in vivo *37*: 1236-1245 (2023)
doi:10.21873/invivo.13200

Efficacy of Ascorbic Acid, Thiamine, and Hydrocortisone Combination Therapy: Meta-analysis of Randomized Controlled Trials

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Abstract. *Background/Aim: Sepsis is a life-threatening biological condition that induces systemic tissue and organ dysfunction and confers a high mortality risk. Although the use of hydrocortisone in combination with ascorbic acid and thiamine (HAT therapy) significantly reduced mortality from sepsis or septic shock in a previous study, it did not improve mortality in subsequent randomized controlled trials (RCTs). Therefore, no definitive conclusion has been established on the benefits of HAT therapy for sepsis or septic shock. We performed a meta-analysis to assess the treatment outcomes of HAT therapy in patients with sepsis or septic shock. Patients and Methods: We searched databases (PubMed/MEDLINE, Embase, Scopus and Cochrane Library) for RCTs using the terms "ascorbic acid", "thiamine", "sepsis", "septic shock", and "RCT". The primary outcome of this meta-analysis was the mortality rate, and the secondary outcomes were the incidence of new-onset acute renal injury (AKI), intensive care unit (ICU) length of stay (ICU-LOS), change in the Sequential Organ Failure Assessment (SOFA) score within 72 hours, and duration of vasopressor use. Results: Nine RCTs were identified and included in the outcome evaluation. HAT therapy did not improve the 28-day and ICU mortality, new-onset AKI, ICU-LOS, or SOFA scores. However, HAT therapy significantly shortened the duration of vasopressor use. Conclusion: HAT therapy did not improve mortality, the SOFA score, renal injury, or ICU-LOS. Further studies are needed to confirm whether it shortens the duration of vasopressor use.*

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Key Words: Sepsis, HAT therapy, mortality, SOFA.

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Sepsis is recognized as a life-threatening biological condition that induces systemic tissue and organ dysfunction and is associated with 5.3 million annual deaths worldwide (1). Standardized management and care for septic shock has improved sepsis-related mortality from 40% to approximately 20% (2), but the overall disease burden remains high.

Ascorbic acid helps repair vascular endothelial cells that are damaged by inflammatory mediators and oxidative stress and is therefore administered to patients with sepsis (3). Despite receiving standard enteral and parenteral ascorbic acid supplementation, 88% of patients with sepsis have hypovitaminosis C. Moreover, 38% of these patients have severe ascorbic acid deficiency (<11 μmol/l) (4), which is associated with impaired catecholamine synthesis as well as an attenuated vasomotor response to α-adrenergic stimulation (5, 6) and may increase the mortality risk (3).

Thiamine inhibits the metabolism of ascorbic acid to oxalic acid, which is a reducing substance. One third of all patients with sepsis have thiamine deficiency (7, 8). Although thiamine deficiency is not associated with mortality of these patients (7), thiamine supplementation improves lactate clearance (9).

Hydrocortisone facilitates expression of sodium-dependent ascorbate cotransporter (SVCT) that increases cellular uptake of ascorbic acid (10), and thus plays an essential role in enhancing the function of ascorbic acid. Furthermore, approximately 60% of patients with severe sepsis have adrenal

insufficiency and critical illness-related corticosteroid insufficiency (CIRCI), which is due to decreased glucocorticoid receptor activity (11, 12). Because both ascorbic acid and thiamine deficiencies and CIRCI occur frequently in patients with severe sepsis, the use of hydrocortisone in combination with ascorbic acid and thiamine (HAT therapy) constitutes a rational strategy for the treatment of patients with sepsis. In a retrospective, observational study, Marik *et al.* reported that HAT therapy was associated with significantly lower mortality (13). Subsequently, several randomized controlled trials (RCTs) of HAT therapy have been conducted. HAT therapy led to an improvement in the Sequential Organ Failure Assessment (SOFA) score in the HYVCTTSSS trial (14), but not in the ACTS and ORANGESs trials (15, 16). There is currently no consensus on the benefit of HAT therapy in the treatment of sepsis or septic shock. We performed a meta-analysis to elucidate whether HAT therapy is effective in the treatment of sepsis or septic shock.

Patients and Methods

Study identification and eligibility criteria. The present meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. We searched the available articles published between January 1940 and May 2022 by using the PubMed/MEDLINE, Embase, Scopus and Cochrane Library. Google Scholar was used as an additional source. Search terms used to identify RCTs on HAT therapy included "ascorbic acid", "thiamine", "sepsis", "septic shock", and "randomized controlled trial (RCT)". We identified RCTs of HAT therapy or hydrocortisone monotherapy for sepsis or septic shock. The exclusion criteria were as follows: 1) duplicate publications; 2) research protocols and meta-analyses; and 3) studies with inadequate data for meta-analysis.

Data extraction. Two reviewers independently screened the titles and abstracts of all identified studies for eligibility. The information extracted from the abstracts and full-texts included patient characteristics, publication year, study setting, study outcome, and interventional methods. The endpoints of the extracted studies included 28-day mortality rate, intensive care unit (ICU) mortality rate, incidence of new-onset acute kidney injury (AKI), ICU length of stay (ICU-LOS), change in the SOFA score within 72 h, and duration of vasopressor use. Mean scores, standard deviations (SD), and sample sizes were extracted from the included studies.

Outcomes and data analysis. The primary outcome of this meta-analysis was the mortality rate; the secondary outcomes were incidence of new-onset AKI, ICU-LOS, change in the SOFA score within 72 h, and duration of vasopressor use. After collecting relevant data from the included studies in accordance with the requirements for a meta-analysis, statistical analysis was conducted using the meta-analysis software Review Manager Version 5.4 (Cochrane Collaboration, Oxford, UK). The results of the primary and secondary outcome analyses, along with the respective 95% confidence intervals, were presented in forest plots developed using fixed-effects model (when including <4 studies) and random-effects model (when including ≥4 studies). Statistical heterogeneity was evaluated using the I2 statistic. Relevant statistical heterogeneity was considered for studies with I^2>50% and p<0.05.

Risk of bias assessment. Using the Cochrane risk-of-bias tool (ToB 2.0), two reviewers independently assessed the risk of bias according to the following criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Each quality domain was reported as having a "low" risk of bias, or "some concerns". RCTs rated as having "high" risk of bias were excluded.

Results

Selection of included studies. We identified 1,375 articles by using the following search strategies: PubMed (n=85), Cochrane Library (n=42), Scopus (n=82), EMBASE (n=172), and Google Scholar (n=172). After excluding duplicates, 86 articles remained; among them, 41 articles on research protocols and meta-analyses were excluded, and another 36 articles were excluded due to the inadequacy of data for this meta-analysis (n=35) and/or the presence of high risk of bias (n=1). Subsequently, 9 articles met the selection criteria. Figure 1 depicts a flow diagram of the screening strategy for study inclusion in this meta-analysis.

Study characteristics. Nine RCTs were identified and included in the outcome evaluation (14-22). The basic characteristics of these studies are presented in Table I. The studies were conducted in eight countries: the USA (15, 16, 20), India (19, 21), China (14), Australia (18), New Zealand (18), Brazil (18), Egypt (17), and Iran (22). Five studies were conducted at a single center, and four studies were conducted at multiple centers. The mean or median age was <65 years and ≥65 years in five and four studies, respectively. The median proportion of male participants was 56.4% (range=47-72.4%). The interventional regimens were similar in each RCT (1.5 g ascorbic acid every 6 h, 100-200 mg thiamine every 6-12 h, and 50 mg hydrocortisone every 6 h).

Mortality rate after HAT therapy. We evaluated the mortality rates after HAT therapy as the primary outcome of the meta-analysis (Figure 2). The 28-day mortality rate was reported in three RCTs. HAT therapy did not significantly reduce the 28-day mortality compared to control (OR=0.88, 95%CI=0.56-1.39, p=0.59, I^2=0%). Likewise, the ICU mortality rate, reported in five studies, did not show significant difference between the intervention and control groups (OR=0.97, 95%CI=0.73-1.30, p=0.86, I^2=0%). No heterogeneity was found in either of the meta-analyses.

Change in SOFA score, incidence of new onset AKI, ICU-LOS, and duration of vasopressor use after HAT therapy. We

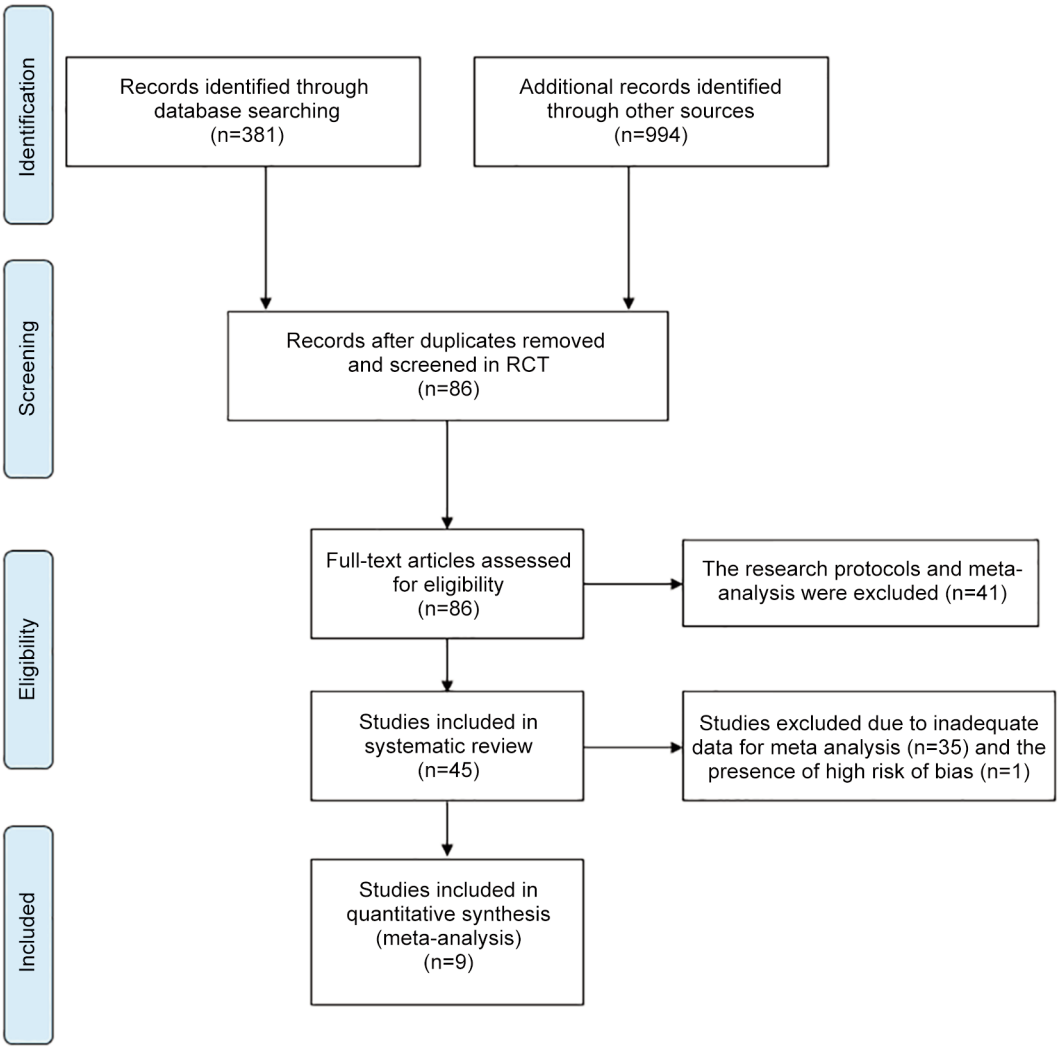

Figure 1. *Flow diagram of the screening of the studies for inclusion in the meta-analysis.*

evaluated the change in the SOFA score within 72 h, incidence of new-onset AKI, ICU-LOS, and duration of vasopressor use as secondary outcomes. The change in the SOFA score and incidence of new-onset AKI, reported in five RCTs, were not significantly different between the intervention and control groups (mean difference of SOFA score: −0.04, 95%CI=−1.31-1.22, p=0.95, I^2=85%; incidence of AKI: OR=1.10, 95%CI=0.77-1.57, p=0.60, I^2=0%; Figure 3A and Figure 4). The change in the SOFA score showed strong heterogeneity; however, no heterogeneity was found in the incidence of new-onset AKI. A sub-analysis of the change in the SOFA score between single-center and multicenter studies showed high heterogeneity in both groups (mean difference: −0.94, 95%CI=−1.45-−0.42, p=0.0004, I^2=89% for single-center studies; mean difference: 0.15, 95% CI=−0.66-0.97, p=0.71, I^2=75% for multicenter studies; Figure 3B and C). In single-center studies, the SOFA score was significantly improved.

Two studies were included in the analysis of ICU-LOS. There were no significant differences in ICU-LOS between the intervention and control groups (mean difference: 0.37, 95%CI=−0.89-1.63, p=0.57, I^2=57%; Figure 5), with moderate heterogeneity in this analysis. The duration of vasopressor use was reported in three RCTs. HAT therapy significantly shortened the duration of vasopressor use (mean difference: −19.51, 95%CI=−26.13-−12.88, p<0.00001; I^2=42%; Figure 6), with moderate heterogeneity in this analysis. The risk of bias was low in all studies, as summarized according to the Cochrane literature quality evaluation method in each figure.

Table I. *Characteristics of the studies and patients.*

Author	Design	Country	Baseline mean age, years (SD)	Study, n (IG/CG)	Sex male (%)	Initiation of treatment	SOFA score baseline	Intervention regimen
Hussein *et al.* 2021 (17)	RCT/Single center	Egypt	IG: 65.81(17.02) CG: 61.60 (18.22)	47/47	IG: 25 (53.2) CG: 26 (55.3)	N/A	IG: 8.79±2.30, CG: 8.72±2.08	VC: 1.5 g q6h IV, Thi: 200 mg q12h IV up to 4 days or ICU discharge and HC: 50 mg q6h IV up to 7 days or ICU discharge
Fujii *et al.* 2020 (18)	RCT/Multi center	Australia, New Zealand, and Brazil	IG: 61.9 (15.9) CG: 61.6 (13.9)	107/104	IG:68 (63.6) CG: 65 (62.5)	N/A	IG: 8.6 (2.7), CG: 8.4 (2.7)	VC: 1.5 g q6h IV, Thi: 200 mg q12h IV and HC: 50 mg q6h IV up to 10 days or shock withdrawal
Wani *et al.* 2020 (19)	RCT/Single center	North India	IG: 65, CG:70 (median)	50/50	IG: 28 (56), CG: 31 (62)	Within few hours, in all cases in <24h	IG: 9.22±3.54, CG: 9.36±3.66	VC: 1.5 g q6h IV and Thi: 200 mg q12h IV for 4 days or until discharge from the hospital, HC: 50 mg q6h for 7 days or until ICU discharge followed by a taper over 3 days
Chang *et al.* 2020 (14)	RCT/Single center	China	IG: 59.5 (15.0) CG: 63.7 (12.8)	40/40	IG 22 (57.5) CG: 21 (52.5)	N/A	IG: 9.6±4.5, CG: 10.1±4.0	VC: 1.5 g q6h for 4 days, Thi: 200 mg q12h for 7 days, HC: 50 mg q6h for 4 days
Sevransky *et al.* 2021 (20)	RCT/Multi center	USA	IG: 62, CG: 61 (median)	252/249	IG: 139 (55.2) CG: 134 (53.8)	IG: 15 (8-22), CG: 14 (8-20) (median)	IG: 9 (7-12), CG: 9 (6-11) (median)	VC: 1.5 g q6h, Thi: 100 mg q6h, HC: 50 mg q6h for 4 days or until discharge from the ICU or death
Mohamed *et al.* 2020 (21)	RCT/Single center	South India	IG: 58.69 (14.89) CG: 59.37 (15.01)	45/43	IG: 31 (69) CG: 32 (74)	within six hours of onset of sepsis	IG: 11.22±2.99, CG: 10.89±3.82	VC: 1.5 g q6h IV, Thi: 200 mg q12h IV and HC: 50 mg q6h IV up to 4 days
Jamshidi *et al.* 2021 (22)	RCT/Single center	Iran	IG: 45.4 (19.8) CG: 45.4 (15.8)	29/29	IG: 21 (72.4) CG: 26 (89.7)	N/A	IG: 4.5±1.4, CG: 5.3±1.6	VC: 1.5 g q6h IV, Thi: 200 mg q12h IV and HC:50 mg q6h IV up to 4 days
Iglesias *et al.* 2020 (16)	RCT/Multi center	USA	IG: 70 (12) CG: 67 (14)	68/69	IG: 32 (47) CG: 27 (39)	N/A	IG: 8.3±3.0, CG: 7.9±3.5	VC: 1.5 g q6h, Thi: 200 mg q12h, HC: 50 mg q6h up to 4 days
Moskowitz et al. 2020 (15)	RCT/Multi center	USA	IG: 68.9 (15.0) CG: 67.7 (13.9)	101/99	IG: 57 (56.4) CG: 54 (54.6)	IG: 2.2 (1.7-3.0), CG: 2.0 (1.5-2.7) (median)	IG: 9.1 (3.5), CG: 9.2 (3.2)	VC: 1.5 g q6h, Thi: 100 mg q6h, HC: 50 mg q6h for 4 days or until discharge from the ICU

CG: Control group; HC: hydrocortisone; ICU: intensive care unit; IG: intervention group; N/A: not applicable; Thi: thiamine; VC: ascorbic acid.

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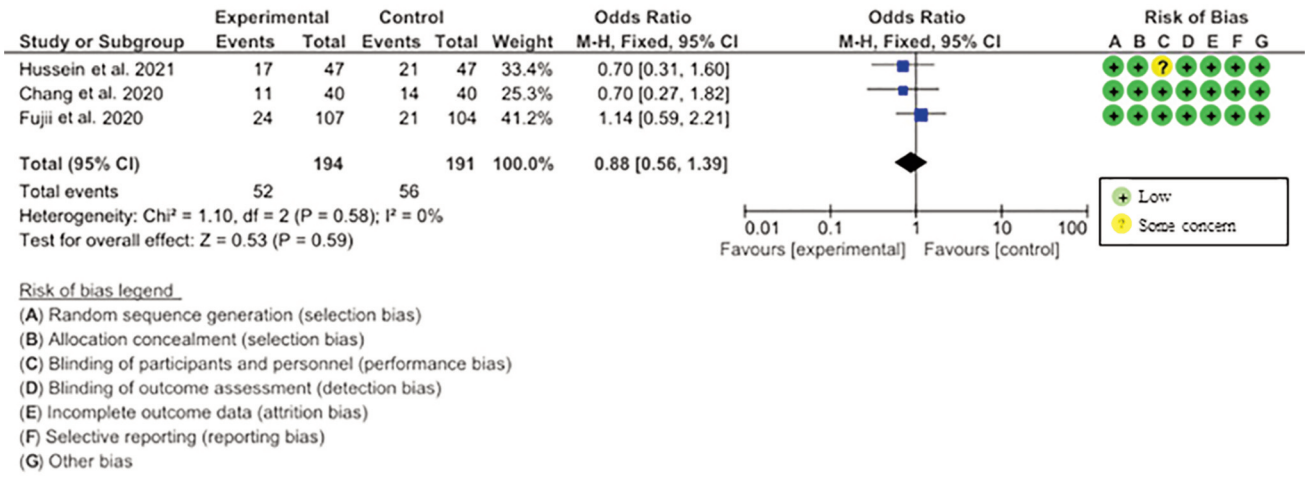

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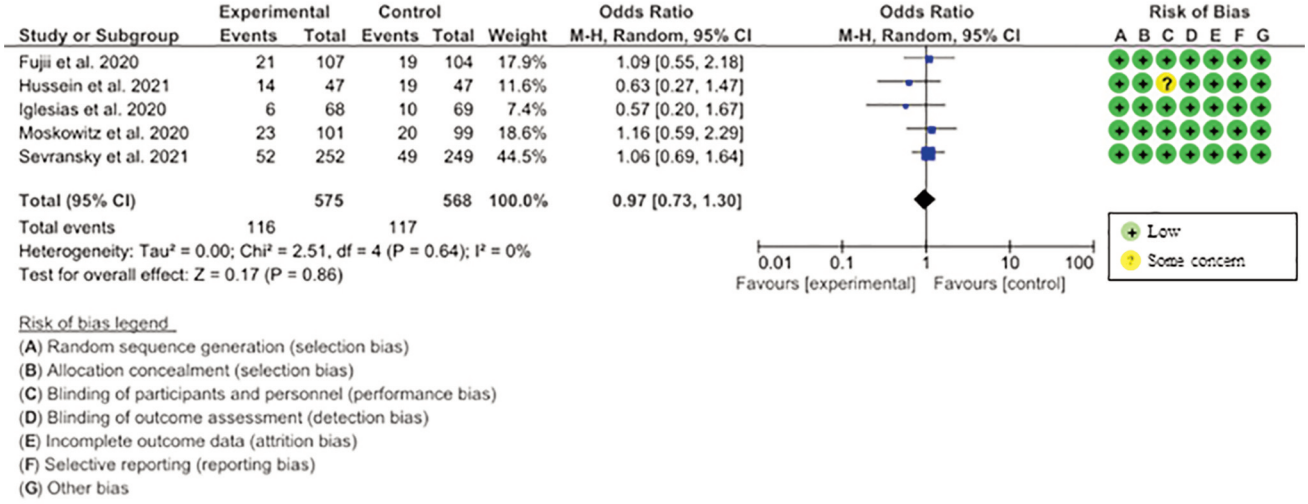

Figure 2. *Forest plot of mortality. HAT therapy did not significantly reduce the 28-day mortality (A: OR=0.88, 95%CI=0.56-1.39, p=0.59, I^2=0%) and ICU mortality (B: OR=0.97, 95%CI=0.73-1.30, p=0.86, I^2=0%). There was no heterogeneity in these analyses. Risk of bias was assessed in seven domains: (A) random sequence generation; (B) allocation concealment; (C) blinding of participants and personnel; (D) blinding of outcome assessment; (E) incomplete outcome data; (F) selective reporting; and (G) other bias. Risk of bias was low in all studies.*

Discussion

We assessed the effectiveness of HAT therapy in patients with sepsis and septic shock. A similar meta-analysis has been reported (23), but the previous meta-analysis did not exclude RCTs with high risk of bias in each quality domain. We included the nine studies that contained low risk of bias in the present analysis. The results suggest that HAT therapy reduced neither the 28-day nor ICU mortality rates or the incidence of AKI events. In addition, the SOFA score within 72 h did not improve with HAT therapy. The duration of vasopressor use, however, was shortened with HAT therapy compared with the duration in the control groups.

Both meta-analyses results for 28-day and ICU mortality rates showed small heterogeneity; therefore, the conclusion that HAT therapy does not improve survival of patients with sepsis and sepsis shock was reliable. Although the 28-day mortality rate did not significantly differ in our analysis, previous reports indicated that HAT therapy reduced the procalcitonin (PCT) level (14, 17). Since high-dose ascorbic acid decreases the PCT level (24), the anti-inflammatory effects of ascorbic acid in HAT therapy might improve

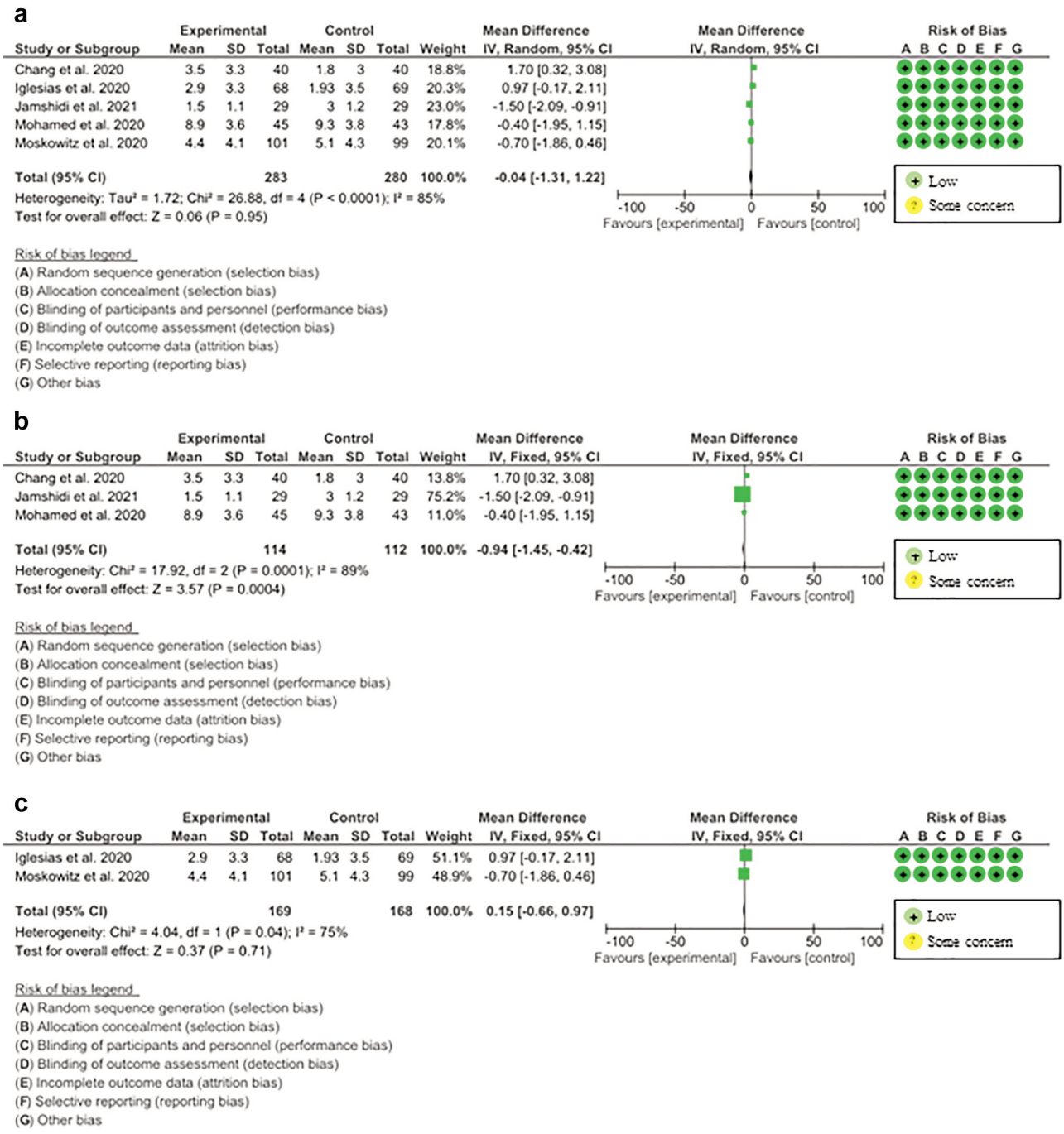

Figure 3. *Forest plot of the change in the Sequential Organ Failure Assessment (SOFA) score. HAT therapy did not significantly improve the SOFA score [(A) mean difference: −0.04, 95%CI=−1.31-1.22, p=0.95, I^2=85%], and heterogeneity was high in this analysis. In a sub-analysis, the SOFA scores of single-center studies (B) and multicenter studies (C) were not improved by HAT therapy [(B) mean difference: –0.94, 95%CI=–1.45-–0.42, p=0.0004, I^2=89%, (C) mean difference: 0.15, 95%CI=–0.66-0.97, p=0.71, I^2=75%]. These RCTs were assessed by seven domains: (A) random sequence generation; (B) allocation concealment; (C) blinding of participants and personnel; (D) blinding of outcome assessment; (E) incomplete outcome data; (F) selective reporting; and (G) other bias. Risk of bias was low in all studies.*

survival in some patients with sepsis. Interestingly, the CITRIS-ALI study showed an improvement in the 28-day mortality rate in sepsis patients with acute respiratory distress syndrome (ARDS) (25) and that high-dose ascorbic acid might control inflammatory reactions in the acute phase. Furthermore, high-dose thiamine supplementation decreased

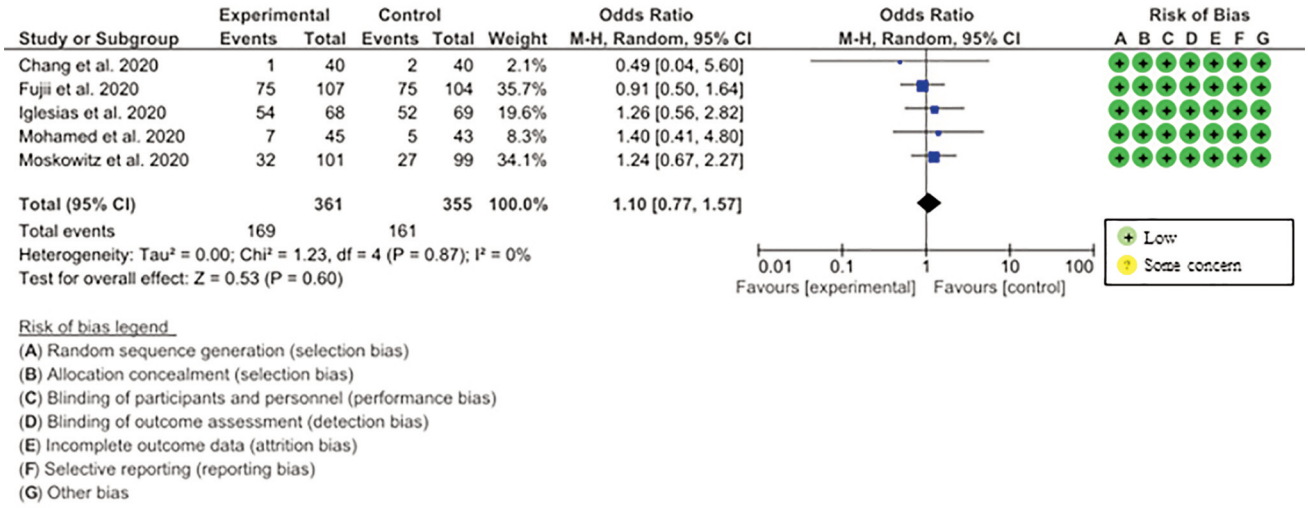

Figure 4. *Forest plot of new-onset acute renal injury (AKI). HAT therapy did not significantly improve the incidence of new-onset AKI in the intervention and control groups (OR=1.10, 95%CI=0.77-1.57, p=0.60, I^2=0%). These RCTs were assessed in seven domains: (A) random sequence generation, (B) allocation concealment, (C) blinding of participants and personnel, (D) blinding of outcome assessment, (E) incomplete outcome data, (F) selective reporting, and (G) other bias. The risk of bias was low in all studies.*

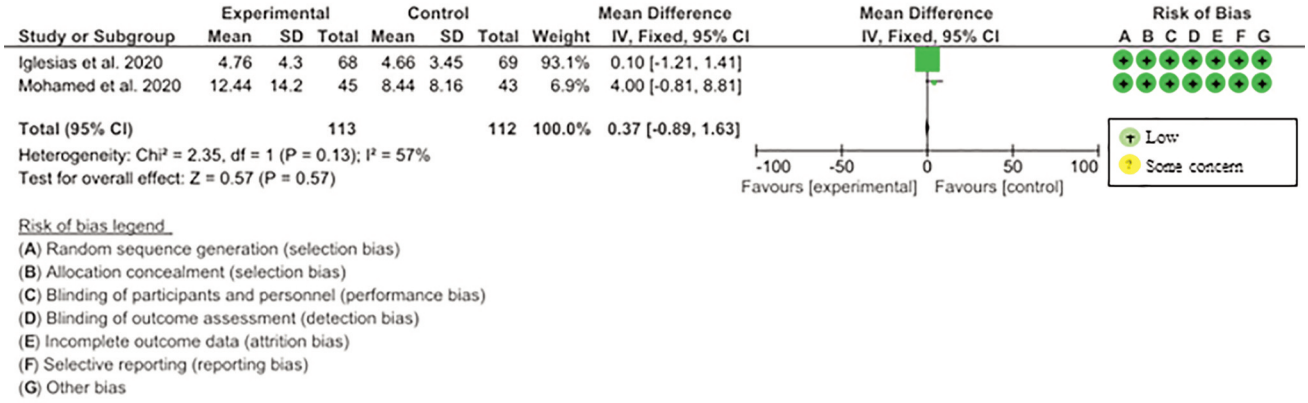

Figure 5. *Forest plot of intensive care unit-length of stay (ICU-LOS). ICU-LOS was not significantly shortened after HAT therapy (mean difference: 0.37, 95%CI=−0.89-1.63, p=0.57, I^2=57%). These RCTs were assessed in seven domains: (A) random sequence generation, (B) allocation concealment, (C) blinding of participants and personnel, (D) blinding of outcome assessment, (E) incomplete outcome data, (F) selective reporting, and (G) other bias. The risk of bias was low in all studies.*

the 28-day mortality in a retrospective study (9). However, high doses of ascorbic acid and thiamine were not evaluated in our meta-analysis, and mortality in ARDS patients, specifically, was not assessed. The previous meta-analysis indicated that HAT therapy with high-dose ascorbic acid did not improve the long term mortality (90 days to one year) (26). Although we assessed a shorter term mortality compared to the previous meta-analysis, our results also did not show evidence of improvement by HAT therapy.

The guideline for the Management of sepsis and septic shock in 2018 (27, 28) recommended the hour-1 bundle to encourage early intervention, and that the timing of HAT therapy initiation may affect prognosis. Nonetheless, five of the studies included in our meta-analysis did not report the timing of HAT therapy initiation (14, 16, 17, 20, 22). It is unclear whether the timing of HAT therapy initiation affected our findings, or if other confounding factors, such as treatment strategies or circulatory management, might have affected the outcomes.

Approximately 40% of patients with sepsis require renal replacement therapy (RRT) (29), therefore, a prophylactic strategy for AKI in patients with sepsis is needed. A retrospective study suggested that HAT therapy reduced AKI events that require RRT (13); yet, the preventive effect of

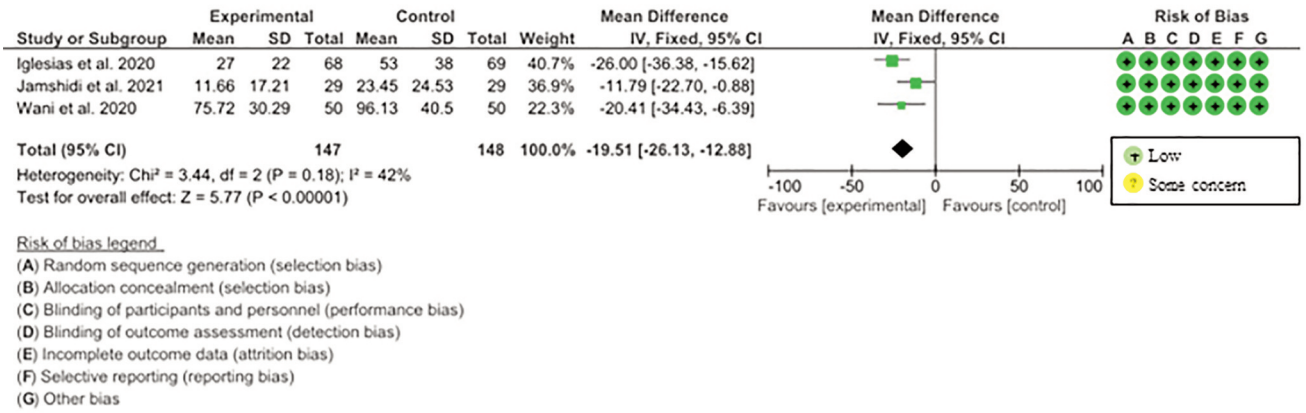

Figure 6. *Forest plot of the duration of vasopressor use. The duration of vasopressor use was significantly shortened after HAT therapy (mean difference: −19.51, 95%CI=−26.13-−12.88, p<0.00001, I^2=42%), and heterogeneity was moderate in this analysis. These RCTs were assessed in seven domains: (A) random sequence generation, (B) allocation concealment, (C) blinding of participants and personnel, (D) blinding of outcome assessment, (E) incomplete outcome data, (F) selective reporting, and (G) other bias. The risk of bias was low in all studies.*

HAT therapy was small in the RCTs that were included in our meta-analysis. Circulatory management should not be ignored when assessing the preventive effect of HAT therapy on AKI incidence. Although the ViCTOR study suggested that the time to reversal of septic shock tended to be shorter in the HAT therapy group than that in the control group, there was no significant difference in the incidence of new-onset AKI (21). The ORANGES trial showed the same result as the ViCTOR study (16). Furthermore, our meta-analysis results, with moderate heterogeneity, are consistent with those reported in the abovementioned RCTs. Previous RCTs did not determine whether hemodynamic instability due to early termination of vasopressor therapy may have resulted in AKI. Similarly, three RCTs in our analysis did not provide details of fluid therapy; thus, it was unclear whether there was hemodynamic instability following the termination of vasopressor therapy. Overall, it seems premature to determine whether HAT therapy directly shortens the duration of vasopressor use based on available clinical data.

Weight gain in critically ill patients leads to prolonged ICU-LOS, and changes in the body weight depend on various factors, such as comorbidities and fluid status (30). The ORANGES trial evaluated the duration of vasopressor use and the ICU-LOS, where the duration of vasopressor use was shortened by 19 h in the intervention group. Nevertheless, there was no significant difference in the ICU-LOS between the intervention and control groups (16). Our meta-analysis showed the same results as the ORANGES trial with moderate heterogeneity detected among the included studies. Although more RCTs are needed to evaluate fluid management, continuation of sufficient vasopressor support until recovery from shock may contribute to shorter ICU-LOS.

Although SOFA score differed from previous meta-analyses (23, 31), these reports evaluated a mix of changes in the SOFA score within 72 h and 96 h, respectively. To evaluate the severity of sepsis during the acute phase, the current meta-analysis excluded the studies that evaluated the changes in the SOFA score within 96 h. Among the five RCTs included in the SOFA score analysis, one study with a small sample size showed a significant improvement (22). The SOFA score is calculated using the PaO_2/FiO_2, platelet count, bilirubin level, blood pressure, Glasgow Coma Scale score, serum creatinine level, and urinary volume. Therefore, the presence of AKI and ARDS were confounding factors in the present analysis, and AKI incidence did not decrease with HAT therapy. In contrast, the results of CITRIS-ALI trial suggested that high-dose ascorbic acid supplementation improved mortality rates in ARDS patients (25). Our results suggest that HAT therapy does not improve systemic inflammation or organ injury, but there was high heterogeneity among the included studies. Moreover, the appropriate doses of ascorbic acid and the effects on ARDS patients have not been evaluated in meta-analyses to date. Further studies of ARDS patients and the ascorbic acid dose are needed.

Our meta-analysis has several limitations that should be considered when interpreting the findings. First, the change in the SOFA score within 72 h showed high heterogeneity, which was also detected in a subgroup analysis. Second, five of the nine RCTs were single-center studies that had small sample sizes. Although the SOFA score was slightly improved in single-center studies, there might be selection bias. Third, some RCTs had an open-label design, and the possibility that use of steroids may have expedited disease recovery cannot be ruled out. Fourth, the severity of sepsis at onset was not consistent across the studies since the time from onset of sepsis to initiation of treatment was not reported in five included RCTs. Finally, there was no publication bias assessment (*i.e.,* funnel plot, Egger's test, meta-regression)

conducted. Since the Cochrane recommends at least 10 studies for the publication bias analysis (32), we did not perform it to avoid reporting potentially misleading information.

In conclusion, HAT therapy did not improve mortality, the SOFA score, renal injury, or ICU-LOS in patients with sepsis or septic shock. The duration of vasopressor use was shortened in the HAT therapy group, yet further studies are needed to definitively ascertain the clinical significance of shortening vasopressor use with HAT therapy in this patient population.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

TK and TM contributed to the study conception, performed the risk-of-bias analysis, screened all identified studies, assessed the risk of bias, analyzed the data, and drafted the manuscript. MN, TN, and SY contributed to the study design. JKL and KT reviewed and drafted the manuscript.

Acknowledgements

This work was supported by JSPS KAKENHI [grant number 21K06696] and the Research Center for Pathogenesis of Intractable Diseases, Research Institute of Meijo University. The Authors thank Yohei Doi for critical review of the manuscript.

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Received February 7, 2023
Revised February 18, 2023
Accepted February 21, 2023