Supplementary Online Content

Fujii T, Luethi N, Young PJ, et al; VITAMINS Trial Investigators. Effect of vitamin C, hydrocortisone, and thiamine vs hydrocortisone alone on time alive and free of vasopressor support among patients with septic shock: the VITAMINS randomized clinical trial [published online January 17, 2020]. *JAMA*. doi:10.1001/jama.2019.22176

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Methods: the VITAMINS Trial Inclusion and Exclusion Criteria

Inclusion criteria	Diagnosis of septic shock All the diagnostic criteria of septic shock (based on the SEPSIS-3 consensus criteria[1]) below has to be fulfilled simultaneously within the last 24 hours, and a vasopressor is infused continuously at the time of enrolment**.** • Definition of septic shock: Sepsis AND Need for vasopressor therapy to maintain mean arterial pressure >65 mmHg for >2 hours AND Lactate >2 mmol/L, despite adequate fluid resuscitation • Definition of sepsis: Suspected or documented infection AND Acute increase of ≥2 SOFA points[2] consequent to the infection (a proxy of organ dysfunction)
Exclusion criteria	1. Age < 18 years 2. Pregnancy 3. DNR (do not resuscitate)/DNI (do not intubate) orders 4. Death is deemed to be imminent or inevitable during this admission, and either the attending physician, patient or substitute decision-maker is not committed to active treatment 5. Patients with known HIV infection[3,4] 6. Patients with known glucose-6 phosphate dehydrogenase (G-6PD) deficiency[5,6] 7. Patients transferred from another ICU or hospital with a diagnosis of a septic shock for > 24 hours 8. Patients with a diagnosis of a septic shock for > 24 hours 9. Patients with known or suspected a. history of oxalate nephropathy or hyperoxaluria b. short bowel syndrome or severe fat-malabsorption c. acute beri-beri disease d. acute Wernicke's encephalopathy e. malaria f. scurvy g. Addison's disease h. Cushing's disease 10. Clinician expects to prescribe systemic glucocorticoids for an indication other than septic shock (not including nebulized or inhaled corticosteroid) 11. Patient is receiving treatment for systemic fungal infection[7] or has documented *Strongyloides* infection[8,9] at the time of randomization 12. Patient with known chronic iron overload due to iron storage and other diseases[10] 13. Patient previously enrolled in this study 14. Clinician expects to prescribe high dose vitamin C for another indication

eAppendix 2. Methods: Criteria for Stopping the Study Treatment in the VITAMINS Trial

1. Shock resolution; defined as when all vasopressors were discontinued for four consecutive hours in the presence of a mean arterial pressure (MAP) >65 mmHg or a target MAP set by the treating clinician
2. 10 days of vitamin C and thiamine has been administered in the Vitamins group
3. 7 days of hydrocortisone and tapering, if applicable, has been delivered in the Control group
4. Death
5. Discharge from the ICU
6. Contraindications to any of the study drugs has arisen
7. Serious adverse events suspected to be related to a study medication has developed
8. Consent has been withdrawn or consent to continue has not been granted

eAppendix 3. Methods: Definitions of Secondary Outcomes in the VITAMINS Trial

<table>
<tr><td colspan="2">Secondary outcomes</td></tr>
<tr><td>28-day mortality</td><td>The proportion of patients who had died by 28 days after randomization</td></tr>
<tr><td>90-day mortality</td><td>The proportion of patients who had died by 90 days after randomization</td></tr>
<tr><td>ICU mortality</td><td>The proportion of patients who had died to ICU discharge</td></tr>
<tr><td>Hospital mortality</td><td>The proportion of patients who had died to hospital discharge</td></tr>
<tr><td>28-day cumulative vasopressor-free days</td><td>The total number of days a patient was alive and not on vasopressor support from randomization to 28 days</td></tr>
<tr><td>28-day mechanical ventilation-free days</td><td>The total number of days a patient was alive and not on mechanical ventilation from randomization to 28 days</td></tr>
<tr><td>28-day renal replacement therapy-free days</td><td>The total number of days a patient was not on renal replacement therapy from randomization to 28 days</td></tr>
<tr><td>Delta SOFA score at day 3</td><td>The change in SOFA score from baseline score measured at randomization to the score at Day 3</td></tr>
<tr><td>28-day ICU free-days</td><td>The number of days alive and free of ICU from randomization to 90 days</td></tr>
<tr><td>Hospital length of stay</td><td>The total duration of stay in the hospital for the first 90 days after randomization</td></tr>
<tr><td colspan="2">Prespecified exploratory outcomes</td></tr>
<tr><td>Acute kidney injury</td><td>Maximum stage of AKI in the first 7 days</td></tr>
<tr><td>Vasopressor dose over 10 days</td><td>The sum of norepinephrine dose and the converted dose of epinephrine and vasopressin. The following conversion scale was adopted from previous critical care research[11].
<table>
<tr><th>Drug</th><th>Dose</th><th>Norepinephrine equivalent</th></tr>
<tr><td>Epinephrine</td><td>0.1 µg/kg/min</td><td>0.1 µg/kg/min</td></tr>
<tr><td>Vasopressin</td><td>0.04 U/min</td><td>0.1 µg/kg/min</td></tr>
</table>
</td></tr>
<tr><td colspan="2">Feasibility outcomes</td></tr>
<tr><td>Number of patients screened</td><td>The number of patients who met eligibility criteria</td></tr>
<tr><td>Reasons for exclusion</td><td>The number of instances of exclusion criteria.</td></tr>
<tr><td>Randomized to the screened patient ratio</td><td>The ratio of patients who had been randomized to that of patients who had been screened.</td></tr>
<tr><td>Monthly recruitment rate</td><td>The monthly randomized to screened patient ratio per active site.</td></tr>
<tr><td>Time to the first dose of the main study drug</td><td>Time from randomization to the first dose of the main study drug. The main drug was vitamin C in the Vitamins group and hydrocortisone in the Control group.</td></tr>
<tr><td>Compliance with drug administration protocol</td><td>The number of protocol deviations</td></tr>
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eAppendix 4. Methods: Post-Hoc Analysis

A. Death or vasopressor re-dependence by day 7.

The number and the proportion of patients who died or had vasopressors resumed before the end of day 7 after the index shock resolution were reported.

B. Duration of vasopressors

Multivariable sensitivity analysis was conducted for the duration of vasopressors to account for baseline imbalance (APACHE III, lactate levels, milrinone usage and white cell count) with results reported as Hazards Ratios (95% CI) comparing the probability of being liberated from vasopressors between the 2 groups. Proportional hazards assumptions were confirmed by determining the linearity of an interaction between treatment and the logarithm of time to vasopressor liberation. Time to event graphs were plotted using STATA Release 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.)

C. Changes in SOFA score over the first 7 days

Changes in SOFA score over the first 7 days were analysed using mixed linear modelling fitting main effects for treatment and time and an interaction between treatment and time to determine if the change in SOFA scores behaved differently between groups over time. Patients were treated as a random effect. Results are presented as box plots using STATA Release 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.)

D. Subgroup analysis

Subgroup analysis for the primary outcome was performed on 4 subgroups determined from baseline variables, namely hydrocortisone administration prior to enrolment, lactate level, vasopressor dose and SOFA score, with the later 3 subgroups created by splitting each variable at the median level to create high and low subgroups. The analysis was performed using quantile regression with an interaction between treatment and subgroup to determine heterogeneity. R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) was used to create the forest plot.

E. Key outcomes stratified by trial sites

The number of enrolled patients, their primary outcome and mortality at each site were reported.

eAppendix 5. Results: Other Feasibility Outcomes and Compliance With the Intervention Protocol

A. Other feasibility outcomes

Randomized to screened patient ratio	1:3.6
Monthly recruitment rate, mean (SD), patients/month per active site	2.2 (1.0)
Time to the first dose of the main study drug, median (IQR), h	1.2 (0.5 to 2.6)

B. Randomization of an ineligible patient

Intervention	Control
0/107	1/104 (1.0%)

C. Failure to comply with the intervention protocol

Study drug	Intervention (n = 107)	Control (n = 104)
Vitamin C, missed or lower dose administered	4 (3.7%)	–
Vitamin C, extra dose administered	21[a] (19.6%)	–
Hydrocortisone, missed or lower dose administered	4 (3.7%)	7 (6.7%)
Hydrocortisone, extra dose administered	7 (6.5%)	4 (3.8%)
Thiamine, missed or lower dose administered	2 (1.9%)	–
Thiamine, extra dose administered	15[b] (14.0%)	–

a. Shock resolution was not recognized in 19/21 (90.5%) patients, which resulted in an extended duration of the intervention.

b. Shock resolution was not recognized in 12/15 (80.0%) patients, which resulted in an extended duration of the intervention.

D. Intravenous thiamine administered to patients in the Control group.

Patients in the control group could receive intravenous thiamine if clinically indicated at the discretion of the attending ICU clinician. As such, the following reports are not a deviation from the study protocol.

Number of patients	8/104 (7.7%)
Dose of thiamine administered, median (IQR)	300 mg/day (275, 300)
Duration of thiamine administered, median (IQR)	2.0 days (1.8, 3.0)

eAppendix 6. Results: Adverse Events, Serious Adverse Events, and Suspected Unexpected Serious Adverse Reactions

A. Adverse events

Event	Intervention (2 events in 2 patients)	Control (1 event in 1 patient)
Fluid overload	1 event in 1 patient	0
Gastrointestinal bleeding	0	1 event in 1 patient
Hyperglycemia	1 event in 1 patient	0

B. Serious adverse events

None reported.

C. Suspected unexpected serious adverse reactions

None reported.

eAppendix 7. Results: Post-Hoc Analysis

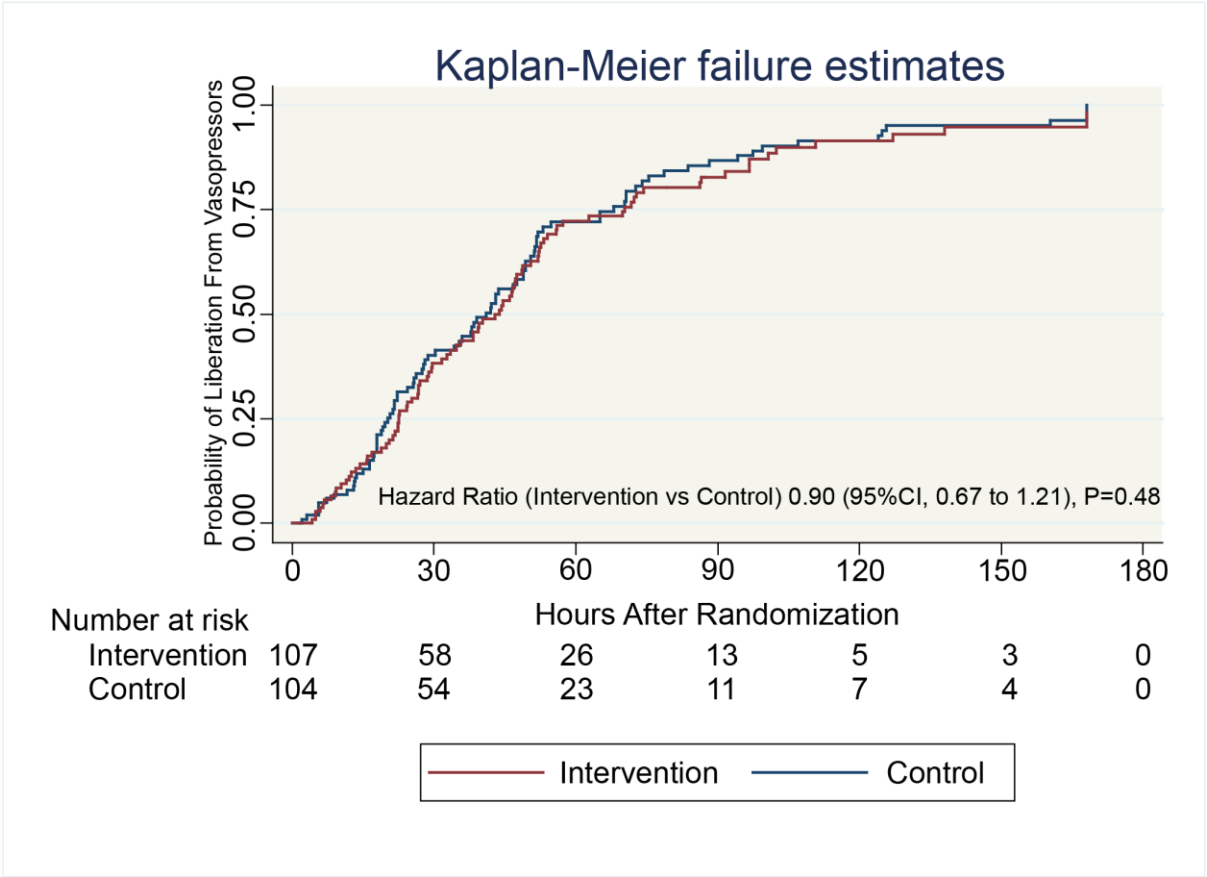
A. Death or vasopressor re-dependence by day 7.

Outcome	Intervention, n/N (%)	Control, n/N (%)	P value
Death by day 7	17/107 (15.9)	15/104 (14.4)	0.77
Resumption of vasopressor dependence after the index shock resolution by day 7	30/ 90 (33.3)	24/ 90 (26.7)	0.33

One patient from each group died between the index cessation of vasopressors and day 7.

B. Duration of vasopressors

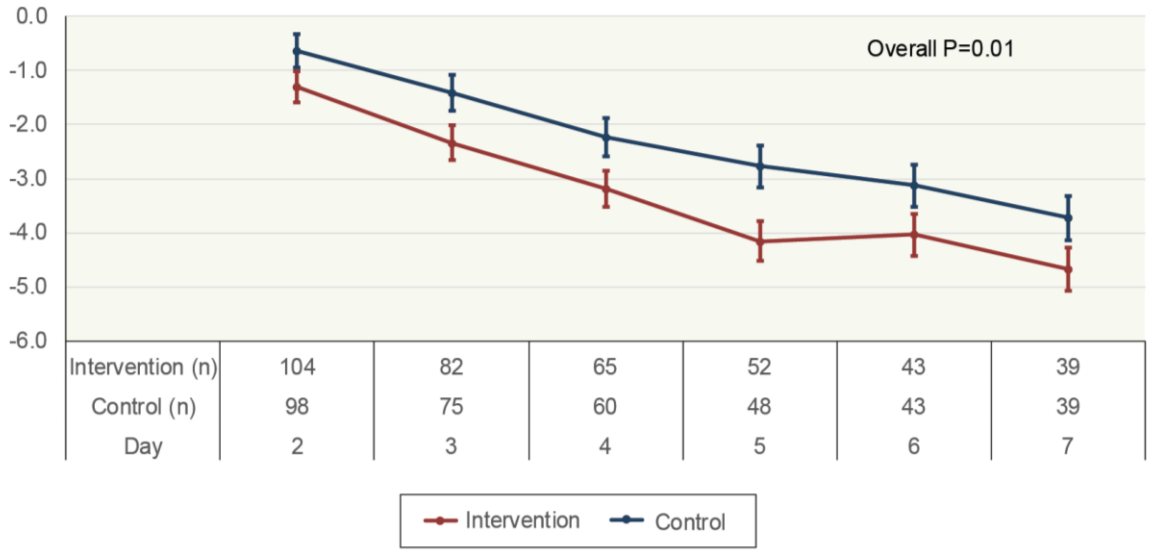
Kaplan-Meier curves for the duration of vasopressors by the randomization group. Proportionality assumptions were met (P = 0.78 for interaction of treatment group with logarithm of time).



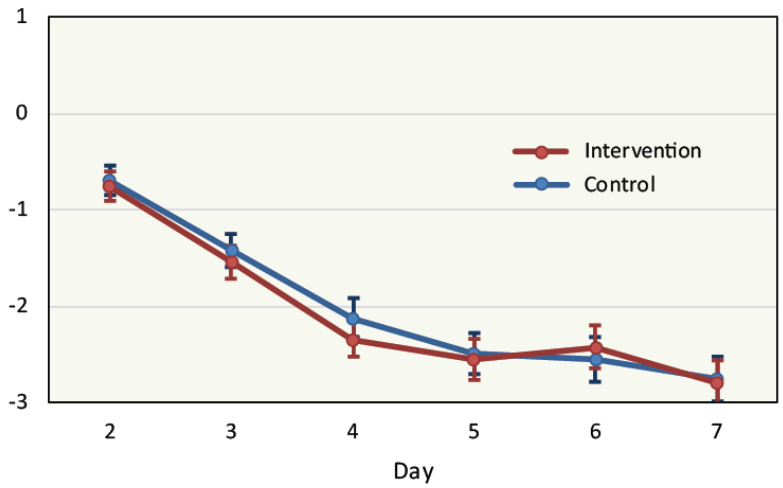
After adjustment for baseline imbalance (APACHE III, lactate levels, milrinone usage and white cell count), there was no significant difference in the probability of being liberated from vasopressors (Hazard ratio intervention vs. control 0.85 [95% CI, 0.63 to 1.15], P = 0.29).

C. Changes in SOFA score over the first 7 days

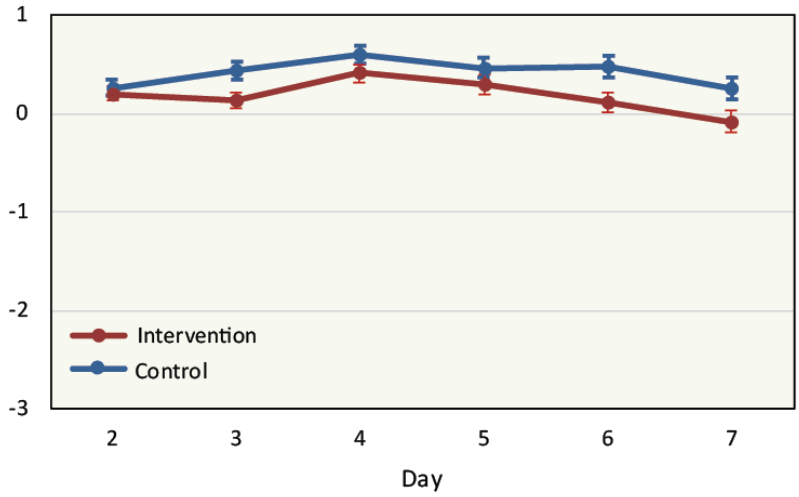
1. Change in Total SOFA score from baseline



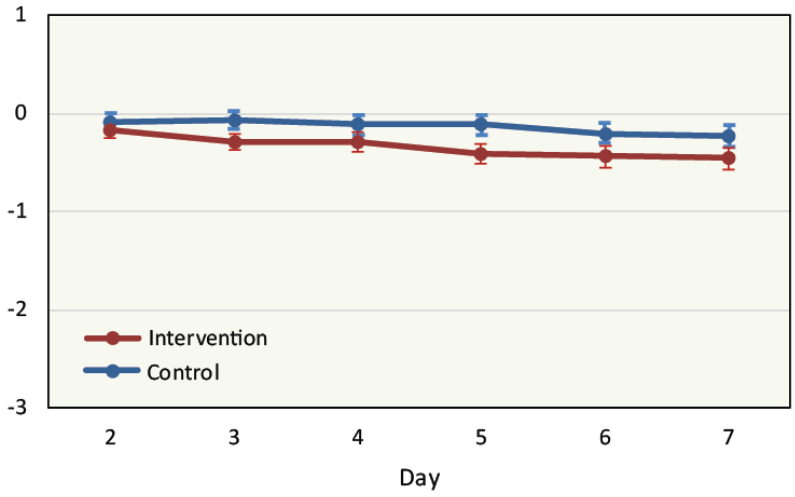
2. Change in Cardiovascular SOFA score from baseline



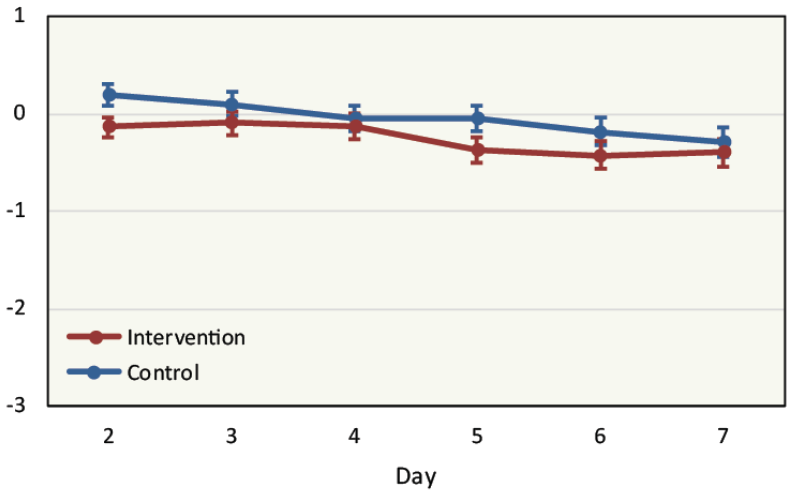
3. Change in Coagulation SOFA score from baseline



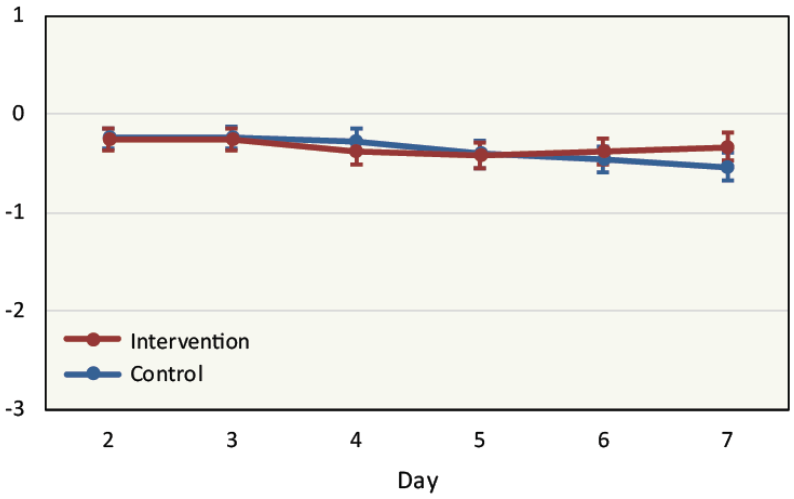
4. Change in Liver SOFA score from baseline



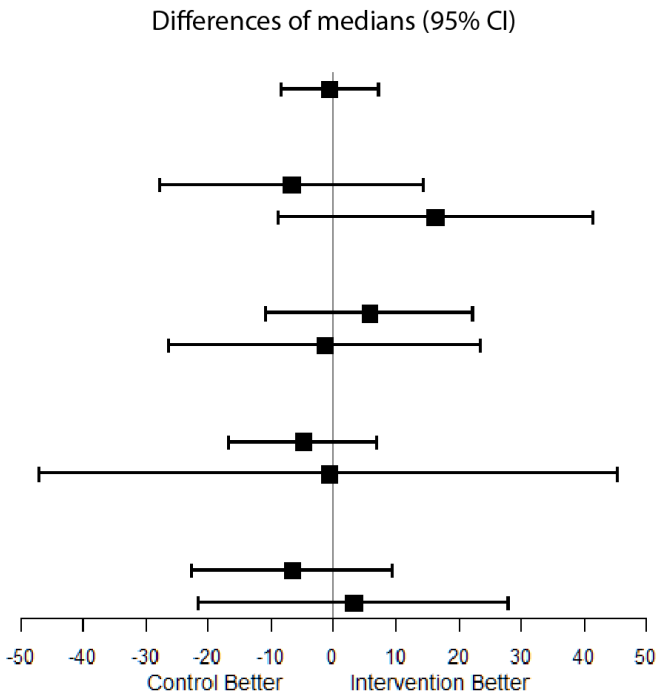
5. Change in Renal SOFA score from baseline



6. Change in Respiratory SOFA score from baseline



D. Subgroup analysis for hours alive and free of vasopressors



Subgroup	No. of Patients (%)	Intervention (h)	Control (h)	Interaction P value
Overall	211 (100)	122.1 (76.3 to 145.4)	124.6 (82.1 to 147.0)	
Lactate (mmol/l)				0.71
> 3.7	104 (49.3)	126.1 (95.8 to 146.6)	132.5 (106.4 to 149.2)	
<= 3.7	107 (50.7)	120.9 (57.3 to 143.7)	103.9 (0 to 137.8)	
SOFA score				0.71
> 8	103 (48.8)	138.5 (114.8 to 151.2)	132.7 (102.9 to 148.3)	
<= 8	108 (51.2)	115.3 (0 to 133.2)	116.6 (0 to 142.4)	
Vasopressor dose (µg/kg/min)				0.83
> 0.18	106 (50.2)	141.0 (120.9 to 152.2)	145.8 (119.1 to 150.1)	
<= 0.18	105 (49.8)	96.1 (0 to 121.6)	97.6 (0 to 133.7)	
Hydrocortisone prior to enrolment				0.50
No	127 (60.2)	123.5 (97.7 to 145.6)	130.1 (97.3 to 150.0)	
Yes	84 (39.8)	119.3 (65.7 to 142.6)	116.0 (44.0 to 140.5)	

E. Key outcomes stratified by trial site

1. Hours alive and free of vasopressors

Site	Intervention		Control		P value
	No.	Median (IQR)	No.	Median (IQR)	
AUS 1	20	138 (96 to 148)	21	144 (119 to 149)	0.47
AUS 2	5	146 (114 to 146)	4	109 (97 to 131)	0.18
AUS 3	17	119 (30 to 132)	16	116 (39 to 142)	0.55
AUS 4	7	134 (123 to 155)	8	60 (0 to 150)	0.05
AUS 5	11	95 (0 to 130)	10	121 (100 to 140)	0.10
AUS 6	14	131 (112 to 156)	13	124 (94 to 150)	0.58
AUS 7	3	121 (116 to 141)	1	118 (118 to 118)	1.00
AUS 8	1	128 (128 to 128)	2	130 (130 to 130)	0.54
NZL 1	23	116 (0 to 151)	23	126 (42 to 147)	0.88
BRA 1	6	117 (2 to 121)	6	90 (0 to 148)	0.94

2. 28-day mortality stratified by site

Site	Intervention n/N (%)	Control n/N (%)	P value
AUS 1	3/19 (15.8)	2/21 (9.5)	0.65
AUS 2	0/ 5 (0)	1/ 9 (25.0)	0.44
AUS 3	4/17 (23.5)	1/16 (6.3)	0.34
AUS 4	0/ 7 (0)	4/ 8 (50.0)	0.08
AUS 5	3/11 (27.3)	1/10 (10.0)	0.59
AUS 6	2/14 (14.3)	3/13 (23.1)	0.65
AUS 7	0/ 3 (0)	0/ 1 (0)	1.00
AUS 8	1/ 1 (100)	0/ 2 (0)	0.33
NZL 1	8/23 (34.8)	6/22 (27.3)	0.59
BRA 1	3/ 6 (50.0)	3/ 6 (50.0)	1.00

eReferences

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