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ORIGINAL ARTICLE

Effect of Dobutamine on Patients with Septic Shock: A Retrospective Nationwide Study

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ABSTRACT

BACKGROUND

Dobutamine is administered to patients with hypoperfusion associated with septic shock; however, its effect on mortality of septic shock remains unknown. We used a national inpatient database to investigate the effect of dobutamine on patients with septic shock.

METHODS

Adults with septic shock who received ≥30 mL/kg fluid and ≥10 μg/min noradrenaline and either vasopressin or adrenaline within 1 day after admission from 1 July 2010 to 31 March 2016 were identified by searching the Japanese Diagnosis Procedure Combination database. Stabilized inverse probability weighting analysis using propensity scores was performed to compare all-cause 28-day mortality and length of stay between patients who had and had not received dobutamine.

RESULTS

Of 4,747 eligible patients, 1,259 had received dobutamine and 3,488 had not. All-cause 28-day mortality did not differ significantly between the groups (risk difference, 0.1%; 95% confidence interval [CI], −3.3 to 3.4; P = 0.975). Receipt of dobutamine was significantly associated with longer hospital stay (difference, 3.8; 95% CI, 0.5–7.2; P = 0.024). Subgroup analysis showed that receipt of dobutamine was not significantly associated with length of stay in patients with cardiovascular disease (difference, −5.1 days; 95% CI, −11.7 to 1.5; P = 0.133), or those who received ≥20 μg/min noradrenaline (difference, 0.5 days; 95% CI, −6.8 to 7.7; P = 0.900).

CONCLUSIONS

Overall all-cause 28-day mortality in patients with septic shock did not significantly differ between patients who had and had not received dobutamine; however, receipt of dobutamine was significantly associated with longer hospital stay.

KEY WORDS

septic shock, dobutamine, mortality

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INTRODUCTION

Septic shock, a life-threating condition, is caused by a host response to infection. Appropriate management of septic shock in its initial stage is important in reducing mortality. Treatments for septic shock include antimicrobial therapy and source control, adequate fluid resuscitation, use of noradrenaline as the first-line vasopressor, use of vasopressin or adrenaline, and use of corticosteroids [1]. Although treatments for septic shock have been standardized and used extensively, its mortality remains high (≥40%) [2].

Dobutamine, an inotropic agent, increases cardiac output through augmentation of stroke volume and may improve tissue hypoperfusion of patients with septic shock by increasing oxygen delivery [3]. Surviving sepsis campaign guidelines recommend early goal-directed therapy, including use of dobutamine [4]. However, early goal-directed therapy did not reduce mortality in several published randomized controlled studies [5–7]. The guidelines continue to recommend use of dobutamine in patients with septic shock and persistent hypoperfusion despite adequate fluid loading and use of high-dose vasopressors [1].

Two previous studies have investigated the effect of inotropes on septic shock [8, 9]. One underpowered study showed that noradrenaline plus dobutamine was not associated with reducing mortality compared with adrenaline. The interventions in that study were heterogeneous, preventing it from determining the effect of dobutamine. The other, a randomized controlled study investigating the effect of levosimendan in patients with septic shock, found that administration of levosimendan did not improve SOFA (Sequential Organ Failure Assessment) scores. Levosimendan is a calcium-sensitizing inotrope that increases the force of myocardial contraction without increasing myocardial oxygen consumption, in contrast with catecholamines [10]. Thus, it remains unclear whether dobutamine reduces mortality of septic shock. The aim of this study was to investigate the effect of dobutamine in patients septic shock by using a national inpatient database in Japan.

METHODS

DATA SOURCE

Inpatient data were extracted from the Japanese Diagnosis Procedure Combination database. More than 1,200 acute care hospitals voluntarily contribute to this database, which covers more than 80% of all tertiary-care emergency hospitals in Japan. The database includes data on approximately seven million inpatients, representing approximately 50% of all discharges from acute care hospitals in Japan. These data include hospital identification numbers, patients' sexes and ages; body weights and heights; conscious state on admission; dates of hospitalization and discharge; main diagnoses; pre-existing comorbidities on admission, and complications that occurred during hospitalization recorded with International Classification of Diseases, tenth revision (ICD-10) codes and text in Japanese; surgical and non-surgical procedures and dates on which the procedures were performed; dates and doses of drugs or blood products administered during the hospitalization; and discharge status. Recorded diagnoses and procedures in the database have been validated in a previous study [11], which found that the specificity of diagnoses exceeded 96%, sensitivity of diagnoses was 50%–80%, and the specificity and sensitivity of procedures both exceeded 90%.

The institutional Review Board of The University of Tokyo approved this study. The requirement for informed consent was waived because only anonymized data were studied.

PATIENT SELECTION

In this study, data from 1 July 2010 to 31 March 2016 were used. Data on patients aged ≥15 years who were diagnosed with sepsis (**Supplement 1**) and had received antibiotics, and ≥30 mL/kg fluid, and ≥10 μg/min noradrenaline, and either vasopressin or adrenaline within 1 day after admission were included [1]. Patients who had undergone cardiopulmonary resuscitation within 1 day after admission were excluded because adrenaline was administered during cardiopulmonary resuscitation.

The patients were divided into two groups: (I) patients who received dobutamine within 1 day after admission (dobutamine group); and (II) those who did not receive dobutamine within 1 day after admission (control group).

BASELINE CHARACTERISTICS AND OUTCOMES

Baseline characteristics included the following: age; sex; body mass index (BMI); conscious state on admission; Charlson comorbidity index (CCI); fiscal year; comorbidities including acute respiratory distress syndrome (ICD-10 codes: J80), cardiovascular disease (I05–09, I11.0, I13.2, I20–25, I34–37, I39, I42–45, I47–48, I49.1–5, I49.8, I49.9, I50, I51.1, I51.2, I51.8, I51.9), chronic kidney disease (N18), pulmonary disease (J41–47, J84.1, J84.8,

J84.9), and hematologic disorder (C81–85, C88, C90–96, D46–47, D60, D70, D80); surgery for infection within 1 day after admission (**Supplement 2**); use of mechanical ventilation within 1 day after admission; continuous renal replacement therapy within 1 day after admission; intermittent renal replacement therapy within 1 day after admission; rehabilitation within 1 day after admission; and administered drugs within 1 day after admission including vasopressin, adrenaline, corticosteroids, dopamine, milrinone, sodium bicarbonate, dexmedetomidine, propofol, midazolam, neuromuscular blockers, morphine, fentanyl, landiolol, amiodarone, proton pump inhibitors, H2-blockers, penicillin (ampicillin or ampicillin/sulbactam), cephem (first, second, or third generation cephem, which are ineffective against *Pseudomonas*-group, or cephamycin), azithromycin, cotrimoxazole, anti-methicillin-resistant-*Staphylococcus aureus* drugs (vancomycin, teicoplanin, daptomycin, linezolid, quinupristin/dalfopristin, or arbekacin), anti-*Pseudomonas*-group drugs (third generation cephem with *Pseudomonas*-group activity, fourth generation cephem, aminoglycoside, carbapenem, new quinolone, piperacillin, piperacillin/tazobactam, colistin, or monobactam), anti-fungal drugs (azoles, amphotericin B, or echinocandins); and total amounts of crystalloid solution, albumin preparation, red blood cells, fresh frozen plasma, and platelet concentrate. Conscious state on admission was evaluated using Japan Coma Scale (JCS) scores [12]. The JCS is widely used in Japan and JCS and Glasgow Coma Scale scores correlate well [13, 14]. A JCS score of 0 indicates alertness, 1 to 3 indicates wakefulness without any stimuli, 10 to 30 indicates arousal in response to some stimuli, and 100 to 300 indicates coma. The CCI, a well-validated scoring system for disease burden, also predicts mortality well and has been widely used as a factor in risk adjustment [15]. CCI scores were classified into five groups: 0, 1, 2, 3–5, and ≥6. Doses of noradrenaline were classified into two groups: 10–20 μg/min, and ≥20 μg/min. To adjust for the severity of patients' conditions, all components of SOFA scores except for liver dysfunction were selected as baseline characteristics; namely, use of mechanical ventilation, continuous renal replacement therapy, conscious state on admission (JCS), and transfusion of platelet concentrate [16].

The primary outcome was all-cause 28-day mortality. The secondary outcome was length of stay.

STATISTICAL ANALYSIS

Stabilized inverse probability weighting (IPW) analysis using propensity scores (PS) to balance the patient backgrounds between the dobutamine and control groups was performed. To calculate the PS for receipt of dobutamine, a multivariable logistic regression model including baseline characteristics was used. C-statistics were calculated to evaluate the model's discrimination of receipt of dobutamine. Patients who received dobutamine were weighted by stabilized IPW calculated as p(N)/PS, whereas patients who did not receive dobutamine were weighted by (1 − p(N))/(1 − PS), where p(N) is the probability of receiving dobutamine in this patient cohort and PS is the individual's PS for receiving dobutamine [17]. Average treatment effect was estimated using stabilized IPW. Standardized differences for covariates were calculated; absolute standardized differences of less than 10% indicate good balance [18, 19].

Continuous variables are presented as median and interquartile ranges (IQR), whereas categorical variables are presented as number and proportions. Averages of continuous variables were compared using *t*-tests, and proportions of categorical variables were compared using χ^2 tests. The threshold for significance was $P < 0.05$. All analyses were performed using STATA/MP version 15.0 software (STATA, College Station, TX, USA).

RESULTS

We identified 5,581 patients aged ≥15 years who had received antibiotics and ≥30 mL/kg fluid and ≥10 μg/min noradrenaline and either vasopressin or adrenaline within 1 day after admission. **Fig. 1** is a flow chart of patient selection. There were 4,747 eligible patients, 1,259 of whom were assigned to the dobutamine group and the remaining 3,488 to the control group.

Table 1 shows patients' baseline characteristics according to study groups prior to and after IPW. Patients in the dobutamine group were more likely to be male; have cardiovascular disease; and receive mechanical ventilation, adrenaline, dopamine, albumin preparations, dexmedetomidine, propofol, midazolam, milrinone, neuromuscular blocker, sodium bicarbonate, and amiodarone. Fiscal years were imbalanced. After stabilized IPW analysis, all variables were well-balanced.

The overall all-cause 28-day mortality was 36.5% (1732/4747), and the average length of stay was 25 days (IQR, 8–51). All-cause 28-day mortality was not significantly higher in the dobutamine than the control group (38.7% vs. 35.7%, P = 0.059). Length of stay was 26 days (IQR, 9–54) in the dobutamine group and 25 days (IQR, 8–51) in the control group.

In the stabilized IPW analysis, the C-statistic was

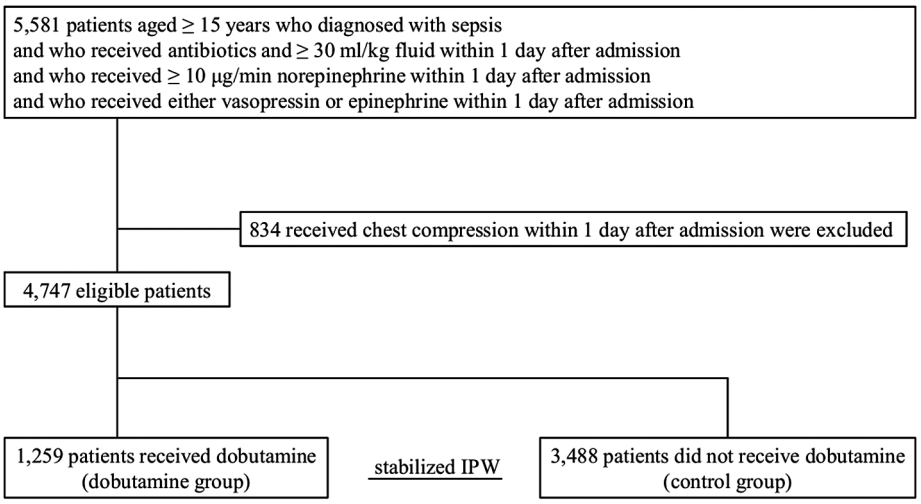

Fig. 1 Flow chart of patient selection

IPW; inverse probability of weighting.

0.66. There were no significant differences between the dobutamine and control groups in terms of all-cause 28-day mortality (risk difference, 0.1%; 95% confidence interval [CI], −3.3 to 3.4; P = 0.975) (**Table 2**). Length of stay was significantly longer in the dobutamine than the control group (difference, 3.8; 95% CI, 0.5 to 7.2; P = 0.024) (**Table 3**).

In the subgroup analysis, use of dobutamine was not significantly associated with all-cause 28-day mortality, irrespective of past history of cardiovascular disease or dose of noradrenaline (**Table 2**). Use of dobutamine was not significantly associated with length of stay in patients with cardiovascular disease (difference, −5.1 days; 95% CI, −11.7 to 1.5; P = 0.132), or receipt of ≥20 μg/min noradrenaline (difference, 0.5 days; 95% CI, −6.8 to 7.7; P = 0.898) (**Table 3**).

DISCUSSION

Our study showed all-cause 28-day mortality in patients with septic shock did not differ significantly between those who did and did not receive dobutamine. Use of dobutamine was associated with longer hospital stay. Regardless of past history of cardiovascular disease, use of dobutamine was not associated with all-cause 28-day mortality of patients with septic shock.

In our study, use of dobutamine was associated with longer length of stay without improving all-cause 28-day mortality. Dobutamine for septic shock may increase cardiac output and raise mean arterial pressure of patients with tissue hypoperfusion; however, the effects of dobutamine may be temporary in such patients. In the present study, use of dobutamine was associated with prolonged length of stay but not with reduction in mortality of patients with septic shock. Unlike the overall findings, use of dobutamine was not associated with longer length of stay in patients with cardiovascular disease or those who received high-dose noradrenaline. One possible explanation for this apparent discrepancy is that dobutamine could not improve the cardiac output of patients with cardiovascular disease or increase the mean arterial pressure of those receiving high-dose noradrenaline. Another possible explanation is that adverse effects of dobutamine, such as ventricular arrhythmia and vasodilation, affected patients with cardiovascular disease or receiving high-dose noradrenaline [3].

The present study had several limitations. First, the data were provided per day unit. Data on the clock time at which dobutamine was started, and the sequence of vasopressor and dobutamine were not available. Second, the database did not include indicators of cardiac output and tissue hypoperfusion. The guidelines state that the best way to determine when to use dobutamine is by monitoring the response of indices of perfusion to measured increases in cardiac output. The absence of indicators of cardiac output and tissue hypoperfusion may have resulted in selection bias. Additionally, patients with normal cardiac function were unlikely to receive dobutamine and it may have had little effect in such patients.

Table 1 **Patient characteristics according to control and dobutamine groups prior to adjustment and after stabilized inverse probability weighting analysis**

Variables	Unadjusted group			Stabilized IPW group		
	Control group	Dobutamine group	Standardized difference (%)	Control group	Dobutamine group	Standardized difference (%)
Sex (male), n (%)	1963 (56.3)	777 (61.7)	11.1	(57.4)	(57.4)	0.1
Age, years (SD)	71.2 (13.4)	70.9 (13.8)	2.6	71.3 (18.2)	70.3 (34.5)	3.6
Body Mass Index, n (%)			7.2			1.0
18.50–24.99	1911 (54.8)	690 (54.8)		(57.3)	(57.0)	
18.50<	799 (22.9)	293 (23.3)		(24.1)	(24.3)	
25.00–29.99	473 (13.6)	185 (14.7)		(14.6)	(14.8)	
≥30.00	138 (4.0)	47 (3.7)		(4.1)	(4.0)	
Missing	167 (4.8)	44 (3.5)				
Japan coma scale, n (%)			4.8			1.8
0 (alert)	1312 (37.6)	485 (38.5)		(37.8)	(37.1)	
1-digit (wakefulness)	923 (26.5)	336 (26.7)		(26.7)	(26.6)	
2-digit (somnolence)	486 (13.9)	155 (12.3)		(13.7)	(13.9)	
3-digit (coma)	767 (22.0)	283 (22.5)		(21.8)	(22.4)	
Charlson comorbidity index, n (%)			7.5			2.4
0	2193 (62.9)	762 (60.5)		(62.2)	(62.5)	
1	334 (9.6)	128 (10.2)		(9.8)	(9.7)	
2	686 (19.7)	265 (21.0)		(19.9)	(19.9)	
3–5	184 (5.3)	79 (6.3)		(5.5)	(5.2)	
≥6	91 (2.6)	25 (2.0)		(2.6)	(2.8)	
Fiscal year, n (%)			14.5			3.1
2010	155 (4.4)	79 (6.3)		(4.9)	(5.3)	
2011	303 (8.7)	139 (11.0)		(9.2)	(9.5)	
2012	428 (12.3)	165 (13.1)		(12.2)	(12.5)	
2013	590 (16.9)	230 (18.3)		(17.0)	(16.8)	
2014	972 (27.9)	316 (25.1)		(27.6)	(27.6)	
2015	1040 (29.8)	330 (26.2)		(29.2)	(28.3)	
Cardiovascular disease	526 (15.1)	315 (25.0)	25.0	(17.4)	(17.3)	0.3
Acute respiratory distress syndrome, n (%)	127 (3.6)	67 (5.3)	8.1	(4.1)	(4.1)	0.0
Chronic kidney disease, n (%)	182 (5.2)	87 (6.9)	7.1	(5.8)	(5.6)	0.9
Pulmonary disease, n (%)	113 (3.2)	47 (3.7)	2.7	(3.4)	(3.2)	1.1
Hematologic disorder, n (%)	100 (2.9)	38 (3.0)	0.9	(2.9)	(3.0)	0.5
Dose of noradrenaline, n (%)						1.2
10–20 μg/min	2795 (80.1)	959 (76.2)	9.6	(79.1)	(78.6)	
≥20 μg/min	693 (19.9)	300 (23.8)		(20.9)	(21.4)	
Adrenaline, n (%)	1238 (35.5)	548 (43.5)	16.5	(37.5)	(37.2)	0.6
Vasopressin, n (%)	2644 (75.8)	916 (72.8)	7.0	(75.1)	(75.4)	0.8

IPW; inverse probability of weighting.

Table 1-2 Patient characteristics according to control and dobutamine groups prior to adjustment and after stabilized inverse probability weighting analysis

Variables	Unadjusted group			Stabilized IPW group		
	Control group	Dobutamine group	Standardized difference (%)	Control group	Dobutamine group	Standardized difference (%)
Dopamine, n (%)	1295 (37.1)	532 (42.3)	10.5	(38.5)	(39.3)	1.7
Milrinone	79 (2.3)	66 (5.2)	15.7	(3.0)	(3.1)	0.6
Landiolol	394 (11.3)	138 (11.0)	1.1	(11.4)	(11.9)	1.6
Amiodarone	87 (2.5)	61 (4.8)	12.5	(3.0)	(2.9)	0.4
Corticosteroids, n (%)	2122 (60.8)	820 (65.1)	8.9	(62.6)	(63.7)	2.3
Mechanical ventilation, n (%)	2775 (79.6)	1088 (86.4)	18.3	(81.4)	(82.3)	2.3
Continuous renal replacement therapy, n (%)	1210 (34.7)	595 (47.3)	25.8	(38.4)	(39.0)	1.2
Intermittent renal replacement therapy, n (%)	129 (3.7)	30 (2.4)	7.7	(3.2)	(3.4)	0.9
Sodium bicarbonate, n (%)	1402 (40.2)	645 (51.2)	22.3	(43.2)	(43.4)	0.6
Total infusion of crystalloid, mL (SD)	14245 (12346)	15049 (10583)	−7.0	14503 (13246)	14484 (12218)	0.2
Total infusion of albumin preparation, mL (SD)	484 (819)	597 (809)	−13.8	520 (989)	523 (701)	0.4
Total transfusion of fresh frozen plasma, mL (SD)	634 (4462)	738 (1109)	−3.2	667 (4269)	648 (984)	0.6
Total transfusion of platelet concentrate, mL (SD)	1276 (17092)	1526 (3045)	−2.0	108 (1316)	104 (221)	0.4
Total transfusion of red blood cell concentrate, mL (SD)	960 (12265)	1118 (4293)	−1.7	559 (6492)	515 (2060)	0.9
Dexmedetomidine, n (%)	902 (25.9)	406 (32.2)	14.1	(27.6)	(28.1)	0.9
Propofol, n (%)	1481 (42.5)	612 (48.6)	12.4	(43.9)	(43.4)	0.9
Midazolam, n (%)	1653 (47.4)	735 (58.4)	22.1	(50.2)	(50.5)	0.6
Fentanyl, n (%)	2262 (64.9)	865 (68.7)	8.2	(65.9)	(66.3)	0.8
Morphine, n (%)	64 (1.8)	41 (3.3)	9.0	(2.2)	(2.2)	0.0
Neuromuscular blockers, n (%)	1817 (52.1)	744 (59.1)	14.1	(53.9)	(53.8)	0.2
Surgery, n (%)	1250 (35.8)	423 (33.6)	4.7	(35.4)	(35.7)	0.6
Proton pump inhibitors, n (%)	888 (25.5)	299 (23.7)	4.0	(24.7)	(24.3)	0.8
H2-blockers, n (%)	720 (20.6)	279 (22.2)	3.7	(21.2)	(21.3)	0.3
Penicillin, n (%)	395 (11.3)	162 (12.9)	4.7	(11.7)	(11.5)	0.8
Cephem, n (%)	816 (23.4)	348 (27.6)	9.8	(24.2)	(24.2)	0.0
Anti-methicillin-resistant *Staphylococcus aureus* drugs, n (%)	906 (26.0)	367 (29.2)	7.1	(26.6)	(26.4)	0.4
Anti-*Pseudomonas* group drugs, n (%)	3122 (89.5)	1121 (89.0)	1.5	(89.7)	(90.1)	1.5
Azithromycin, n (%)	195 (5.6)	81 (6.4)	3.5	(5.7)	(5.8)	0.5
Cotrimoxazole, n (%)	31 (0.9)	13 (1.0)	1.5	(1.0)	(1.0)	0.4
Anti-fungal drugs, n (%)	214 (6.1)	86 (6.8)	2.8	(6.5)	(6.2)	0.9
Rehabilitation, n (%)	232 (6.7)	59 (4.7)	8.5	(6.1)	(5.9)	0.9

IPW; inverse probability of weighting.

Table 2 All-cause 28-day mortality in patients who did and did not receive dobutamine

	Risk difference	95% confidence interval	P value
Crude	3.0	−0.1 to 6.1	0.059
stabilized IPW	0.1	−3.1 to 3.2	0.975
Subgroup analysis			
Cardiovascular disease			
Yes	4.3	−2.7 to 11.5	0.225
No	−0.9	−4.6 to 2.9	0.660
Dose of noradrenaline			
10–20 μg/min	0.0	−3.8 to 3.8	0.997
≥20 μg/min	0.1	−7.2 to 7.4	0.980

IPW; inverse probability of weighting.

Table 3 Length of stay in patients who did and did not receive dobutamine

	Difference	95% confidence interval	P value
Crude	4.0	1.1 to 7.0	0.007
stabilized IPW	3.8	0.5 to 7.1	0.024
Subgroup analysis			
Cardiovascular disease			
Yes	−5.1	−11.7 to 1.5	0.132
No	5.7	1.9 to 9.5	0.003
Dose of norepinephrine			
10–20 μg/min	4.7	1.0 to 8.5	0.013
≥20 μg/min	0.5	−6.8 to 7.7	0.898

IPW; inverse probability of weighting.

CONCLUSIONS

Our stabilized IPW analyses using a national inpatient database showed that dobutamine was not associated with reducing mortality. Further studies are required to further investigate the effect of dobutamine on mortality.

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