ASTR

ORIGINAL ARTICLE
pISSN 2288-6575 • eISSN 2288-6796
https://doi.org/10.4174/astr.2021.100.6.356
Annals of Surgical Treatment and Research

Combined hydrocortisone, ascorbic acid, and thiamine therapy for septic shock with complicated intraabdominal infection: before and after cohort study

Yong Oh Kim[1], Kee Sang Yoo[2], Kyoung Won Yoon[2], Hyo Jung Park[3], Chi-Min Park[2]

[1]Department of Emergency Medicine, Dankook University Hospital, Dankook University School of Medicine, Cheonan, Korea
[2]Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[3]Department of Pharmaceutical Services, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Purpose: The aim of this study was to assess the efficacy of intravenous hydrocortisone, ascorbic acid, and thiamine (HAT) combination therapy in complicated intraabdominal infection (cIAI) patients with septic shock.
Methods: This was a single-center, retrospective before-after clinical study comparing clinical outcomes of cIAI patients with septic shock treated with HAT in a surgical intensive care unit (ICU). Delta modified sequential organ failure assessment (mSOFA) scores were evaluated to assess recovery of organ dysfunction. Additional outcomes included procalcitonin level change, daily vasopressor dosage, mean number of days free of mechanical ventilation in 28 days, and renal replacement therapy days.
Results: The delta mSOFA score (ICU admission mSOFA score minus 7th-day mSOFA score) was significantly higher in the HAT group than in the control group on the 7th day (2.30 *vs*. –0.90, P = 0.003). The median 7-day change in procalcitonin score was higher in the control group than in the HAT group (5.94 *vs*. 10.72, P = 0.041). The difference in vasopressor score between the 1st day and the 4th day was significantly higher in the HAT group (17.63 *vs*. 9.91, P = 0.005).
Conclusion: In our study of cIAI in patients with septic shock, administration of HAT therapy may improve the recovery from organ dysfunction.
[Ann Surg Treat Res 2021;100(6):356-363]

Key Words: Ascorbic acid, Hydrocortisone, Intraabdominal infections, Thiamine

INTRODUCTION

Sepsis incidence rate has been found to be up to 535 cases per 100,000 person-years [1]. Its in-hospital mortality remains high at 25%–30% [2]. Intraabdominal infection (IAI) is the second most common cause of infectious mortality in intensive care units (ICUs) [3]. Complicated IAI (cIAI) has a reported mortality rate as high as 30% [4,5]. Source control is considered fundamental to the treatment of most patients with IAI [6,7]. However, it remains the leading cause of death in the ICUs with a huge healthcare cost in spite of major advances in diagnostics and surgical and antimicrobial treatment [8,9]. Additional interventions to improve outcomes of patients with septic shock have been presented. Recently, several studies have reported the outcome of a combination of hydrocortisone, ascorbic acid, and thiamine (HAT) therapy in the treatment of sepsis and septic shock. In one study of septic ICU patients, the combination of HAT has dramatically improved organ injury,

Received November 10, 2020, **Revised** March 1, 2021,
Accepted March 23, 2021

Corresponding Author: Chi-Min Park
Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
Tel: +82-2-3410-6399, **Fax:** +82-2-2148-7088
E-mail: dr99.park@samsung.com
ORCID: https://orcid.org/0000-0002-8496-3546

time to shock reversal, and mortality [10]. Another retrospective before-after cohort study has shown that such combination therapy can improve chest radiologic findings of patients with severe pneumonia and tend to reduce their mortality [11]. A double-blinded randomized control study for the treatment of sepsis and septic shock following cardiac surgery has shown that such combination therapy is effective in reducing vasopressors dosage and mortality in postoperative adult cardiac surgical patients with septic shock [12]. However, there is no report about the effect of such HAT therapy for septic shock with cIAIs.

In the present study, we hypothesized that the HAT therapy could prevent organ dysfunction, promote recovery from shock, and reduce ICU length of stay (LOS) and mortality of cIAI patients with septic shock. To test this hypothesis, we performed a retrospective before-after cohort study and assessed the efficacy of HAT therapy for cIAI patients with septic shock.

METHODS

This was a single-center, retrospective before-after clinical study comparing clinical outcomes of cIAI patients with septic shock treated with intravenous HAT during 12 months with a control group conventionally treated in surgical ICU during the preceding 36 months. This study was conducted at Samsung Medical Center in Seoul, Korea. This study was approved by the Institutional Review Board of Samsung Medical Center (No. SMC 2019-10-117). The requirement for informed consent was waived due to its retrospective nature. Patients who were admitted between January 2018 and December 2018 were all treated with the HAT therapy protocol (the HAT group). Patients who were admitted to the same ICU between June 2015 and January 2017 were not treated with the HAT protocol (the control group). The period to have enough patients for the control group was longer than that for the HAT treatment group because fewer patients were enrolled in the control group than in the HAT group when the same period was considered.

Patients aged 18 years or older who had septic shock with cIAI treated by emergency surgery were included. Septic shock was defined as sepsis with persisting hypotension requiring vasopressors to maintain the mean arterial pressure (MAP) ≥ 65 mmHg and serum lactate level > 2 mmol/L (18 mg/dL) despite adequate volume resuscitation [13]. Those who had bilateral ureteric obstruction, chronic hemodialysis, iron overload, hemochromatosis, hyperuricemia, gout, cystinuria, glucose-6-phosphate dehydrogenase (G6PD) deficiency, or kidney oxalate stone were excluded [14].

Treatment protocol

The overall treatment was similar for patients with septic shock in control and treatment groups except that HAT therapy was used for those in the treatment group. During the treatment period, cIAI patients were treated with HAT therapy which included intravenous vitamin C of 1,500 mg every 6 hours, intravenous hydrocortisone of 50 mg every 6 hours, and intravenous thiamine of 200 mg every 12 hours according to the Marik protocol [10]. This treatment was started within 12 hours after ICU admission and continued for 4 days or until ICU discharge in addition to routine treatment for septic shock.

All patients received treatment for septic shock per our hospital's protocol. According to the protocol, fluid resuscitation was performed by fluid challenge of 500 mL plasma solution every 15 minutes until an MAP of >65 mmHg was reached. When the MAP was still less than 65 mmHg during or after 30 mL/kg of intravenous crystalloid, vasopressor was added. Norepinephrine is the vasopressor of the first choice, targeting an MAP of >65 mmHg. For patients who failed to achieve this target with norepinephrine dose of >0.2 mg/kg/minute, fixed-dose vasopressin at 0.03 units/minute was then added followed by epinephrine. For the management of infection, broad-spectrum intravenous antibiotics were given as soon as possible after septic shock was diagnosed. The protocol did not change during the inclusion period.

Data collection

Patients' clinical and demographic data, including age, sex, comorbidities, presence of bacteremia, and whether the patient was being treated with mechanical ventilation and/or renal replacement therapy were abstracted from the electronic medical record (EMR). In addition, the severity of illness at the time of ICU admission was recorded. It was assessed using Simplified Acute Physiology Score III (SAPS III) and sequential organ failure assessment (SOFA) score. Lambden et al. [15] recommend that if no value is recorded prior to intubation, then a normal value (Glasgow Coma Scale [GCS], 15/15) is often inferred. And formal assessment of GCS can be undertaken 24 hours after the cessation of sedative medication by infusion. In our study, daily GCS measuring was difficult because many patients were intubated for their surgery or sedated because of postoperative pain control. Thus, we eliminated the central nervous system (GCS) score from the SOFA score. We called it a modified SOFA (mSOFA) score. To obtain the mSOFA score, 5 organ systems were scored, with a maximum score of 20. We selected the worst value for each SOFA parameter at specified time points (4:00 AM, 9:00 AM, 2:00 PM, 9:00 PM) every day for a week in the ICU using the EMR program for automatic calculation of SOFA score. In our surgical ICU, procalcitonin levels were routinely monitored on days 0, 4, and 7 for early detection, monitoring, and guiding antibiotic treatment of septic shock [16]. These data were extracted.

Vasopressor data collected included agents used and their

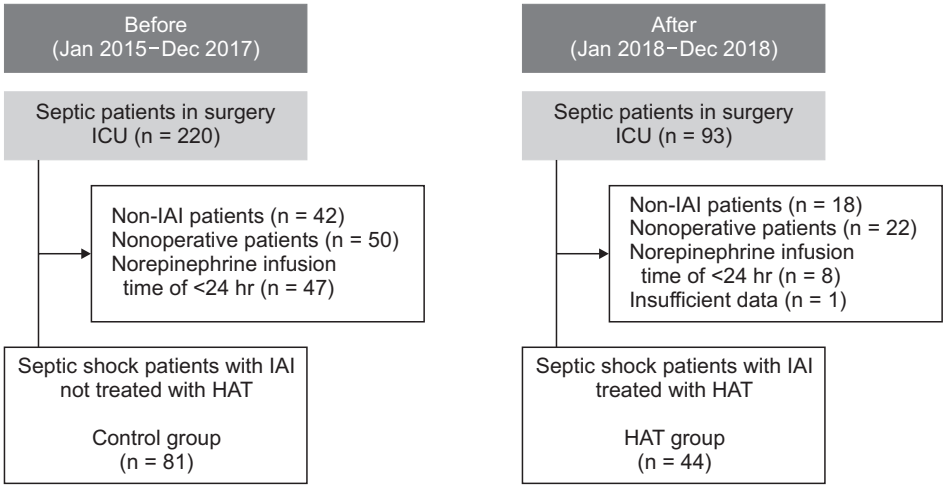

Fig. 1. Disposition of patients in this study. ICU, intensive care unit; IAI, intraabdominal infection; HAT, hydrocortisone, ascorbic acid, and thiamine combination therapy.

Table 1. Baseline characteristics of total control and HAT groups

Characteristic	Group		P-value
	Control	HAT	
No. of patients	81	44	
Age (yr)	67.7 ± 17.92	68.9 ± 11.52	0.632
Male sex	50 (61.7)	25 (56.8)	0.553
Operation and infection site			
Upper GI tract	31 (38.3)	17 (38.6)	0.968
Lower GI tract	35 (43.2)	19 (43.2)	0.998
Biliary	10 (12.3)	2 (4.5)	0.212
Liver	2 (2.5)	4 (9.1)	0.183
Others	3 (3.7)	2 (4.5)	>0.999
Comorbidity			
Diabetes mellitus	25 (30.9)	12 (27.3)	0.674
Hypertension	41 (50.6)	28 (63.6)	0.190
Malignancy	70 (86.4)	35 (79.5)	0.320
Coronary artery disease	10 (12.3)	2 (4.5)	0.212
Liver cirrhosis	3 (3.7)	4 (9.1)	0.241
CVA	17 (21.0)	5 (11.4)	0.223
CKD	11 (13.6)	7 (15.9)	0.792
SAPS III	58.6 ± 15.6	61.4 ± 13.3	0.308
Predicted death	35.8 ± 24.2	40.3 ± 22.5	0.315
Mechanical ventilation	41 (50.6)	27 (61.4)	0.249
CRRT	6 (7.4)	9 (20.5)	0.032
Pathogen type in blood culture			
Gram positive alone	12 (14.8)	6 (13.6)	0.858
Gram negative alone	10 (12.3)	6 (13.6)	0.837
Mixed	1 (1.2)	0 (0.0)	0.648
Others	1 (1.2)	2 (4.5)	0.283
No pathogen	57 (70.4)	30 (68.2)	0.840
Pathogen type in abdomen fluid culture			
Gram positive alone	12 (14.8)	6 (13.6)	0.858
Gram negative alone	10 (12.3)	8 (18.2)	0.375
Mixed	20 (24.7)	16 (36.4)	0.169
Others	1 (1.2)	3 (6.8)	0.125
No pathogen	38 (46.9)	11 (25.0)	0.017

Values are presented as number only, mean ± standard deviation, or number (%).
HAT, hydrocortisone, ascorbic acid, and thiamine combination therapy; GI, gastrointestinal; CVA, cerebrovascular accident; CKD, chronic kidney disease; SAPS III, Simplified Acute Physiology Score III; CRRT, continuous renal replacement therapy.

dosages during treatment. Vasopressor dosages were converted to norepinephrine equivalents using the following formula:

Norepinephrine equivalents = [norepinephrine (μg/min)] + [dopamine (μg/kg/min) ÷ 2] + [epinephrine (μg/min)] + [phenylephrine (μg/min) ÷ 10] + [vasopressin (units/hr) × 8.33] [17,18].

Statistical analyses

Recovery from organ dysfunction was the primary outcome. The mSOFA scores were evaluated to assess organ dysfunction. Delta mSOFA score (mSOFA score on ICU admission day minus scores on each day from the 4th to the 7th ICU day and maximum mSOFA score on the first day minus scores on each day from the 4th to the 7th ICU day) were evaluated to assess recovery of organ dysfunction. Secondary outcomes included ICU and hospital LOS and ICU and hospital mortality. Additional outcomes included procalcitonin level change, daily vasopressor dosage, mean number of days free of mechanical ventilation in 28 days, and renal replacement therapy days.

All data are presented as means ± standard deviations for continuous variables and numbers (percentages) for categorical variables. Data were compared using Student t-test for continuous variables and the chi-square test or Fisher exact test for categorical variables. All tests were 2-sided and P-values of <0.05 were considered statistically significant. Data were analyzed using IBM SPSS Statistics ver. 20 (IBM Corp., Armonk, NY, USA).

RESULTS

During the treatment period, 93 septic patients received the HAT therapy. Of these, 49 patients were excluded because of the following reasons: (1) the focus of infection was not abdomen; (2) they were treated without surgery; (3) they had short norepinephrine infusion time or insufficient data. During the control period, 220 septic patients were admitted to the surgical ICU. Of these patients, 139 were excluded because they were non-cIAI patients or nonoperative patients or they had short norepinephrine infusion time. The remaining 44 patients were assigned to the HAT treatment group while 81 patients were included for the control group (Fig. 1).

Characteristics of patients in the 2 groups at baseline were

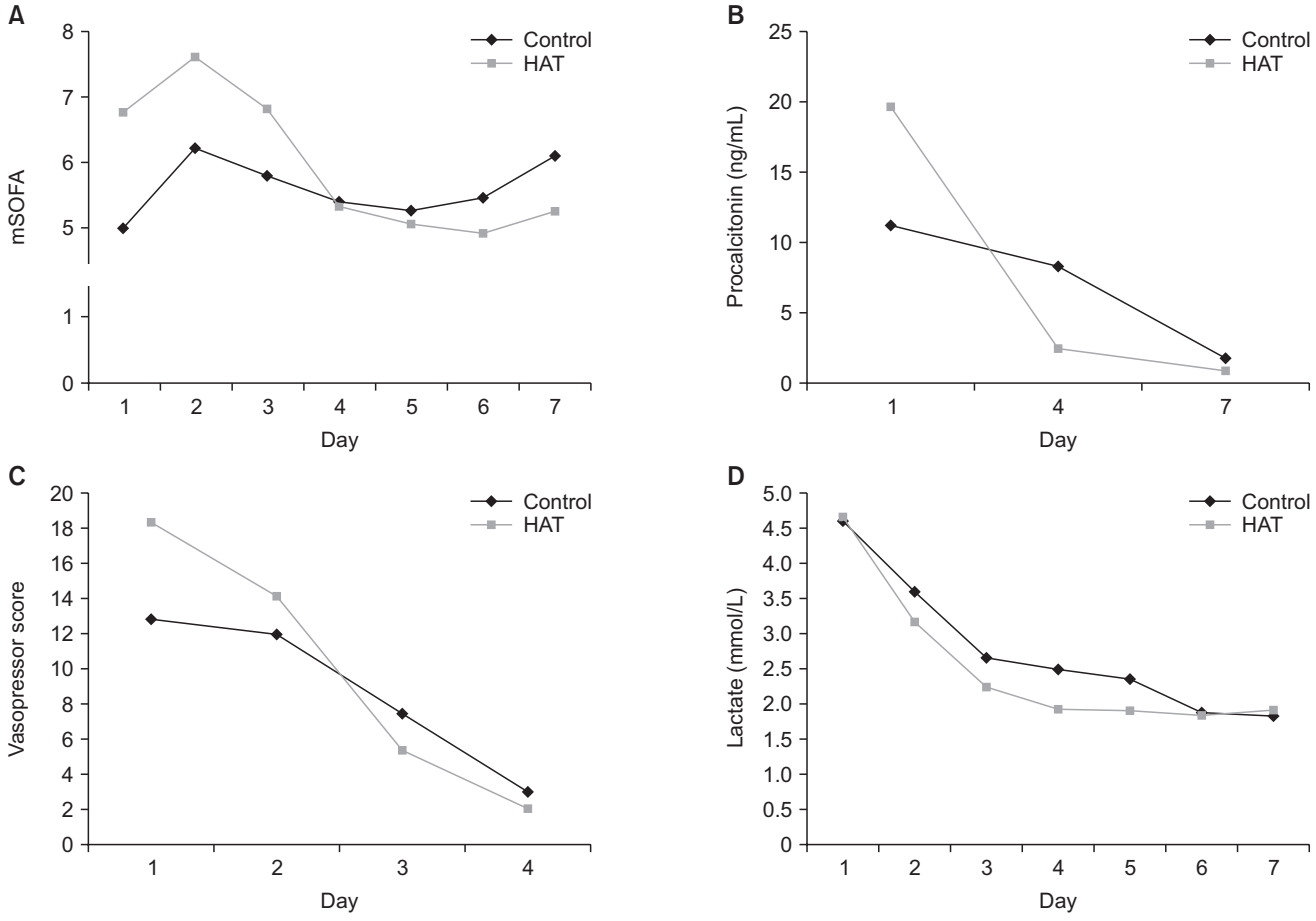

Fig. 2. Graph displaying change of each value over treatment period (A) modified sequential organ failure assessment (mSOFA) score, (B) procalcitonin, (C) vasopressor score, and (D) lactate.

similar (Table 1). There were no significant differences in age, sex, or comorbidities. The most common infection in both groups was lower gastrointestinal infection (38.6% in the HAT group *vs.* 38.3% in the control group, P < 0.968), followed by upper gastrointestinal infection and biliary or liver infection. Initial SAPS III scores were similar in both groups (58.59 in the HAT group *vs.* 61.43 in the control group, P = 0.308). Those in the HAT group were more likely to require renal replacement therapy than those in the control group (20.5% *vs.* 7.4%, P = 0.032).

There was no significant (P = 0.785) difference in the percentage of patients and the pathogen type in blood culture between the 2 groups. The HAT therapy group had more positive abdomen fluid cultures than the control group (75.0% *vs.* 53.1%, P = 0.017). However, there was no significant (P = 0.576) difference in pathogen type in abdomen fluid culture between the 2 groups.

Primary outcome

Trends of daily mSOFA scores are shown in Fig. 2A. The mSOFA scores on day 1 and 2 in the control group were higher than those in the HAT group (day 1: 6.80 in the HAT group *vs.* 5.05 in the control group, P = 0.004; day 2: 7.61 in the HAT group *vs.* 6.25 in the control group; P = 0.019). The mSOFA scores from the 3rd day to the 7th day were similar between the 2 groups (Table 2). The delta mSOFA score (ICU admission mSOFA score minus 4th–7th day mSOFA score) was significantly higher in the HAT group than in the control group on the 4th–7th day (Table 3). Another delta SOFA score (maximum mSOFA score during the first 3 days minus the 7th day mSOFA score) was also significantly high in the HAT group (maximum SOFA score).

Secondary outcomes

There was no significant difference in procalcitonin score on the 1st, the 4th, or the 7th day between the 2 groups. However, the median (interquartile range) 7-day change in procalcitonin score (ng/mL) was higher in the HAT group than in the control group (5.94 [1.7–10.5] in the HAT group *vs.* 10.72 [2.2–34.30] in the control group, P = 0.041) (Table 4). Trends of procalcitonin scores are shown in Fig. 2B.

There was no significant difference in each daily vasopressor

Table 2. Comparison of daily mSOFA scores between groups

Day	No. of patients		mSOFA score		P-value
	Control group	HAT group	Control group	HAT group	
1	81	44	5.05 ± 2.17	6.80 ± 3.19	0.004
2	81	44	6.25 ± 2.24	7.61 ± 3.11	0.019
3	81	44	5.83 ± 2.60	6.84 ± 3.66	0.339
4	79	43	5.44 ± 2.91	5.37 ± 3.21	0.798
5	65	37	5.31 ± 3.11	5.11 ± 2.90	0.886
6	53	31	5.49 ± 3.06	4.97 ± 2.88	0.589
7	39	20	6.13 ± 3.00	5.30 ± 3.17	0.425

Values are presented as number only or mean ± standard deviation.
mSOFA, modified sequential organ failure assessment; HAT, hydrocortisone, ascorbic acid, and thiamine combination therapy.

Table 3. Delta mSOFA scores between the mSOFA scores of day 1 and day 4–7

Day	No. of patients		ΔmSOFA score		P-value
	Control group	HAT group	Control group	HAT group	
1–4	79	43	–0.48 ± 2.60	1.44 ± 2.86	<0.001
1–5	65	38	–0.29 ± 3.06	2.13 ± 3.20	<0.001
1–6	53	31	–0.47 ± 3.10	2.48 ± 3.03	<0.001
1–7	39	20	–0.90 ± 2.96	2.30 ± 3.80	0.003

Values are presented as number only or mean ± standard deviation.
mSOFA, modified sequential organ failure assessment; HAT, hydrocortisone, ascorbic acid, and thiamine combination therapy.
Delta (Δ) mSOFA score is mSOFA score on the intensive care unit (ICU) admission day minus scores on each day from the 4th to the 7th ICU day and maximum mSOFA score on the first day minus scores on each day from the 4th to the 7th ICU day.

Table 4. Comparisons of procalcitonin at day 1, 7, 4 and delta procalcitonin of day 1–7

Day	No. of patients		Procalcitonin (ng/mL)		P-value
	Control group	HAT group	Control group	HAT group	
1	53	58	11.27 (1.89–28.89)	19.77 (2.00–58.20)	0.454
4	33	36	8.36 (2.29–22.57)	2.53 (1.98–4.21)	0.737
7	31	26	1.72 (0.70–6.29)	0.91 (0.37–5.45)	0.166
Δ1–7	25	24	5.94 (1.7–10.5)	10.72 (2.2–34.30)	0.041

Values are presented as number only or median (interquartile range).
HAT, hydrocortisone, ascorbic acid, and thiamine combination therapy.
Delta (Δ) 1–7 procalcitonin score is procalcitonin score on ICU admission day minus scores on 7th ICU day.

Table 5. Comparison of the daily vasopressor score and delta vasopressor score

Day	Vasopressor score		P-value
	Control group (n = 81)	HAT group (n = 44)	
1	12.88 ± 10.78	18.43 ± 19.23	0.082
2	11.98 ± 12.65	14.19 ± 16.37	0.093
3	7.48 ± 13.91	5.39 ± 10.27	0.354
4	2.97 ± 7.84	2.01 ± 4.78	0.158
Δ1–3	5.40 ± 13.38	14.00 ± 18.00	0.004
Δ1–4	9.91 ± 11.49	17.63 ± 18.33	0.005

Values are presented as number only or mean ± standard deviation.
HAT, hydrocortisone, ascorbic acid, and thiamine combination therapy.
Vasopressor score: norepinephrine equivalents = [norepinephrine (μg/min)] + [dopamine (μg/kg/min) ÷ 2] + [epinephrine (μg/min)] + [phenylephrine (μg/min) ÷ 10] + [vasopressin (units/hr) × 8.33]. Delta (Δ) vasopressor score is vasopressor score on ICU admission day minus scores on each ICU day.

score between the 2 groups (Table 5, Fig. 2C). However, the difference in vasopressor score between the 1st day and the 4th day was significantly higher in the HAT group (17.63 in the HAT group *vs.* 9.91 in the control group, P = 0.005).

Daily lactate levels were not significantly different between the 2 groups. The difference in lactate level between the 1st day and the 7th day was similar between the 2 groups (median: 3.15 in the HAT group *vs.* 3.29 in the control group, P = 0.573). Trends of daily lactates are shown in Fig. 2D. There was no significant difference in the median number (interquartile range) of days on continuous renal replacement therapy (CRRT: 12 [6.5–16.8] in the HAT group, n = 6 *vs.* 4 [3.5–9.5] in the control group, n = 9; P = 0.066) or the ventilator-free day (median [interquartile range]: 25 [17.5–26.0] in the HAT group, n = 41 *vs.* 26 [23.5–26.5] in the control group, n = 27; P = 0.052).

The time to discharge from the ICU was similar between the 2 groups (median [interquartile range] days of CRRT: 4.0 [3.00–8.75] in the HAT group *vs.* 4.6 [2.72–10.42] in the control group, P = 0.873). The median (interquartile range) hospital LOS was also similar between the 2 groups (28.10 [15.84–44.40] in the HAT group *vs.* 33.9 [13.23–51.28] in the control group, P = 0.860). The ICU mortality (13.6% in the HAT group *vs.* 11.1% in the control group, P = 0.678) and hospital mortality (25.0% in the HAT group *vs.* 33.0% in the control group, P = 0.417) failed to show significant difference between the 2 groups.

DISCUSSION

In this study, whether HAT therapy could be effective for cIAI patients with septic shock was evaluated. Major findings of this study were as follows: (1) changes in the SOFA score between initial and 7th-day SOFA scores in the HAT group were significantly greater than those in the control group. Changes between maximal SOFA scores within 3 days and the 7th day in the HAT group were also significantly greater than those in the control group; (2) changes in vasopressor and procalcitonin levels also were remarkable in the HAT therapy group; (3) HAT therapy did not shorten ICU LOS or hospital LOS; and (4) HAT therapy did not improve mortality when compared to the control. We found that HAT was effective for recovering organ dysfunction and tapering vasopressor in septic patients with cIAI.

Results of combined therapy are different among studies. Marik et al. [10] have demonstrated significant decreases in mortality and end-organ dysfunction in patients with severe sepsis and septic shock after receiving HAT therapy. A similar before-after study by Kim et al. [11] found that patients who received the HAT therapy had a substantial mortality benefit. On the contrary, in a propensity score-based analysis of a before-after cohort study, Shin et al. [19] found that there was no mortality benefit in the early administration of vitamin C and thiamine in the overall patient population. A randomized controlled trial by Fowler et al. [20] found that a 96-hour infusion of vitamin C compared with placebo did not improve organ dysfunction or levels of biomarkers indicating inflammation or vascular injury by 168 hours. On the contrary, vitamin C compared with placebo was associated with a significant reduction in 28-day all-cause mortality, with significantly increased ICU-free days to day 28 and hospital-free days to day 60. Why such a result was obtained was not known. Differences in outcomes among studies might be due to different characteristics of patients and various doses of vitamin C used in different studies.

The main strength of our study was the inclusion of patients with cIAI who had surgical source control. These patients were different from general medical patients with septic shock. For patients with cIAI, source control is needed to eliminate the source of infection, to control ongoing contamination, and to restore premorbid anatomy and function. Antimicrobial therapy is also needed to prevent local and hematogenous spread while reducing late complication [21]. Although cIAI has been treated with surgery for source control and antibiotics, these patients may also need organ function support in case of septic shock.

Our study has several limitations. First, our data reflected observations at a single center with a relatively small sample size that might not be generalizable to other settings. Second, due to the retrospective nature of this study, other unknown factors might have influenced the results of this study. Furthermore, the HAT treatment and control periods occurred during different seasons. There was an inevitable time difference in before and after intervention study. Advancing of medical knowledge, procedure, or drug might give better outcomes to patients admitted later. We cannot exclude positive

effects of these factors. However, there were no major treatment or policy changes implemented between both periods of the study. Third, we had a large number of missing values. We could not obtain SOFA score after patients were discharged from ICU because daily laboratories were not continued in a general ward. Procalcitonin was not ordered for all patients. It is a possible source of selection bias. Fourth, we did not measure vitamin C or thiamine level before, during, or after treatment. Thus, we do not know how many patients had vitamin deficiency, how much increase in vitamin level during and after treatment, and how much of these vitamins is needed for shock patients. Moreover, it remains possible that there were differences between the combined treated and conservative treated groups in terms of vitamin C levels. Such a difference is a possible source of selection bias. Fifth, the duration for the control group was not the same as that for the treatment group. There were fewer cIAI patients in the control group compared to the control group. It may be the result of missing data of cIAI. Sixth, on days 1 and 2, the mSOFA score, vasopressor score, and procalcitonin score were higher in the combined HAT treatment group than control group. We thought there was a difference in severity between the 2 groups due to the retrospective nature of this study. However, our data shows that the mSOFA score, vasopressor score, and procalcitonin score were markedly decreased in the HAT treatment group compared to the control group. Despite these limitations, our study illustrated the potential positive impact of combined HAT treatment for the management of cIAI patients with septic shock.

In our study of cIAI in patients with septic shock, administration of intravenous HAT therapy may improve the recovery from organ dysfunction, even though it has been treated with surgery for source control. Further research is needed to evaluate the potential role of HAT therapy in other outcomes of cIAI patients with septic shock.

ACKNOWLEDGEMENTS

We would like to thank the all nurses of the surgical intensive care unit at Samsung Medical Center.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

ORCID iD

Yong Oh Kim: https://orcid.org/0000-0001-8713-0753
Kee Sang Yoo: https://orcid.org/0000-0001-6476-8471
Kyoung Won Yoon: https://orcid.org/0000-0002-9829-5024
Hyo Jung Park: https://orcid.org/0000-0002-3875-0224
Chi-Min Park: https://orcid.org/0000-0002-8496-3546

Author Contribution

Conceptualization: CMP
Formal Analysis: YOK, HJP
Investigation: YOK, KSY, KWY
Methodology: CMP, HJP
Project Administration: CMP, KSY
Writing – Original Draft: YOK, KWY, HJP
Writing – Review & Editing: KSY, CMP

REFERENCES

1. Walkey AJ, Lagu T, Lindenauer PK. Trends in sepsis and infection sources in the United States. a population-based study. Ann Am Thorac Soc 2015;12:216-20.
2. Cohen J, Vincent JL, Adhikari NK, Machado FR, Angus DC, Calandra T, et al. Sepsis: a roadmap for future research. Lancet Infect Dis 2015;15:581-614.
3. Brun-Buisson C, Doyon F, Carlet J, Dellamonica P, Gouin F, Lepoutre A, et al. Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. A multicenter prospective study in intensive care units. French ICU Group for Severe Sepsis. JAMA 1995;274:968-74.
4. Choi WH, Hwang SY, Jun SY, Choi YC, Lee EH, Yu WS. Usefulness of the Sequential Organ Failure Assessment (SOFA) score in patients with sepsis due to intra-abdominal infection. J Korean Surg Soc 2009;76:273-8.
5. Mulier S, Penninckx F, Verwaest C, Filez L, Aerts R, Fieuws S, et al. Factors affecting mortality in generalized postoperative peritonitis: multivariate analysis in 96 patients. World J Surg 2003;27:379-84.
6. Lee SH, Kim HW, Lee JG. Infection control strategy for severe sepsis and septic shock in critically ill surgical patients. J Acute Care Surg 2014;4:1-6.
7. Mazuski JE, Tessier JM, May AK, Sawyer RG, Nadler EP, Rosengart MR, et al. The Surgical Infection Society revised guidelines on the management of intra-abdominal infection. Surg Infect (Larchmt) 2017;18:1-76.
8. Morr M, Lukasz A, Rübig E, Pavenstädt H, Kümpers P. Sepsis recognition in the emergency department: impact on quality of care and outcome? BMC Emerg Med 2017;17:11.
9. Sartelli M, Viale P, Catena F, Ansaloni L, Moore E, Malangoni M, et al. 2013 WSES guidelines for management of intra-abdominal infections. World J Emerg Surg

2013;8:3.
10. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. Chest 2017;151:1229-38.
11. Kim WY, Jo EJ, Eom JS, Mok J, Kim MH, Kim KU, et al. Combined vitamin C, hydrocortisone, and thiamine therapy for patients with severe pneumonia who were admitted to the intensive care unit: propensity score-based analysis of a before-after cohort study. J Crit Care 2018;47:211-8.
12. Balakrishnan M, Gandhi H, Shah K, Pandya H, Patel R, Keshwani S, et al. Hydrocortisone, vitamin C and thiamine for the treatment of sepsis and septic shock following cardiac surgery. Indian J Anaesth 2018;62:934-9.
13. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801-10.
14. Zabet MH, Mohammadi M, Ramezani M, Khalili H. Effect of high-dose ascorbic acid on vasopressor's requirement in septic shock. J Res Pharm Pract 2016;5:94-100.
15. Lambden S, Laterre PF, Levy MM, Francois B. The SOFA score-development, utility and challenges of accurate assessment in clinical trials. Crit Care 2019;23:374.
16. Schroeder S, Hochreiter M, Koehler T, Schweiger AM, Bein B, Keck FS, et al. Procalcitonin (PCT)-guided algorithm reduces length of antibiotic treatment in surgical intensive care patients with severe sepsis: results of a prospective randomized study. Langenbecks Arch Surg 2009;394:221-6.
17. Russell JA, Walley KR, Singer J, Gordon AC, Hébert PC, Cooper DJ, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med 2008;358:877-87.
18. Ensor CR, Sabo RT, Voils SA. Impact of early postoperative hydrocortisone administration in cardiac surgical patients after cardiopulmonary bypass. Ann Pharmacother 2011;45:189-94.
19. Shin TG, Kim YJ, Ryoo SM, Hwang SY, Jo IJ, Chung SP, et al. Early vitamin C and thiamine administration to patients with septic shock in emergency departments: propensity score-based analysis of a before-and-after cohort study. J Clin Med 2019;8:102.
20. Fowler AA 3rd, Truwit JD, Hite RD, Morris PE, DeWilde C, Priday A, et al. Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: the CITRIS-ALI randomized clinical trial. JAMA 2019;322:1261-70.
21. Blot S, De Waele JJ. Critical issues in the clinical management of complicated intra-abdominal infections. Drugs 2005;65:1611-20.