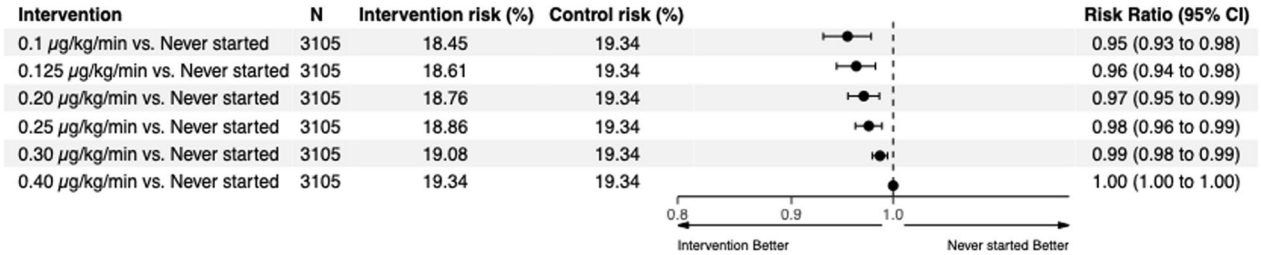

Fig. 4 Forest plot of risk difference of 30-day ICU mortality according to norepinephrine equivalent dose threshold for vasopressin introduction versus an intervention that never allows for vasopressin start

Discussion

Key findings

In this study, we emulated a hypothetical target trial and found that, after adjustments, patients with septic shock who received early adjunctive vasopressin therapy (≤ 6 h) had a lower risk ratio for 30-day ICU mortality than patients who never received vasopressin or who received late vasopressin therapy (> 6 h). Moreover, this effect was progressively diminished as vasopressin start occurred after 12 h, 18 h and 24 h. Similarly, the beneficial mortality effect was strongest when the NED was 0.1 $\mu g.kg^{-1}.min^{-1}$ and diminished as the NED at the start of vasopressin moved to 0.125 and then 0.2 $\mu g.kg^{-1}.min^{-1}$ and was absent at 0.25 $\mu g.kg^{-1}.min^{-1}$ or above. The beneficial effect of vasopressin was pervasive and significant in all groups (high or low lactate, ventilated or not ventilated, APACHE score < 80 or ≥ 80).

Relationship to previous studies

There are limited data available on outcomes relating to early initiation of adjunctive vasopressin therapy in septic shock patients. The only multicentre randomised controlled trial to consider a timing threshold, the VANISH study, enrolled patients within six hours of shock onset [4]. Similar to our patient cohort, these patients had a 'low dose' vasopressor requirement with a median norepinephrine dose of 0.16 $\mu g.kg^{-1}.min^{-1}$. Furthermore, in the VANISH study, less than 60% of patients were mechanically ventilated and the median lactate was 2.3 $mmol.L^{-1}$. This study did not identify any significant difference in mortality rates between the examined groups, in contrast with our results. However, the VANISH study included vasodilatory shock patients who are known to have different outcomes when compared to septic shock [16]. In addition, the study was underpowered, limiting the reliability of its conclusions. Notably, the study did not observe a beneficial effect of hydrocortisone treatment, a finding that contrasts with results from larger randomized controlled trials such as APPROACHS and ADRENAL, which have suggested its beneficial effects regarding ICU length of stay, duration of shock, and duration of mechanical ventilation [33, 34].

A signal of benefit for early adjunctive vasopressin use compared with late initiation has been assessed in retrospective studies [5, 9]. White et al. showed that, among septic shock patients, later time to vasopressin initiation was independently associated with hospital mortality [9]. This is consistent with our finding of higher mortality risk with late vasopressin initiation. However, in our study, we extended such findings by target trial emulation and found that compared to no vasopressin use, early vasopressin was associated with a decreased risk of death.

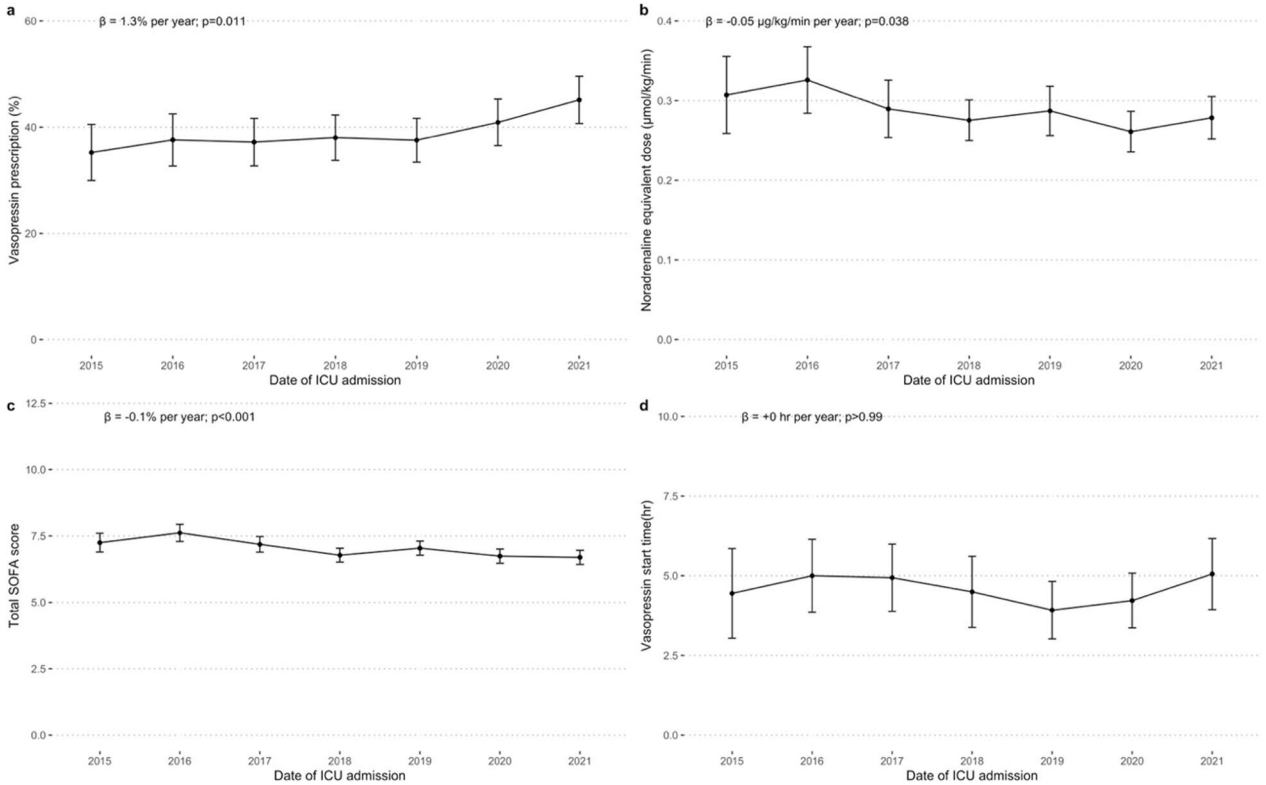

Fig. 5 Evolution over the study period of **a** vasopressin administration; **b** noradrenaline equivalent dose at vasopressin start time; **c** Total SOFA score at vasopressin start time; **d** time from vasopressor start to first vasopressin administration

Sacha et al.'s study showed a linear association between hospital mortality and lactate concentration at time of vasopressin initiation [5]. Furthermore, the odds of death increased with increasing lactate concentration at vasopressin initiation when time from shock onset to vasopressin initiation increased. However, there was no independent association between hospital mortality and timing of vasopressin initiation. These results suggest a longer duration of hyperlactatemia without adjunctive treatment (and possibly 'decatecholaminisation') may be detrimental [1]. Similarly, in our study, the beneficial effect of early vasopressin was particularly strong when the lactate was > 4 mmol.L^{-1}. Thus, a lactate > 4 mmol.L^{-1}, despite a norepinephrine-equivalent infusion dose ≤ 0.25 µg.kg^{-1}.min^{-1}, may be an important clinical trigger to commence adjunctive vasopressin in the first six hours of septic shock management.

Kalimouttou et al. have shown that in patients experiencing septic shock, a reinforcement learning model suggests the earlier and more frequent administration of vasopressin [35]. Key factors influencing the decision to start vasopressin according to this model include the duration since shock onset, the SOFA score, the norepinephrine dosage, and the serum lactate levels at the time of vasopressin administration. These findings align closely with our results.

Implications of study findings

To our knowledge, this is the first target trial emulation of early adjunctive vasopressin use in septic shock patients. This is an important cohort of patients to consider given the time critical nature of septic shock treatment and current international guidelines, which do not advocate adjunctive vasopressor therapies below a norepinephrine base infusion dose threshold of 0.25 µg.kg^{-1}.min^{-1}.

Our study provides important findings to help better inform patient selection and interventions for a prospective randomised-control trial for early adjunctive vasopressin use in septic shock. It implies that early vasopressin therapy may be desirable. Moreover, it implies that initiation at lower doses of norepinephrine administration (> 0.125 µg.kg^{-1}.min^{-1} but < 0.25 µg.kg^{-1}.min^{-1} of norepinephrine tartrate) than currently recommended by the Surviving Sepsis Campaign guidelines (between 0.25 and 0.50 µg.kg^{-1}.min^{-1} of norepinephrine base) may also be desirable. In addition, it suggests that patients with a lactate > 4 mmol.L^{-1} and patients on mechanical ventilation may be easily

identifiable candidates in whom early administration of vasopressin may be particularly beneficial. Finally, our results highlight the limited magnitude of effect that investigators should expect when designing such trials.

Strengths and limitations

This study had several strengths. In particular, this target trial emulation cohort was sampled from a large, comprehensive ICU patient database covering nearly all ICU admissions in a large state of Australia. This population is generalisable to the wider Australian population and likely to other high-income countries. Moreover, our highly granular study data was electronically extracted from a mature clinical information system in daily clinical use at all twelve study sites. There were minimal missing data points. In addition, the methods to emulate a hypothetical target trial, selection and adjustment for confounding variables and strict eligibility criteria minimise immortal time bias and confounding by indication and prespecified sensitivity analyses were performed with results consistent with our primary analysis. Finally, our study design encompassed all patients with the condition of interest, avoiding the selection bias frequently found in randomized controlled trials.

We acknowledge some limitations. First, the groups differed significantly at baseline, with the treatment group having a higher severity of illness. This raises the possibility of residual confounding. However, the adjustments performed with target trial emulation methodology are likely to have addressed such differences. Second, we do not have data to explain why clinicians commenced vasopressin early or late in this patient cohort. Therefore, despite being reduced by the study design, there may still be confounding factors due to vasopressin being given to patients whom clinicians judge most likely to survive. However, early initiation of vasopressin may also easily indicate greater illness severity and such indication bias may have actually decreased the true magnitude of the benefits associated with vasopressin. Third, although there is a significant effect across all subgroups, the severity of patients may impact outcomes. Fourth, we only admitted patients diagnosed with septic shock during the first six hours of their ICU stay, which limits the applicability of these results to other groups. Fifth, a time-related effect might have affected our results as we covered a six-year period. Finally, despite the imputation method we performed, missing values may have biased our results.

Conclusion

In this emulation of a hypothetical target trial, patients with septic shock benefited from early vasopressin administration even when the NED was low, the peak serum lactate was > 4 mmol.L^{-1}, or mechanical ventilation was being applied. These findings can help design prospective randomised-control trials of early adjunctive vasopressin use in septic shock.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05401-y.

Supplementary material 1

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Author contributions

The study conception and design (all authors); data acquisition (K.W); analysis (A.C, K.W); interpretation of data (all authors); article drafting (R.C.P, A.C, R.B, K.W), article revision for important intellectual content (all authors); final approval of the version submitted for publication (all authors); agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and materials

Data cannot be shared publicly due to institutional ethics, privacy, and confidentiality regulations. Data released for the purposes of research under section 280 of the Public Health Act 2005 requires an application to the Director-General of Queensland Health (PHA@health.qld.gov.au).

Declarations

Ethics approval and consent to participate

The study was approved by the Metro South Hospital and Health Service Human Research Ethics Committee (HREC/2022/QMS/82024) with an individual waiver of consent granted.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

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