Original Article

Association between fluid overload and delirium/coma in mechanically ventilated patients

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Aim: Several studies have shown an association between fluid overload (FO) and mortality or duration of mechanical ventilation in critically ill patients. However, the association between FO and delirium duration remains unclear.

Methods: This retrospective observational cohort study was undertaken at University of Tsukuba Hospital (Tsukuba, Japan) from April 2015 to March 2017. Mechanically ventilated patients who stayed in the intensive care unit for more than 7 days were eligible for inclusion. Univariate analysis was carried out with the Mann–Whitney *U*-test for continuous variables and Fisher's exact test for categorical variables. A multivariate proportional odds logistic regression model was used to evaluate the association between FO and delirium/coma days (DCDs) during the 7-day study period.

Results: A total of 118 patients were included and divided into FO and non-FO groups. Fluid overload occurred in 40% of patients. The FO group had a higher APACHE II score than the non-FO group (19 [16–26] versus 23 [20–29], $P = 0.017$). Cumulative fluid balance at day 3 was higher in the FO group (3,238 [281–6,530] versus 7,886 [4,106–10,631], $P < 0.001$). Delirium days within 7 days was longer in the FO group (1 [0–3] versus 2 [1–3], $P = 0.048$) and DCDs was longer in the FO group (4 [1–5] versus 6 [3–7], $P = 0.002$). After adjusting for covariates, there were significant associations between FO and DCDs (odds ratio, 2.16; 95% confidence interval, 1.05–4.47).

Conclusions: Our findings suggest that FO is associated with increased DCDs in mechanically ventilated patients.

Key words: Brain dysfunction, delirium, fluid, fluid overload, intensive care

INTRODUCTION

FLUID ADMINISTRATION IS a fundamental and essential treatment in critically ill patients. Fluid therapy is one of the most important treatments in order to increase oxygen delivery during circulatory failure. However, it frequently leads to the development of significant fluid overload (FO), which could advance organ edema, tissue ischemia, and further organ dysfunction. Recent studies have indicated an association between FO and increased mortality and morbidity.[1,2] This association has been reported in studies involving patients with severe sepsis,[3] acute respiratory distress syndrome,[4] acute renal failure,[5] and severe burn.[6] In contrast, a restrictive fluid therapy strategy could decrease FO and potential harmful effects.[7,8] A recent systematic review reported that conservative fluid strategy could improve morbidity in critically ill patients.[9]

Fluid overload results in tissue edema, and can also worsen myocardial, renal, liver, and intestinal function.[10] However, an association between FO and brain function remains unclear, due to the difficulty of assessing cognitive impairment. In clinical settings, delirium and coma are phenotypes caused by brain dysfunction. We hypothesize that a FO affects acute brain dysfunction (delirium and coma).

The objective of this study was to investigate the association between FO and delirium/coma days in mechanically ventilated patients.

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METHODS

THIS RETROSPECTIVE OBSERVATIONAL cohort study was approved by the Ethics Committee of University of Tsukuba Hospital (H27-087). Informed consent was waived by the Institutional Review Board, because of the retrospective design of the study.

Patients

The study was undertaken between April 2015 and March 2017 at University of Tsukuba Hospital (Tsukuba, Japan). All patients admitted to the hospital's intensive care unit (ICU) (12 of a total of 800 hospital beds) during this period were screened for eligibility, and those patients who met the inclusion criteria of mechanical ventilation for ≥48 h and ICU admission for ≥7 days, were enrolled in the study. For the purpose of assessing delirium, exclusion criteria were set. Exclusion criteria were: (i) post-resuscitation after cardiac arrest, which we term post-cardiac arrest syndrome (PCAS), (ii) a history of psychosis or neurologic disease, (iii) mechanical ventilation for ≥24 h before the ICU admission.

Study protocol

All patient data were collected from the electronic medical records retrospectively. Demographic data, comorbidities, reason for ICU admission, disease severity score, laboratory values, duration of mechanical ventilation, length of ICU stay, and ICU and hospital outcomes were recorded.

Delirium and coma assessment

Delirium was diagnosed using the Confusion Assessment Method for the ICU.[11] The diagnosis of coma was made using the Richmond Agitation Sedation Scale,[12] with a score of −4 to −5 indicating coma. Primary outcome was delirium and coma days (DCDs) within the 7-day study period. Delirium and coma days are defined as days with acute brain dysfunction (delirium and coma) within the study period.

Sedation and delirium management

In our ICU, sedation protocol was not applied in clinical settings. As recommended in the recent PADIS guidelines,[13] clinicians selected propofol and dexmedetomidine with priority. To avoid deep sedation, benzodiazepine was withheld. Delirium monitoring was routinely carried out. If the patient developed delirium, ICU nurses and clinicians would seek and treat what delirium occurred. The ICU nurses initiated non-pharmacological interventions such as environmental adjustment. Thereafter, treatment with a psychotropic drug was considered.

Fluid balance and weight change

Fluid balance was calculated by subtracting fluid output from fluid input. Fluid intake included all enterally and parenterally administered fluids (i.v. fluids, medications, blood products, and all forms of nutritional support). Fluid output included urine, fluid removal by dialysis, stool, blood loss, drain output, and nasogastric tube output. Fluid balance on the first ICU day was calculated by subtracting fluid output from fluid input. Body weight was measured using a bed scale. Weight change on the first ICU day was calculated by subtracting body weight as measured on ICU hospitalization or general ward from body weight as measured on the second day. Fluid overload was defined when the recorded body weight was 10% higher than that at baseline.[14]

Statistical analysis

Descriptive data are presented as numbers and percentages and continuous data are described using medians and interquartile ranges. Categorical variables were compared using Fisher's exact test. The comparison of continuous variables was undertaken using the Mann–Whitney *U*-test. Proportional odds logistic regression was used to evaluate the relationship between FO and DCDs. Furthermore, we also adjusted for the following additional covariates chosen a priori in our model: Acute Physiology and Chronic Health Evaluation II (APACHE II), days of mechanical ventilation, sex, and sedatives (benzodiazepine, propofol, dexmedetomidine, and fentanyl) given in the ICU. Differences with *P*-values <0.05 indicated statistical significance. All analyses were undertaken using SPSS version 25 (SPSS, Chicago, IL, USA).

RESULTS

Characteristics and clinical outcomes

AFTER EXCLUDING THOSE who did not meet the inclusion criteria, 118 participants were enrolled in the study (Fig. 1). Baseline characteristics of patients are summarized in Table 1. The median age was 67 (58–75) years and 60% of patients were men. The median APACHE II score was 21 (17–28), and number of ventilator days was 8 (5–16). The mortality rate was 14.4%. Presence of delirium within the first 7 days was 69%, and weekly DCDs were 4 (2–6).

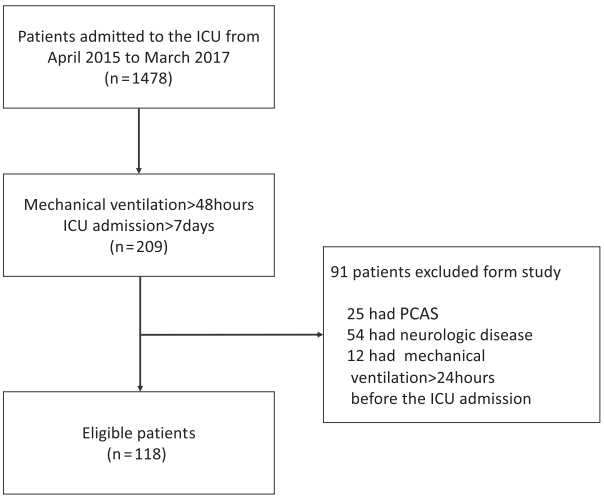

Fig. 1. Flowchart representing the study cohort of mechanically ventilated patients, including exclusion criteria and final enrollment of patients for investigation of the association between fluid overload and delirium/coma. ICU, intensive care unit; PCAS, post-cardiac arrest syndrome.

Approximately 40% of patients experienced FO during their stay in the ICU. Baseline APACHE II score (19 [16–26] versus 23 [20–29], $P = 0.017$) was statistically different between the two groups. Fluid balance differences in the first ICU day was significantly higher in the FO group (2,063 [25–6,283] versus 7,881 [4,244–10,551] mL, $P < 0.001$). Cumulative fluid balance at day 3 was significantly higher in the FO group with a between-group difference of 4,648 mL (3,238 versus 7,886 mL, $P < 0.001$).

Fluid overload patients experienced a median of 2 delirium days (1–3) during the week after admission to the ICU, whereas non-FO patients experienced a median of 1 delirium day (0–3). Similarly, FO patients experienced a median of 2 coma days (1–4) during the week after admission in the ICU, whereas non-FO patients experienced a median of 1 coma day (0–3). Thus, FO patients experienced longer DCDs compared with non-FO patients (6 [3, 7] versus 4 [1, 5], $P = 0.002$).

Concerning clinical outcomes, there were no statistically significant differences between the groups in duration of mechanical ventilation, length of ICU stay, or ICU mortality.

Fluid overload as a risk factor for acute brain dysfunction

Proportional odds regression analysis was undertaken to evaluate the association between FO and DCDs. Results of univariate and multivariate analyses are presented in Table 2. In the adjusted analysis, FO factors (odds ratio [OR] = 2.16, 95% confidence interval [CI] = 1.05–4.47), APACHE II (OR = 1.08, 95% CI = 1.03–1.14), days of mechanical ventilation (OR = 1.1, 95% CI = 1.03–1.18), benzodiazepine (OR = 2.79, 95% CI = 1.12–6.94), and propofol (OR = 1.01, 95% CI = 1.01–1.01) were associated with DCDs. This indicates that these factors were independently associated with prolonged acute brain dysfunction during the 7-day ICU admission period. Only use of fentanyl (OR = 0.99, 95% CI = 0.99–0.99) was independently associated with decreased acute brain dysfunction during the 7-day ICU admission period.

DISCUSSION

THIS IS THE first study examining the potential negative effects of FO on acute brain dysfunction in mechanically ventilated critically ill patients. We found significant associations between FO and prolonged acute brain dysfunction (measured as delirium/coma days).

In our study, 40% of patients were exposed to FO and they were of a higher severity of disease and required a greater amount of fluid administration. Several studies have reported that fluid management of critically ill patients could affect their outcomes.[1,4,5,15–18] Conversely, a conservative fluid strategy limiting fluid intake and even promoting fluid removal improved clinical outcomes.[7,8,19,20] A prospective cohort study reported that patient weight gain on days 3–5 of an ICU stay was associated with increased ICU mortality.[21] It is plausible that higher severity of illness requires a greater amount of fluid to achieve cardiovascular optimization, thus resulting in body weight gain. Therefore, fluid balance and body weight change could be considered biomarkers of critical illness.[22]

In our study, patients in the FO group experienced a longer duration of delirium and coma. In addition, multivariate regression analysis adjusted for covariates including APACHE II, days of mechanical ventilation, and sedatives showed that FO was independently associated with DCDs. One previous study showed that severity of disease was an independent risk factor for developing delirium.[23] Also, sedative medication such as benzodiazepine and propofol have been shown to be strongly associated with delirium.[24,25] Our present study excluded patients with PCAS and neurological illness on admission, meaning that the reason for coma was limited to treatment with sedative medications or acute onset of neurological abnormalities. Thus, adjustment for APACHE II, days of mechanical ventilation, and sedatives could help elucidate the relationship between FO and delirium/coma days.

Table 1. Demographics and clinical outcome among mechanically ventilated patients (n = 118)

Variable	Total (n = 118)	No fluid overload (n = 71)	Fluid overload (n = 47)	P-value
Age, years; median (IQR)	67 (58, 75)	67 (57, 74)	67 (58, 78)	0.411
Male sex, n (%)	71 (60)	48 (68)	23 (49)	0.055
BMI, median (IQR)	21.8 (19.7, 25.1)	22.2 (19.8, 26)	21.8 (19.1, 25.1)	0.340
APACHE II score, median (IQR)	21 (17, 28)	19 (16, 26)	23 (20, 29)	0.017
Charlson comorbidity index, median (IQR)	2 (1, 3)	2 (1, 3)	1 (1, 2)	0.199
Disease, n (%)				0.014
Cardiovascular	50 (42)	23 (32)	27 (57)	
Respiratory	27 (23)	23 (32)	4 (9)	
Abdominal surgery	21 (18)	13 (18)	8 (17)	
Sepsis	12 (10)	6 (9)	6 (13)	
Other	8 (7)	6 (9)	2 (4)	
Fentanyl, μg/kg/day, median (IQR)†	14.5 (9.7, 20.5)	16.3 (11.1, 21.7)	13 (6.7, 18.8)	0.038
Propofol, mg/kg/day; median (IQR)†	2.2 (0.4, 12.4)	1.7 (0.2, 6.0)	4.4 (0.5, 15.8)	0.076
Dexmedetomidine, μg/kg/day; median (IQR)†	5.2 (2.2, 8.4)	5 (2.2, 7.8)	6.1 (2.1, 8.6)	0.388
Benzodiazepine, n (%)	29 (25)	18 (25)	11 (23)	1
Length of ICU stay, days; median (IQR)	12.5 (9.0, 18.0)	12.5 (8, 16)	13 (9, 17)	0.458
ICU mortality, n (%)	17 (14)	14 (20)	3 (6)	0.06
Mechanical ventilation, days; median (IQR)	8 (5.0, 16.0)	9.5 (5, 14.3)	8 (5, 15.5)	0.802
Fluid balance on first ICU day, mL; median (IQR)	2,969 (278, 7,410)	2,063 (25, 6,283)	7,881 (4,244, 10,551)	<0.001
Fluid balance on day 2, mL; median (IQR)	511 (−303, 1,937)	525 (−240, 1,891)	394 (−326, 2,426)	0.952
Fluid balance on day 3, mL; median (IQR)	38 (−1,058, 1,305)	273 (−633, 1,412)	−532 (−1,465, 602)	0.06
Cumulative fluid balance from day 1 to day 3, mL; median (IQR)	5,663 (1,868, 8,803)	3,238 (281, 6,530)	7,886 (4,106, 10,631)	<0.001
Weight change on first ICU day, kg; median (IQR)	3.6 (0.9, 7.6)	2.5 (0.5, 3.8)	8.5 (6.9, 10.9)	<0.001
CVP on first ICU day, mmHg; median (IQR)	13 (11, 17)	12 (9, 16)	13 (11, 18)	0.134
RASS on first ICU day, median (IQR)	−4 (−5, −1)	−3 (−5, 0)	−5 (−5, −3.5)	<0.001
Prevalence of delirium within 7 days, n (%)	81 (69)	45 (63)	36 (77)	0.158
Delirium days, median (IQR)	1 (0, 3)	1 (0, 3)	2 (1, 3)	0.048
Coma days, median (IQR)	2 (1, 4)	1 (0, 3)	2 (1, 4)	0.012
DCDs within 7 days, median (IQR)	4 (2, 6)	4 (1, 5)	6 (3, 7)	0.002

APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; CVP, central venous pressure; DCD, delirium and coma day; ICU, intensive care unit; IQR, interquartile range; RASS, Richmond agitation sedation scale.
†Used average of days of mechanical ventilation.

According to the Frank–Starling principle, increased capillary transmural hydrostatic pressure increases transmural fluid leak into the interstitial tissue, causing organ edema and leading to organ dysfunction. Additionally, based on the venous return theory,[26] central venous pressure can be used as a parameter of back pressure that reflects venous resistance and is associated with the organ dysfunction. In the Vasopressin in Septic Shock Trial, Boyd and colleagues reported that FO and increased central venous pressure cause an increase in mortality of critically ill patients.[3] Theoretically, FO could cause acute brain dysfunction and long-term cognitive impairment. However, Mikkelsen *et al.*[27] reported cognitive and psychiatric morbidities were long-lasting in survivors of critical illness and they found an association between conservative fluid management strategy and long-term cognitive impairment. The findings of the Mikkelsen *et al.* study conflict with our hypothesis, however, they could not show indirect evidence for reduced cerebral perfusion. Thus, we considered two possible mechanisms connecting fluid balance and brain dysfunction. First,

Table 2. Results of multivariate proportional odds logistic regression model for prolonged delirium/coma days in mechanically ventilated patients

Variable	Unadjusted OR	95% CI	*P*-value	Adjusted OR	95% CI	*P*-value
Fluid overload (yes/no)	2.95	(1.51–5.75)	0.002	2.16	(1.05–4.47)	0.037
Covariates						
Sex	1.56	(0.81–2.98)	0.183	1.54	(0.76–3.13)	0.228
APACHE II	1.10	(1.05–1.15)	<0.001	1.08	(1.03–1.14)	0.001
Days of mechanical ventilation	1.06	(1.01–1.11)	0.016	1.10	(1.03–1.18)	0.005
Benzodiazepine (yes/no)	2.74	(1.25–6.01)	0.012	2.79	(1.12–6.94)	0.027
Dexmedetomidine[†]	1.00	(0.99–1.01)	0.552	1.00	(0.94–1.01)	0.789
Fentanyl[†]	0.99	(0.99–1.00)	0.510	0.99	(0.99–0.99)	0.002
Propofol[‡]	1.01	(1.00–1.01)	<0.001	1.01	(1.01–1.01)	<0.001

APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; OR, odds ratio.
[†]Used accumulated dosage per body weight, μg/kg.
[‡]Used accumulated dosage per body weight, mg/kg.

brain dysfunction might occur with FO, which can lead to organ edema and organ dysfunction. Second, brain dysfunction might be caused by microcirculatory disturbance with reduced fluid administration. Both FO and reduced fluid administration could be the cause of brain dysfunction.

Our data showed that only increased dosage of fentanyl decreased DCDs. In general, excessive administration of sedative drugs and opioid analgesics induces delirium and coma;[28,23] however, severe pain negatively affects outcomes in critically ill patients.[29] Thus, the negative side-effects of opioid analgesics do not exceed their benefits in terms of delivering efficacious pain management, the provision of which could be protective against acute brain dysfunction.

Our findings are not intended to limit the use of aggressive fluid resuscitation in appropriate clinical settings. Instead, if the associations presented in our study reflect an actual causal relationship between FO and delirium/coma days as a phenotype of acute brain dysfunction, those involved in critical care should be aware of the potential risks of fluid provision and approach it carefully. An awareness of the factors that increase the risk for delirium in the ICU is crucial for better understanding this complex syndrome and for the design of prevention programs.

There are important limitations of this study to consider. First, this was a retrospective cohort study of patients at a single center, and thus was able to examine only a limited number of patients. Second, we decided to set the criterion for patients who stayed in the ICU for more than 7 days in order to examine the deterioration of the DCDs. Therefore, more severe critically ill patients, who died within a short period, were not included in this analysis, yielding potential selection bias. Finally, although our study partially indicated an association between FO and DCDs, there was no evidence for reduced cerebral perfusion as the intermediator for the observed association. Our results, however, indicate that FO is a potential risk factor for brain dysfunction.

CONCLUSION

IN CONCLUSION, OUR findings suggest that FO was associated with increased DCDs in mechanically ventilated patients. This is a hypothesis-generating study; therefore, further prospective studies are needed to investigate whether FO can cause acute brain dysfunction or prolonged cognitive outcomes in mechanically ventilated critically ill patients.

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DISCLOSURE

Approval of the research protocol: This study was approved by the Ethics Committee of the University of Tsukuba Hospital, Tsukuba, Japan (H27-087).
Informed consent: N/A.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.
Conflict of interest: None.

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