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ORIGINAL PAPER

The impact of intravenous isotonic and hypotonic maintenance fluid on the risk of delirium in adult postoperative patients: retrospective before-after observational study

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Abstract

Purpose To assess the impact of intravenous isotonic and hypotonic maintenance fluid on the risk of delirium in adult postoperative patients, we conducted retrospective before-after study in a tertiary teaching hospital.

Methods We examined all adult patients admitted ICU after an elective operation for head and neck cancer, or esophageal cancer from February 2014 to January 2017. From February 2014 to July 2015, patients were administered hypotonic fluid (sodium; 35 mmol/L) as the National Institute for Health and Care Excellence (NICE) have recommended. From August 2015 to January 2017, patients were administered isotonic fluid (sodium; 140 mmol/L). We defined the incidence of delirium as the primary outcome. The delirium was defined as the Intensive Care Delirium Screening Checklist during the ICU stay ≥ 4. A propensity score-matched model was used to adjust confounders.

Results As postoperative intravenous maintenance fluid, hypotonic fluid was administered to 119 patients and isotonic fluid was administered to 92 patients. Among those total cohorts, the incidence of postoperative delirium in the hypotonic group was 21.8%, which was significantly higher than that (9.8%) in the isotonic group ($p = 0.019$). After propensity score matching, we selected 77 patients in each group. The incidence of delirium during the ICU stay in the hypotonic group was 26.0%, which was significantly higher than the incidence of 11.7% in the isotonic group ($p = 0.023$).

Conclusions In this study, the use of postoperative hypotonic maintenance fluid was associated with a higher risk of postoperative delirium than that when isotonic maintenance fluid was used.

Keywords Delirium · Fluid therapy · Hyponatremia · Postoperative period · Sodium

Introduction

Fluid therapy plays an important role in perioperative management. The goal of postoperative fluid therapy is to maintain normal fluid and electrolyte balance in postoperative patients who are unable to control their own fluid intake [1]. The National Institute for Health and Care Excellence (NICE) have recommended the administration of 25–30 ml/kg/day of water with 33–40 mmol/L of sodium as a routine maintenance fluid for hospitalized adult patients [2]. Then, it is reported that hypotonic fluid was one of the major maintenance fluids used in the postoperative patients who required intensive care [3]. Furthermore, based on the small randomized controlled trial, the British consensus guidelines on intravenous fluid therapy for adult surgical patients recommended to use a hypotonic fluid with a low sodium concentration as postoperative intravenous maintenance fluid [4]. Considering these facts, hypotonic fluid with low sodium concentration might be one of the major choices for postoperative intravenous maintenance fluid.

However, the use of hypotonic fluids has been reported to be associated with an increased risk of postoperative hyponatremia [5]. Then, it is known that hyponatremia is one of the risk factors of postoperative delirium [6]. In this regard, it is unfortunate that there has been no study comparing the effects of hypotonic and isotonic postoperative maintenance fluids on the incidence of postoperative delirium.

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Accordingly, we conducted a retrospective before-after study to assess the impact of intravenous isotonic and hypotonic maintenance fluid on the risk of delirium in adult postoperative patients, as a hypothesis generating preliminary study.

Methods

Study design

This study was a single-center retrospective before-after study. The study site is a tertiary teaching hospital with 30 intensive care unit (ICU) beds. This study is to explore the impact of the select of postoperative maintenance fluid on the postoperative delirium as patients' centered outcome following the previous study [5] with new protocol and fresh ethics approval. Accordingly, some of included patients were overlapped with previous study [5]. The Kobe University Hospital Ethics Committee approved this investigation (No 180026, approved on April 20, 2018). The committee waved the need for informed consent for the current study.

Patients and postoperative fluid management

We examined all adult patients admitted ICU after an elective operation for head and neck cancer, or esophageal cancer from February 2014 to January 2017. Inclusion criteria for the current study were patients required postoperative intensive care for >48 h. During the study period, the attending physician decided to discharge a patient from the ICU when the patient's physiologic status had stabilized as like free from the instability of hemodynamics and no fear of the requirement of mechanical ventilation or renal replacement therapy. We excluded patients who received other types of intravenous maintenance fluid. We also excluded patients with missing information.

Patients admitted to the ICU from February 1, 2014, to July 31, 2015, were administered intravenous maintenance fluid contained 35 mmol/L of sodium (hypotonic group) as NICE guideline recommended. And patients admitted to the ICU from August 1, 2015, to January 31, 2017, were administered intravenous maintenance fluid contained 140 mmol/L of sodium (isotonic group) (supplemental Table 1). The maintenance fluid was given with approximately "body weight (kg) + 20 ml/hour". Ringer's solution was administrated for correction of hypovolemia in both groups. In the afternoon of postoperative day (POD) 2, enteral nutrition was routinely started.

Patients' information

We obtained age, sex, body weight, American Society of Anesthesiology physical status (ASA-PS), Acute Physiology and Chronic Health Evaluation (APACHE) II score, operation category, and serum creatinine level at ICU admission as patients' baseline characteristics from the hospital's electronic medical records. We further collected the presence of hypertension, smoking history, alcohol history, the past history of cerebral infarction and dementia, the proportion of respiratory component in sequential organ failure assessment (SOFA) score equal or more than 2 ($PaO_2/F_IO_2 \leq 300$ mmHg) [7] and the presence of metabolic acidosis (Base excess < -2 mmol/L and pH < 7.35) during first 24 h after ICU admission.

Postoperative delirium

During the study period, we routinely evaluated the Intensive Care Delirium Screening Checklist (ICDSC) every 8 h after the operation during the ICU stay. We defined the presence of delirium as at least one item of the ICDSC during the ICU stay being equal to or more than 4. We also routinely assessed the Richmond Agitation Sedation Scale (RASS) score simultaneously with the ICDSC to define subtypes of delirium. At the point of ISDSC ≥ 4, we defined hyperactive delirium as an RASS score of equal to or more than $+1$ and we defined hypoactive delirium as an RASS score of 0 to -3. For patients who had both hyperactive delirium and hypoactive delirium during the ICU stay, we defined the delirium as mixed delirium.

Perioperative intravenous infusion, urine output, catecholamine administration, the use of midazolam, dexmedetomidine, haloperidol and analgesia

We collected information on intraoperative and postoperative intravenous infusion and urine output from ICU admission to 6 a.m. of POD 3. Patients were administrated catecholamine to maintain systemic blood pressure more than 90 mmHg. Thus, we have collected the presence or absence of postoperative catecholamine administration.

We further collected the postoperative use of midazolam, dexmedetomidine, haloperidol, acetaminophen and flurbiprofen axetil, and the total dose of fentanyl administrated from ICU admission to 6 a.m. of POD 3.

Postoperative serum sodium concentration and estimated serum osmolality

The cumulative dose of intravenous sodium administration was calculated. During the study period, at ICU admission and at every 6 a.m., serum sodium concentration (mmol/L) and glucose concentration (mg/dL) were measured by ABL800 FLEX ® (Radiometer, Copenhagen, Denmark). Blood urea nitrogen (BUN) concentration (mg/dL) was

also measured using the urease-GLDH method. They were stored electronically and retrieved for this study. We calculated estimated serum osmolality (mOsm/kg) using the following formula: 2*sodium(mmol/L) + glucose(mg/dL)/18 + BUN(mg/dL)/2.8 [8].

Statistical analysis

The results are shown as medians with inter-quartile range (IQR) or *n* (%). We defined the incidence of delirium during ICU stay as the primary outcome. Included patients were separated into a hypotonic group and an isotonic group. We compared these two groups using the chi-squared test and Mann–Whitney *U* test as appropriate.

To calculate the sample size for the current study, we considered a relative difference of 50% in the incidence of delirium to be meaningful. Assuming delirium would be 35%, the number of operation in each period would be same, an α level of 0.05, and a power of 0.80, approximately 110 participants were required in each cohort. With considering approximately 66.6% of patients underwent an elective target operations had required postoperative intensive care for more than 48 h, those of 20% might use other types of intravenous maintenance fluid, and 10% of patients was excluded due to lack of reliable information. Therefore, we have planned to screen 450 adult patients. As study site performed about 150 those operation per year, and study period was decided as February 2014 to January 2017 (3 years).

Given the differences between the characteristics of two groups, propensity score matching was used to identify a cohort of patients with similar characteristics. We used age, sex, weight, ASA-PS, APACHE II score, operation categories, operation time, and serum sodium and creatinine levels at ICU admission as covariates. Matching was conducted with 1:1 matching using nearest-neighbor matching without replacement, with a caliper width equal to 0.02 in propensity score units. We used the standardized mean difference (SMD) to measure covariate balance, with an absolute standardized mean difference above 0.1 representing meaningful imbalance. Then we compared the matched hypotonic group and isotonic group.

To understand the association of hyponatremia and blood glucose level with the risk of delirium, we compared the incidence of hyponatremia using log-rank test and the blood glucose level using Mann-whiney test between patients with and without delirium.

This study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. We used R to perform statistical analysis. A p value < 0.05 was defined as a statistically significant difference.

Results

Study flow

A total of 427 patients underwent an elective target operations during the study period (Fig. 1). Among them, 286 patients stayed in the ICU for > 48 h. Of those 286 patients, we excluded 45 patients with missing data. There were 30 patients who received other types of intravenous maintenance fluid. Finally, we included 211 patients in the current study. Among the 211 study patients, there were 119 patients who received hypotonic fluid (hypotonic group) and 92 patients who received isotonic fluid (isotonic group).

Comparison of the characteristics of patients in the hypotonic group and isotonic group in the total cohort

There was no significant difference of patients' characteristics except for operation time between the hypotonic group and isotonic group in the total cohort (Table 1, left). The median operation time in the hypotonic group

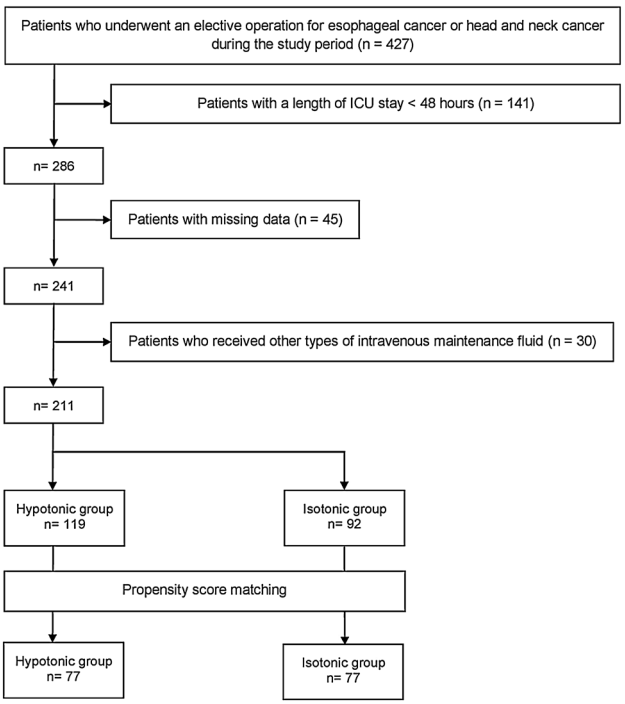

Fig. 1 Study flow. A total of 427 patients underwent an elective operation for esophageal cancer or for head and neck cancer during the study period. Among them, there were 286 patients who stayed in the ICU for more than 48 h. Finally, we included 211 patients (119 patients who received hypotonic fluid and 92 patients who received isotonic fluid) in this study. After propensity score matching, we selected 77 patients in each group

Table 1 Comparison of the characteristics of patients in the hypotonic and isotonic groups

	Before matching (total cohort)				After matching (propensity score-matched cohort)			
	hypotonic group ($n=119$)	isotonic group ($n=92$)	p value	S.M.D.	hypotonic group ($n=77$)	isotonic group ($n=77$)	p value	S.M.D.
Age (years old)	68 (61, 74)	69 (60, 74)	0.70	0.04	67 (62, 74)	69 (60, 74)	0.93	0.02
Male *n* (%)	86 (72.3%)	70 (76.1%)	0.53	0.09	55 (71.4%)	56 (72.7%)	0.86	0.03
Body weight (kg)	55.4 (49.3, 62.8)	56.0 (50.5, 64.9)	0.37	0.07	55.4 (49.5, 62.2)	55.7 (50.2, 64.9)	0.59	0.03
ASA-PS	2 (2, 2)	2 (2, 2)	0.84	0.03	2 (2, 2)	2 (2, 2)	0.99	0
APACHE II	11 (9, 13)	11 (9, 14)	0.29	0.18	11 (10, 14)	11 (9, 14)	0.53	0.06
Operation categories								
Esophageal cancer *n* (%)	54 (45.4%)	34 (37.0%)	0.22	0.17	27 (35.1%)	30 (39.0%)	0.62	0.08
Head and neck cancer *n* (%)	65 (54.6%)	58 (63.0%)	0.22	0.17	50 (64.9%)	47 (61.0%)	0.62	0.08
Operation time (min)	688 (622, 753)	659 (575, 709)	0.01	0.23	671 (608, 744)	662 (579, 710)	0.24	0.08
Serum sodium level at ICU admission (mmol/L)	139 (137, 141)	139 (137, 141)	0.93	0.03	139 (137, 141)	139 (137, 141)	0.71	0.09
Serum creatinine level at ICU admission (mg/dL)	0.79 (0.65, 0.93)	0.80 (0.65, 0.96)	0.55	0.13	0.77 (0.63, 0.95)	0.78 (0.63, 0.96)	0.83	0.07
Propensity score	0.41 (0.36, 0.47)	0.45 (0.40, 0.51)	0.001	0.38	0.43 (0.39, 0.51)	0.44 (0.39, 0.51)	0.95	0.007
Incidence of delirium *n* (%)	26 (21.8%)	9 (9.8%)	0.019	-	20 (26.0%)	9 (11.7%)	0.023	-

The results are shown as median with inter-quartile range or as *n* (%)

SMD standardized mean difference, *ASA-PS* American Society of Anesthesiology physical status, *APACHE* acute physiology and chronic health evaluation

was 688 min, which was significantly longer than that of 659 min in the isotonic group ($p=0.01$). The incidence of postoperative delirium in the hypotonic group was 21.8%, which was significantly higher than that (9.8%) in the isotonic group ($p=0.019$) (Table 1, left bottom).

Since we found significant heterogeneity between the hypotonic and isotonic groups, we conducted propensity score matching to adjust for the potentially confounding variables. After propensity score matching, we selected 77 patients in each group (Fig. 1). After propensity score matching, the standardized mean differences were less than 0.1 among all variables (Table 1, right). Thus, the covariate balance in the matched cohort appeared to be considerably improved. We also found that the presence of hypertension (31.2% vs 33.8%, SMD = 0.06), smoking history (61.0% vs 63.6%, MSD = 0.05), alcohol history (57.1% and 58.4%, MSD = 0.03) and the past history of cerebral infarction (7.8% vs 7.8%, MSD = 0) and dementia (2.6% vs 1.3%, MSD = 0.09), the respiratory component in SOFA score ≤ 2 (44.2% vs 48.1%, MSD = 0.07), the presence of metabolic acidosis (16.9% and 15.6%, MSD = 0.03) were well balanced between two cohorts.

Perioperative intravenous infusion, urine output, catecholamine administration, the use of midazolam, dexmedetomidine, haloperidol and analgesia in the propensity score-matched cohort

In the propensity score-matched cohort, the median total volume of intravenous fluid during operation and from ICU admission to POD 3 (6 a.m.) was not significantly differed between two groups (hypotonic vs isotonic; during operation, 5052 ml [IQR:4326, 5877] vs 5258 ml [IQR:4519, 6013], $p=0.36$; from ICU admission to POD 3, 5060 ml [IQR: 4565, 5646] vs 5060 ml [IQR: 4450, 5651], $p=0.43$). There was also no significant difference in total urine volume during operation and from ICU admission to POD 3 (6 a.m.) (hypotonic vs isotonic; during operation, 1085 ml [IQR:714, 1985] vs 1210 ml [IQR:647, 1932], $p=0.54$; from ICU admission to POD 3, 4205 mL [3342, 5043] vs 3965 ml [3300, 4366], $p=0.14$).

From ICU admission to POD 3, the patients administrated dopamine or noradrenaline was 41.6% and 6.5% in hypotonic group, which is not significantly differed with

those of 30.0% ($p = 0.13$) and 5.2% ($p = 0.73$). There was also no significant difference on the use of midazolam ($p = 0.73$), dexmedetomidine ($p = 0.10$), haloperidol ($p = 0.21$), acetaminophen ($p = 0.51$) and flurbiprofen axetil ($p = 0.13$), and the total dose of fentanyl administrated ($p = 0.68$) between two groups.

Postoperative cumulative dose of intravenous sodium administration in the propensity score-matched cohort

Figure 2 shows the cumulative doses of intravenous sodium administration in the two groups. Patients in the isotonic group received a significantly higher dose of sodium than did patients in the hypotonic group ($p < 0.001$).

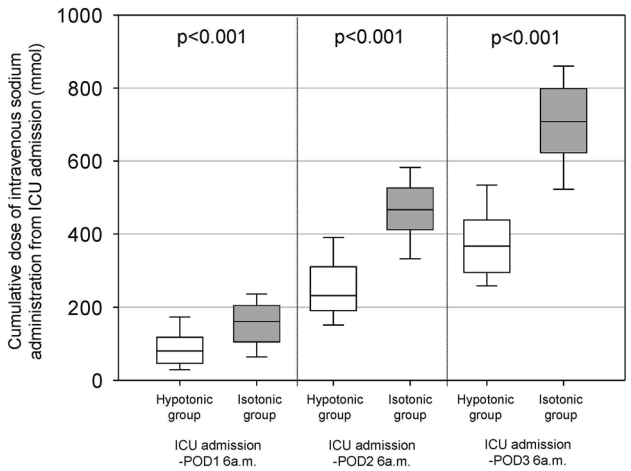

Fig. 2 Comparison of the cumulative doses of intravenous sodium administration in the propensity score-matched cohort. Gray box plots (isotonic group) and white box plots (hypotonic group) indicate the cumulative doses of intravenous sodium administration from ICU admission to POD 1 (left), POD 2 (middle) and POD 3 (right). Patients in the isotonic group received a significantly higher dose of sodium than did patients in the hypotonic group ($p < 0.001$)

Serum sodium concentration and estimated serum osmotic pressure in the propensity score-matched cohort

Table 2 shows a comparison of postoperative serum sodium concentrations and estimated values of serum osmolality in the two groups in the propensity score-matched cohort. At ICU admission, there were no significant difference in serum sodium concentration and estimated serum osmolality (sodium: $p = 0.60$, osmolality: $p = 0.54$). From POD 1 to POD 3, the hypotonic group had significantly lower serum sodium concentrations compared with isotonic group. The postoperative estimated values of osmolality in the hypotonic group were significantly lower than those in the isotonic group at POD2 and POD3.

Incidences of postoperative delirium in the hypotonic and isotonic groups in the propensity score-matched cohort

Among the 154 patients in the propensity score-matched cohort, the incidence of postoperative delirium in the hypotonic group was 26.0%, which was significantly higher than that (11.7%) in the isotonic cohort (odds ratio, 2.65; 95% CI, 1.12–6.28; $p = 0.023$) (bottom line in Table 1). In the isotonic group, the postoperative delirium was first diagnosed at median of POD 3 (IQR: 3, 4), which was not significantly different with those of POD 3 (IQR: 3, 4) in the hypotonic group ($p = 0.19$). Figure 3 shows the incidences of each subtype of delirium in the hypotonic and isotonic cohort.

There are no significant difference of blood glucose level between patients with and without delirium (with delirium vs without delirium, ICU admission; median of 141 mg/dL vs 141 mg/dL, $p = 0.12$, POD1; 155 mg/dL vs 167 mg/dl, $p = 0.07$, POD2; 133 mg/dL vs 132 mg/dL, $p = 0.56$, POD3; 136 mg/dL and 140 mg/dL, $p = 0.57$). The incidence of hyponatremia was significantly higher in patients with delirium in compared with those without delirium ($p = 0.043$) (Fig. 4).

Table 2 Comparison of serum sodium concentrations and estimated values of serum osmolality in the hypotonic and isotonic groups

	Serum sodium concentration (mmol/L)			Estimated serum osmolality (mOsm/kg)		
	Hypotonic group ($n = 77$)	Isotonic group ($n = 77$)	p value	Hypotonic group ($n = 77$)	Isotonic group ($n = 77$)	p value
ICU admission	139 (137, 141)	139 (137, 141)	0.60	290 (287, 296)	290 (286, 294)	0.54
POD1	137 (135, 139)	138 (136, 140)	0.003	288 (282, 291)	289(285, 292)	0.066
POD2	135 (132, 137)	138 (136, 140)	< 0.0001	282 (276, 287)	289 (284, 294)	< 0.0001
POD3	135 (132, 138)	138 (136, 141)	< 0.0001	281 (277, 287)	290 (284, 294)	< 0.0001

POD postoperative day

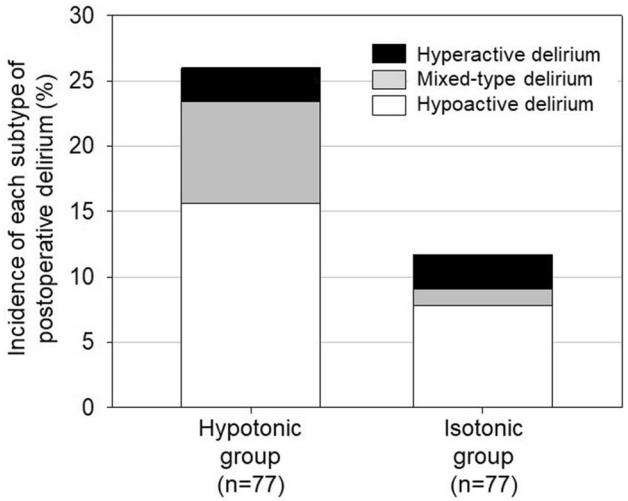

Fig. 3 Incidence of each subtype of postoperative delirium. The bars indicate the incidence of each type of postoperative delirium in the propensity score-matched cohort. The white, gray and black bars indicated the incidence of hypoactive, mixed-type and hyperactive delirium, respectively. The incidence of postoperative delirium in the hypotonic group was 26.0%, which was significantly higher than that (11.7%) in the isotonic group (odds ratio, 2.65; 95% CI, 1.12–6.28; $p = 0.023$)

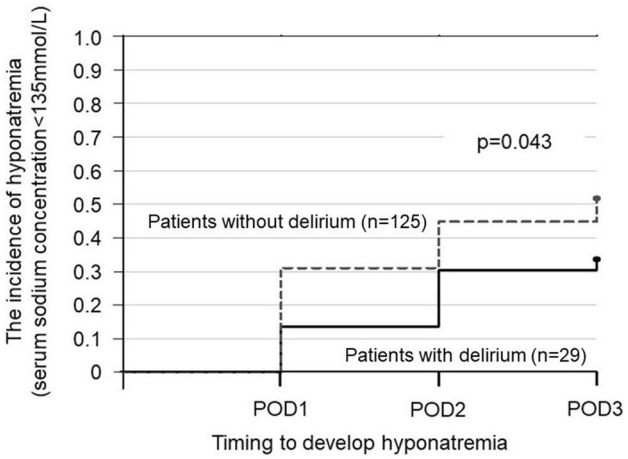

Fig. 4 Comparison of the incidence of hyponatremia between patients with and without delirium in the propensity score-matched cohort. The black and dotted lines indicated the incidence of hyponatremia (serum sodium concentration < 135 mmol/l) in patients with and without delirium. The incidence of hyponatremia was evaluated using log-rank test. The incidence of hyponatremia was significantly higher in patients with delirium in compared with those without delirium ($p = 0.043$)

Discussion

In our retrospective before-after observational, when the postoperative maintenance fluid contained 35 mmol/L of sodium as NICE guideline recommended was used, there was a significantly higher risk of postoperative delirium in compared with when those contained 140 mmol/L of sodium was used. We also found that the use of hypotonic solution as postoperative maintenance fluid was significantly associated with lower estimated osmolality than that with the use of isotonic fluid. As there has been no study comparing the effects of hypotonic and isotonic maintenance fluids on the incidence of delirium in adult postoperative critically ill patients, current findings might be novel and relevant.

Although it is very common to use a maintenance fluid in adult postoperative critically ill patients, there is limited evidence on the optimal intravenous maintenance fluids in the postoperative period. Postoperative stimuli including volume depletion, hypotension, pain, stress, nausea, vomiting, hypoxemia, hypercapnia, and hypoglycemia may cause the increase of arginine vasopressin (AVP) levels [9, 10]. Since such an excess of AVP may decrease excretion of free water and result in hyponatremia, the common knowledge seen in healthy human being might not be able to be generalized to postoperative critically ill patients [11].

These have been two randomized controlled trials in which the effects of the different regimens for postoperative maintenance fluid were compared. Lobo and colleagues conducted a randomized controlled trial to compare the effects of a postoperative intravenous fluid with ≥ 3 L of water and 154 mmol sodium per day and a postoperative intravenous fluid with ≤ 2 L of water and 77 mmol sodium per day. They included 10 postoperative patients in each arm, and they reported that patients who received ≥ 3 L of water and 154 mmol sodium had delayed recovery of gastrointestinal function, increased complication rate, and extended hospital stay [12]. However, these results were not confirmed in a later randomized controlled trial conducted by MacKay and colleagues [13].

In the above-described two studies, two different hypotonic fluids with different doses were compared. Therefore, there has been no randomized controlled trial to compare the use of isotonic and hypotonic fluids as postoperative maintenance fluids. In this regard, our before-after study may be relevant to generate a hypothesis in this field.

Since there has been no study carried out to assess the difference between isotonic and hypotonic solutions as maintenance fluids in adult acutely ill patients, potentially relevant data may come from the pediatric setting. McNab and colleagues conducted a randomized controlled trial in 676 hospitalized pediatric patients who required intravenous maintenance hydration for > 6 h to compare the effects of an isotonic intravenous fluid containing 140 mmol/L of sodium and a hypotonic fluid containing 77 mmol/L of sodium. They reported that the use of the hypotonic fluid had a higher risk of hyponatremia (4% vs 11%, $p = 0.001$). They also

reported that seizures occurred in only one patient in the isotonic group (0.3%) but occurred in seven patients in the hypotonic group (2%) during the treatment period ($p = 0.07$) [14]. Accordingly, this large randomized controlled trial in a pediatric setting may be in the same line with our study.

The delirium is common complication in postoperative patients [15]. Postoperative delirium has been reported to frequently occur between POD 1 and POD 3. Although the delirium would be usually recovered within a short period [16], patients with postoperative delirium were more likely to die or develop dementia and require institutionalization [17]. Thus, its prevention seems to be important.

The alternation of maintenance fluid would affect to blood glucose level as well [5]. Our study revealed that there was a significant association of the incidence of hyponatremia with delirium, but not blood glucose level. Nonetheless, there is still no direct evidence that prevention of postoperative hyponatremia lowers the incidence of postoperative delirium. However, postoperative hyponatremia has been reported as significant risk factor of delirium [18–20]. It has also been reported to be associated with neuropsychiatric disorders including depression [21]. Additionally, acute hyponatremia has been reported to be a risk factor of hyponatremic encephalopathy [1]. Accordingly, our study may generate the hypothesis that the use of isotonic fluid rather than hypotonic fluid in postoperative critically ill patients may lower the risk of postoperative delirium.

Limitations

There are several limitations in the current study. First, our findings showed just an association but not a causality link, even after adjusted using propensity score matching analysis. Our study, however, might be relevant as a hypothesis-generating study. Second, our small single-center study has weak generalizability, thus external validation should be required. Third, our study is pre-planned retrospective study with power analysis using past information. Our power analysis indicated that 110 patients were required in each groups, thus we included patients for 3 years. However, during the study period, there were 119 and 92 patients in each period. To considering the incidence of delirium in each period, our study had a power of 0.63. In this regards, our study may have a risk of type I error. Thus, our finding should be verified by future studies with enough power. Forth, although our assessment of delirium and critical care management in postoperative patients was standardized throughout the study period, our results may be influenced by time-related differences regarding perioperative management. Therefore, future interventional studies should confirm or refute our findings. Fifth, we have included two types of operation in this study. Thus, this inclusion criteria might skew our results. However, we found that there is no significant interaction of the type of operation on the relationship between the incidence of delirium and the type of maintenance fluid ($p = 0.25$). Therefore, our results might be generalized in postoperative patients after both types of operations. Finally, we used ICDSC for assessment of delirium. Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) is another major tool to assess the postoperative delirium. However, it is reported that both CAM-ICU and ICDSC can be used as screening tools for diagnosis of delirium in critically ill patients [22].

Conclusion

In this study, the use of postoperative isotonic maintenance fluid was shown to be associated with a lower risk of postoperative delirium than that when hypotonic maintenance fluid was used. A future interventional study may be needed to refute or confirm our results.

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Authors' contributions M.N.: Study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, and critical revision of manuscript; M.E.: Study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, and critical revision of manuscript; N.F., M.O. and S.M.: acquisition of data, analysis and interpretation of data, drafting of manuscript, and critical revision of manuscript; SM: Study conception and design, interpretation of data, and critical revision of manuscript; All authors read and approved the final manuscript.

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