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Okada, Masako ; Egi, Moritoki ; Yokota, Yuri ; Shirakawa, Naotaka ; Fujimoto, Daichi ; Taguchi, Shinya ; Furushima, Nana ; Mizobuchi,…

(Citation)
Journal of Anesthesia,31(5):657-663

(Issue Date)
2017-10

(Resource Type)
journal article

(Version)
Accepted Manuscript

Comparison of the incidences of hyponatremia in adult postoperative critically ill patients receiving intravenous maintenance fluids with 140 mmol/L of sodium and 35 mmol/L of sodium: retrospective before-after observational study

Masako Okada M.D.[1], Moritoki Egi M.D. [1], Yuri Yokota M.D. [1], Naotaka Shirakawa M.D. [1], Daichi Fujimoto M.D. [1], Shinya Taguchi M.D. [1], Nana Furushima M.D. [1], Satoshi Mizobuchi M.D.,PhD. [1]

**Affiliation of the authors:**

[1] Department of Anesthesiology, Kobe University Hospital, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe city 650-0017, Japan

**Address for Correspondence to:**

Moritoki Egi, M.D.

Department of Anesthesiology, Kobe University Hospital

7 -5-1 Kusunoki-cho, Chuo-ku, Kobe city 650-0017, Japan

Phone: +81-78-382-6172 ; Fax: +81-78-382-6189

E-mail: moriori@tg8.so-net.ne.jp

Abstract

Purpose: Sodium-poor fluid, which is called hypotonic fluid, is currently recommended as intravenous maintenance fluid in critically ill adult patients. However, the use of such a hypotonic fluid may be associated with increased risk of hyponatremia. The purpose of this study was to compare the incidences of hyponatremia in adult postoperative critically ill patients receiving isotonic and hypotonic maintenance fluids.

Methods: This study was a single-center retrospective before-after observational study. We included patients who had undergone an elective operation for esophageal cancer or for head and neck cancer and who received postoperative intensive care for more than 48 hours during the period from August 2014 to July 2016. In those patients, sodium-poor solution (35 mmol/L of sodium; $Na_{35}$) had been administered as maintenance fluid until July 2015. From August 2015, the protocol for postoperative maintenance fluid was revised to the use of isotonic fluid (140 mmo/L of sodium; $Na_{140}$). The primary outcome was the incidence of hyponatremia (< 135mmol/L) until the morning of postoperative day (POD) 2.

Results: We included 179 patients ($Na_{35}$ cohort: 87 patients, $Na_{140}$ cohort: 92 patients) in the current study. The mean volume of fluid received from ICU admission to POD 2 was 3291 ml in the $Na_{140}$ cohort, which was not significantly different from the mean volume of 3337 ml in the $Na_{35}$ cohort (p=0.84). The incidence of postoperative hyponatremia was 16.3% (15/92) in the $Na_{140}$ cohort, which was significantly lower than that of 52.9% (46/87) in the $Na_{35}$ group (odds ratio=0.17 (95% confidence interval: 0.09-0.35), p<0.001). The incidences of hypernatremia, defined as serum sodium concentration >145 mmol/L, were not significantly different in the two groups.

Conclusion: In this study, the use of intravenous maintenance fluid with 35 mmol/L of sodium was significantly associated with increased risk of hyponatremia compared to that with 140 mmol/L of sodium in adult postoperative critically ill patients.

## Background

The choice of postoperative intravenous fluid is important [1]. The use a sodium-poor fluid, which is called hypotonic fluid [2, 3], continues to be recommended as intravenous maintenance fluid for acutely ill adult patients [4, 5]. However, several studies, mainly in pediatric patients, have suggested that the use of such a hypotonic fluid is associated with an increased risk for the development of hyponatremia [2, 6-8]. Hyponatremia is known to be associated with poor outcomes and, thus, should be avoided [9, 10]. Therefore, it is still unclear whether hyptonic fluid should be used in postoperative patients [3].

In the study site, sodium-poor fluid (35 mmol/L of sodium: $Na_{35}$) was routinely used as intravenous maintenance fluid for postoperative critically ill patients until the end of July 2015. According to the above concern, it was decided to use isotonic fluid (140 mmo/L of sodium: $Na_{140}$) as intravenous maintenance fluid from August 2015. Accordingly, we compared these two periods to determine the effect of sodium concentration in the postoperative intravenous maintenance fluid on the incidence of hyponatremia in adult postoperative critically ill patients

## Methods

*Study design and patients*

We conducted a single-center retrospective before-after study. The Kobe University Hospital Ethics Committee approved this investigation. The committee waived the need for informed consent for studies involving the use of a database. The study site is a tertiary teaching hospital and specialist referral center with 30 ICU beds.

We screened adult patients who underwent an elective operation for esophageal cancer or for head and neck cancer. Among them, we included patients who received postoperative intensive care for more than 48 hours during the period from August 2014 to July 2016. We excluded patients who had abnormalities in sodium concentration at the time of admission to the ICU (serum sodium concentration $<135$ mmol/L or $>145$ mmol/L). We also excluded patients with enteral feeding during the study period.

*Postoperative fluid management*

The study period was defined as the period from ICU admission to 6 am on POD 2. Patients admitted to the ICU in the period between August 1, 2014 and July 31, 2015 were administered sodium-poor solution with 35 mmol/L of sodium as postoperative maintenance fluid ($Na_{35}$ cohort) (Table 1). From August 1, 2015 to July 31, 2016, patients were given isotonic fluid with 140 mmol/L of sodium as maintenance fluid ($Na_{140}$ cohort) (Table 1). From ICU admission to the morning of POD 2, the rate of infusion of postoperative maintenance fluid was fixed at [1 ml/body weight (kg)+20 ml]/hour in both periods (Figure 1). In cases of hypovolemia, Ringer's solution was given in both groups. There was no protocol for correct sodium concentration during the study period.

*Patients' information*

Patient baseline characteristics were extracted from the hospital's electronic medical records. The following characteristics of patients in the $Na_{35}$ and $Na_{140}$ cohorts were compared: gender, age, sex, body weight, body mass index (BMI), operation category, American Society of Anesthesiology physical status (ASA-PS), operating time, serum creatinine level at ICU admission and APACHE (acute physiology and chronic health evaluation) II score [11]. Patients were discharged from the ICU when they did not require an inotrope or mechanical ventilation. We also obtained information on transfusion, amount of fluid received, and amounts of sodium and potassium administered.

*Postoperative sodium and potassium concentrations*

During the study period, serum sodium, potassium and glucose concentrations were routinely measured using ABL800 FLEX® (Radiometer, Copenhagen, Denmark) at ICU admission and at 6 a.m. on POD 1 and POD 2 (Figure 1). Data for serum sodium, potassium and glucose concentrations were stored electronically and retrieved. Enteral nutrition was routinely started in the afternoon of POD 2.

*Statistical analysis*

The primary outcome in this study was the incidence of hyponatremia defined as serum sodium level <135 mmol/L obtained at least once in the morning of POD 1 or POD 2. We also compared the incidences of hypernatremia, defined as serum sodium level >145 mmol/L, and serum sodium, potassium and glucose concentrations at ICU admission and at 6 a.m. on POD 1 and POD 2 as secondary outcomes.

To calculate the sample size for the current study, we hypothesized that the incidence of hyponatremia in the $Na_{35}$ group would be 50% and that the use of $Na_{140}$ fluid as maintenance fluid may be associated with 25% of the absolute difference. Assuming a ratio of patients in the $Na_{35}$ and $Na_{140}$ groups of 1:1, rate of exclusion of 15%, power of 0.90, and α level of 0.05, approximately 200 participants were required. As there were approximately 100 adult patients who underwent an elective operation for esophageal cancer or for head and neck cancer and who required postoperative intensive care for more than 48 hours, we conducted this study within 2 years (1 year for each period).

The results are shown as means with standard deviation or n (%). We divided the patients into an $Na_{35}$ group and an $Na_{140}$ group. We compared these two groups using the t-test, chi square test or two-way repeated ANOVA test as appropriate. We used R to perform statistical analysis. A P value <0.05 was defined as a statistically significant difference. When the two-way repeated ANOVA test showed a statistical difference between the two groups, we further performed post hoc analysis to analyze which time points make the significant difference. For this post-hoc test, a P value <0.0167 was defined as a statistically significant difference. Data were reported in accordance with the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) guidelines.

## Results

### *Study flow*

During the study period, there were 301 patients who underwent an elective operation for esophageal cancer or for head and neck cancer. Among them, 207 patients required postoperative intensive care for more than 48 hours. In those 207 patients, one patient had hypernatremia (serum sodium concentration of 147 mmol/L) and 22 patients had hyponatremia (average sodium concentration of 132.1 mmol/L) at the time of admission to the ICU. There were 5 patients with enteral feeding during the study period. The remaining 179 patients were included in this study. As postoperative maintenance fluid, $Na_{35}$ fluid was used in 87 patients and $Na_{140}$ fluid was used in 92 patients. There were no missing values for this study.

### *Patients' demographics*

Table 2 shows a univariate comparison of the demographics of patients for whom $Na_{35}$ fluid and $Na_{140}$ fluid were used as postoperative maintenance fluid. There was no significant difference in age, sex, body weight, ASA-PS, operation time, operation category, serum creatinine level at ICU admission and severity of illness between the two cohorts. A steroid was not administered in patients who underwent operation for esophageal cancer.

*Postoperative transfusion, postoperative infusion and urine output during the study period.*

Information on postoperative transfusion, fluid infusion and urine output during the study period (from ICU admission to 6 a.m. on POD 2) is shown in Table 3. The study period was not significantly different in the two groups (p=0.34). The amounts of red blood cell transfusion (p=0.12) and albumin transfusion (p=0.24) were not significantly different in the two cohorts.

During the study period, the mean volume of fluid received from ICU admission to POD 2 was 3291 ml in the $Na_{140}$ cohort, which was not significantly different from the mean volume of 3337 ml in the $Na_{35}$ cohort (p=0.68). The mean volume of Ringer's solution used to correct hypovolemia in the $Na_{35}$ cohort was 437 ml. The mean amount of saline infusion for drug delivery was 589 ml in the Na35 cohort, which was not significantly different from the mean amount of 505 ml in the $Na_{140}$ cohort. No patients were administered sodium concentrate to correct hyponatremia.

Patients in the $Na_{140}$ cohort received a total of 450 mmol of sodium on average, which was significantly larger than that of 243 mmol in the $Na_{35}$ group ($p<0.001$). Patients in the $Na_{140}$ group received a smaller amount of potassium ($p<0.001$). Urine output during the study period was not significantly different in the two cohorts (2491 ml vs 2294 ml on average, $p=0.18$).

Postoperative sodium concentration

Figure 2 shows a comparison of postoperative serum sodium concentrations. The postoperative sodium concentration was significantly different in the two cohorts ($p=0.0003$). The average serum sodium concentration at ICU admission in the $Na_{35}$ group was 139.2 mmol/L, which was not significantly different from the average concentration of 138.9 mmol/L in the $Na_{140}$ group (post hoc test; $p=0.36$). On POD 1 and POD 2, the serum sodium concentrations in the $Na_{35}$ group were significantly lower than those in the $Na_{140}$ group (post hoc test; mean sodium concentration on POD 1: 136.8 mmol/L vs 138.0 mmol/L, $p<0.001$; on POD 2: 134.7 mmol/L vs 137.9 mmol/L, $p<0.001$).

Incidences of hyponatremia and hypernatremia

The incidences of hyponatremia and hypernatremia are shown in Figure 3. The incidence of hyponatremia at least once in the morning of POD 1 or POD 2 was 16.3% (15/92) in the $Na_{140}$ group, which was significantly lower than that of 52.9% (46/87) in the $Na_{35}$ group (odds ratio=0.17 (95% confidence interval: 0.09-0.35), $p<0.001$). The incidences of hyponatremia on POD 1 and POD 2 were also significantly lower in the $Na_{140}$ group than in the $Na_{35}$ group (POD 1: 21.8% vs 5.4%, p=0.001, POD 2: 50.6% vs 16.3%, $p<0.001$). The incidences of hypernatremia were not significantly different in the two groups (POD 1: 0% vs 0%, p=1.00, POD 2: 1.2% vs 2.2%, p=0.59).

Postoperative potassium and glucose concentrations

Figure 4 shows a comparison of postoperative serum potassium concentrations. The postoperative serum potassium concentration was not significantly different in the two groups (p=0.23). Figure 5 shows a comparison of postoperative serum glucose concentrations. The postoperative serum glucose concentration was significantly different in the two groups (p=0.0007). In the post hoc test, serum glucose concentrations in the $Na_{140}$ group were significantly lower than those in the $Na_{35}$ group on POD 1 and POD 2. There was no hypoglycemia (defined as <40 mg/dL) in either group.

Postoperative outcomes

There was one non-survivors in each of the $Na_{35}$ and $Na_{140}$ cohorts (Table 2). The number of ICU free-survival days at POD 28 was not significantly different in the two cohorts (24.3 vs 23.8, p=0.34).

**Discussion**

**Key findings**

In this retrospective before-after observational study, we found that the use of postoperative maintenance fluid with 140mmol/L of sodium was associated with a lower incidence of hyponatremia than that when maintenance fluid with 35mmol/L of sodium was used. There was no significant difference between the incidences of hypernatremia in the two groups. We also found that there was no significant difference between serum potassium concentrations with $Na_{35}$ and $Na_{140}$ fluid administration. Since there is little information on the impact of postoperative maintenance fluid therapy on the incidence of hyponatremia in postoperative adult patients, our study is novel and relevant.

Comparison with prior studies.

Hyponatremia is one of the common complications in postoperative patients [12]. The incidences of hyponatremia (defined as serum sodium concentration <135 mmol/L) were reported to be 24.9% in patients who underwent head and neck surgery [13], 27.9% in patients who underwent orthopedic surgery [14] and 59% in patients who underwent cardiac surgery [15]. Hyponatremia was shown to be an independent risk factor of poor outcomes in acutely ill patients [9], and it may contribute to the occurrence of hyponatremic encephalopathy, especially in pediatric patients [10]. It is difficult to treat hyponatremia in acutely ill patients [3, 16]. Therefore, hyponatremia should be avoided in acutely ill patients including postoperative patients.

In normal conditions, humans have the ability to regulate serum sodium concentration despite differences in the environment and fluid or electrolyte intake [17]. This homeostasis of sodium concentration is regulated through the actions of arginine vasopressin (AVP), the renin–angiotensin–aldosterone system, and natriuretic peptides [3]. However, patients after invasive surgery may have states associated with an excess of AVP induced by various conditions including hypotension, pain, hypoxemia and inflammation. This excess AVP impairs excretion of free water and may aggravate hyponatremia [3, 18, 19]. Since postoperative patients have a restriction of oral intake, sodium concentration in postoperative intraoperative infusion fluid would contribute to the incidence of postoperative hyponatremia.

Although most previous studies were conducted in pediatric patients, there have been some interventional studies to assess the safety and efficacy of isotonic fluids compared with sodium-poor fluids for the prevention of hyponatremia in an acute care setting [2, 6-8]. These studies showed that sodium-poor fluids were associated with increased risk for the development of hyponatremia. Nonetheless, sodium-poor fluids continue to be recommended as maintenance fluids in acutely ill patients [4, 5], being based on theoretical calculations before the syndrome of inappropriate antidiuresis was recognized [3]. A lack of evidence regarding this issue in adult patients may be one of the reasons for such a recommendation.

## Limitations

This study has some limitations. First, this was an observational study in nature, which may be influenced by time-related differences regarding preoperative care, operation, anesthesia and postoperative management. Accordingly, this study is a hypothesis-generating study, not a conclusive study. Further interventional study should be conducted to refute or confirm our findings in postoperative critically ill adult patients.

Second, this was a small single-center study with weak generalizability. Thus, our findings should be validated in other study sites.

Third, we included patients who had undergone an elective operation for esophageal cancer or for head and neck cancer. Our findings might not be applicable in patients receiving other types of surgery. In this regard, a future study should be conducted in a different postoperative cohort.

Fourth, there was no information on the secretion of sodium in urine. In a future prospective study, sodium concentration in urine should be measured.

Finally, this study was conducted to assess the association of maintenance fluid with incidence of hyponatremia. Therefore, this study did not have enough power to assess other clinical outcomes. A large well-powered study should be conducted to compare the risks and benefits of hypotonic fluid and isotonic fluid.

## Conclusion

In this retrospective before-after observational study, the use of postoperative maintenance fluid with 35 mmol/L of sodium was significantly associated with increase in the incidence of hyponatremia compared with that using isotonic fluid with 140 mmol/L of sodium. Further study is necessary to refute or confirm this finding.

Figure legends

Figure 1. Summary of study.

POD: postoperative day, ICU: intensive care unit

Figure 2. Comparison of postoperative sodium concentrations.

Black and white circles show the mean serum sodium concentrations at ICU admission and at 6 a.m. on POD 1 and POD 2 in patients who received maintenance fluid with 35 mmol/L of sodium (black) and 140 mmol/L of sodium (white), respectively. Error bar indicates the 95% confidential interval. There was a significant difference between postoperative sodium concentrations in the two groups (two-way repeated ANOVA; $p=0.0003$). In the post-hoc test, serum sodium concentrations on POD 1 and POD 2 in the group with 35 mmol/L of sodium were significantly lower than those in the group with 140 mmol/L of sodium (POD 1: $p<0.001$, POD 2: $p<0.001$).

* at each time point indicates that the post-hoc test revealed a significant difference between the two groups.

POD: postoperative day, ICU: intensive care unit

Figure 3. Comparison of the incidences of postoperative hypernatremia and hyponatremia.

Black and white bars show the incidences of hypernatremia and hyponatremia at 6 a.m. on POD 1 and POD 2 in patients who received maintenance fluid with 35 mmol/L of sodium (black) and 140 mmol/L of sodium (white), respectively. The incidences of hyponatremia on POD 1 and POD 2 were also significantly lower in the group with 140 mmol/L of sodium than in the group with 35 mmol/L of sodium (POD1: $p=0.001$, POD2: $p<0.001$). The incidences of hypernatremia were not significantly different in the two groups (POD 1: $p=1.00$, POD 2: $p=0.59$).

* indicates that there was a significant difference between the two groups.

POD: postoperative day,

Figure 4. Comparison of postoperative potassium concentrations.

Black and white circles show the mean serum potassium concentrations at ICU admission and at 6 a.m. of POD 1 and POD 2 in patients who received maintenance fluid with 35 mmol/L of sodium (black) and 140 mmol/L of sodium (white), respectively. Error bar indicates the 95% confidential interval. There was no significant difference between postoperative sodium concentrations in the two groups (two-way repeated ANOVA; p=0.23).

POD: postoperative day, ICU: intensive care unit,

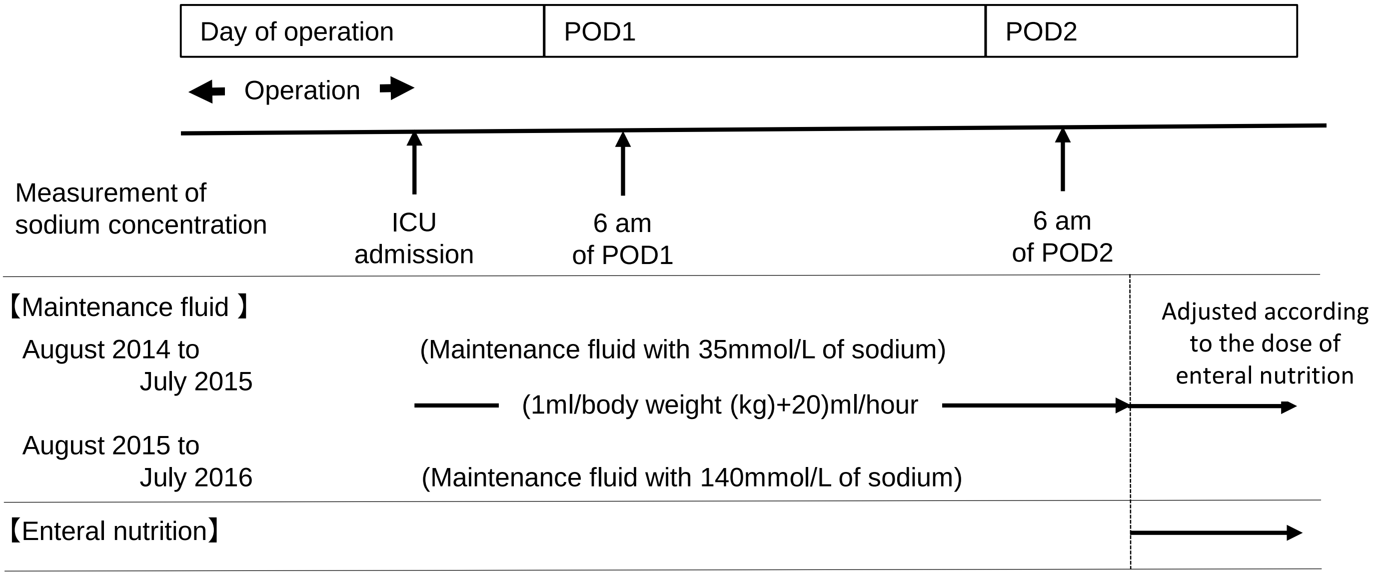
Figure 5. Comparison of postoperative serum glucose concentrations.

Black and white circles show the mean serum glucose concentrations at ICU admission and at 6 a.m. on POD 1 and POD 2 in patients who received maintenance fluid with 35 mmol/L of sodium (black) and 140 mmol/L of sodium (white), respectively. Error bar indicates the 95% confidential interval. There was a significant difference between postoperative serum glucose concentrations in the two groups (two-way repeated ANOVA; p=0.0007). In the post-hoc test, serum glucose concentrations on POD 1 and POD 2 in the group with 35 mmol/L of sodium were significantly higher than those in the group with 140 mmol/L of sodium (POD1: p=0.001, POD2: p=0.001).

* at each time point indicates that the post-hoc test revealed a significant difference between the two groups.

POD: postoperative day, ICU: intensive care unit

Figure 1



Day of operation
POD1
POD2
Operation
Measurement of sodium concentration
ICU admission
6 am of POD1
6 am of POD2
【Maintenance fluid 】
August 2014 to July 2015
(Maintenance fluid with 35mmol/L of sodium)
(1ml/body weight (kg)+20)ml/hour
August 2015 to July 2016
(Maintenance fluid with 140mmol/L of sodium)
Adjusted according to the dose of enteral nutrition
【Enteral nutrition】

Fig 2. Comparison of postoperative sodium concentrations

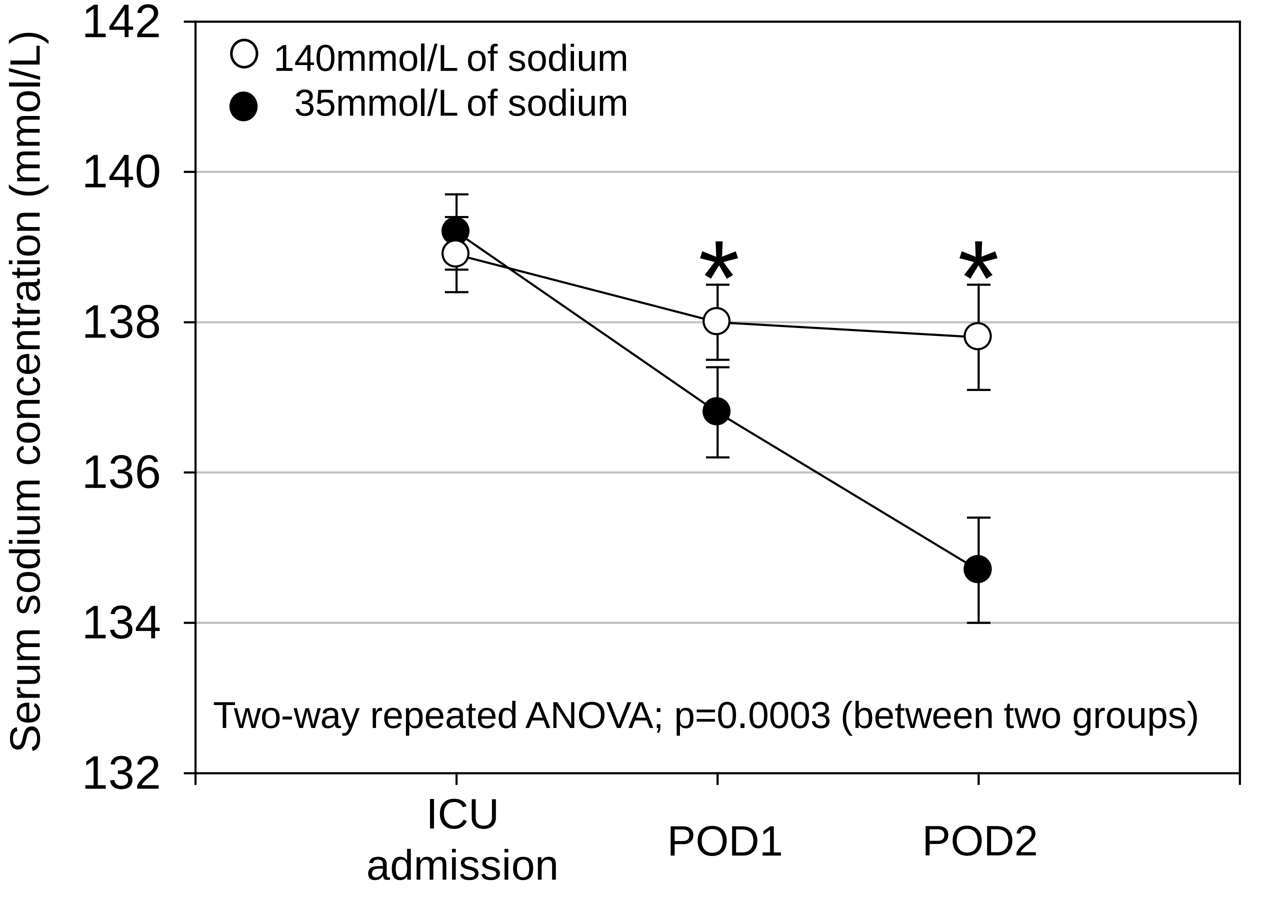


Fig 3. Comparison of the incidence pf postoperative hypernatremia and hyponatremia

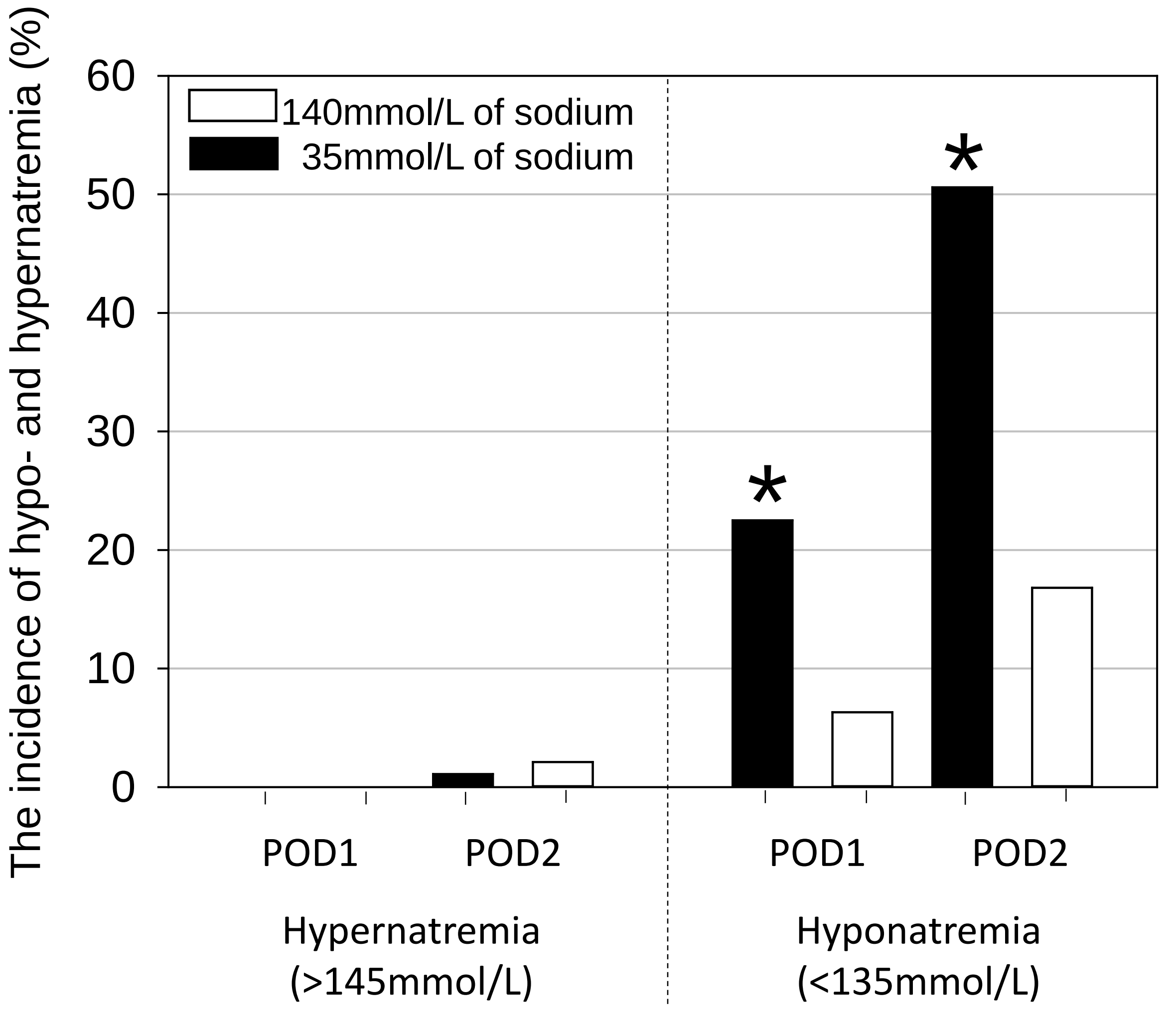


Fig 4. Comparison of postoperative potassium concentrations

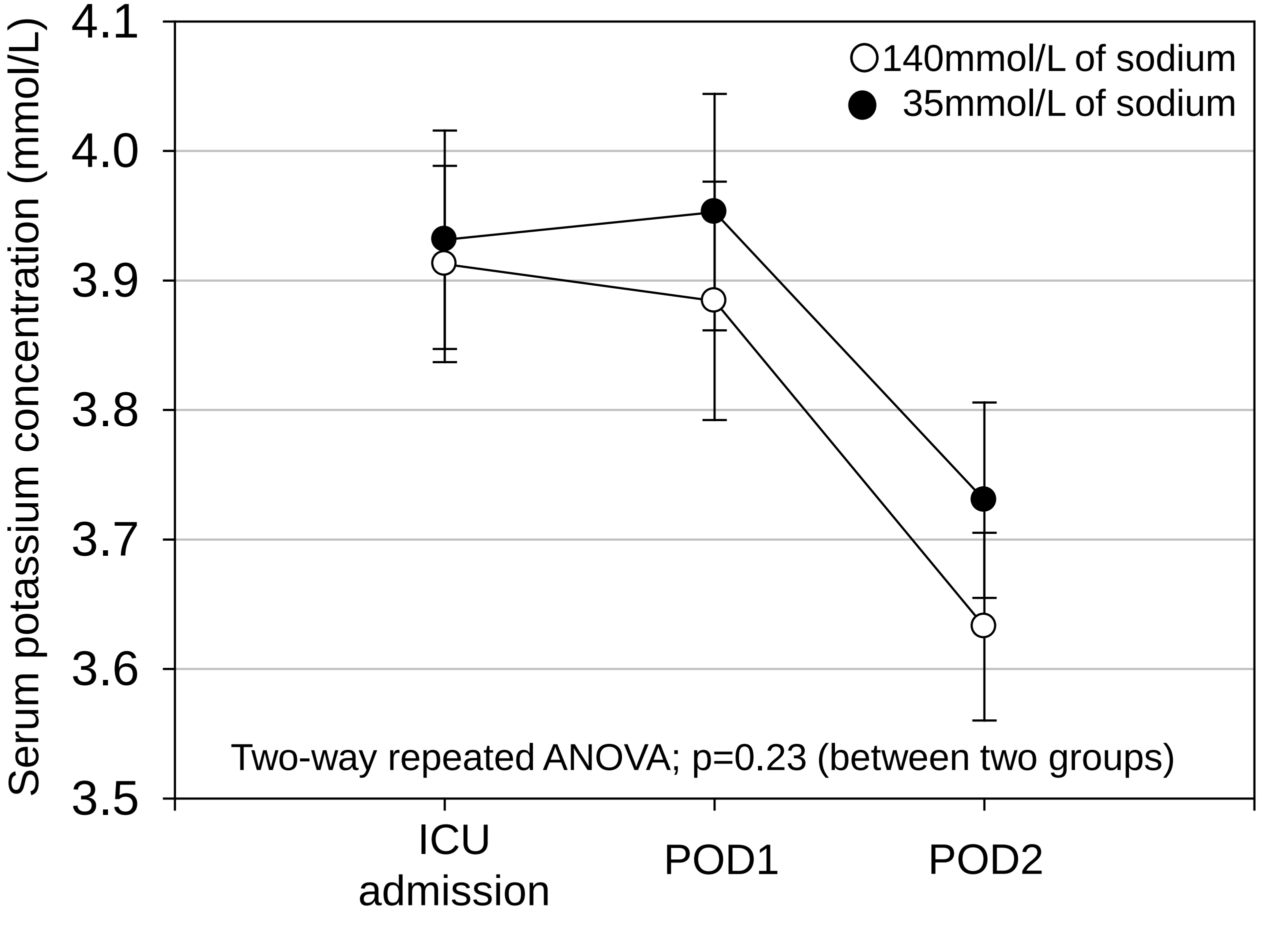


Fig 5. Comparison of postoperative blood glucose concentrations

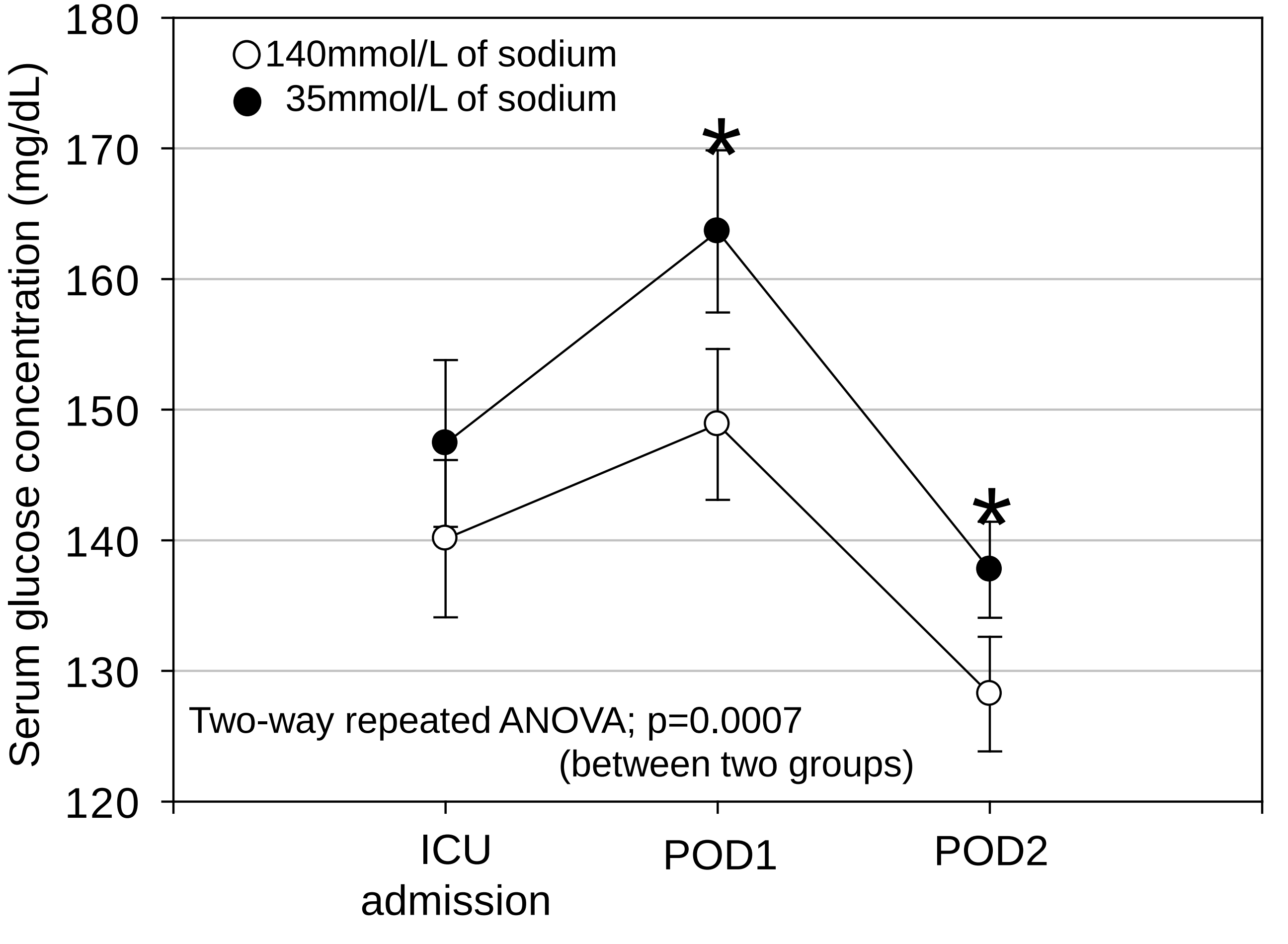


Table 1. Compositions of the two maintenance fluids

| | $Na^+$ (mmol/L) | $Cl^-$ (mmol/L) | $K^+$ (mmol/L) | Glucose (g/L) | Buffer (mEq/L) |
|---|---|---|---|---|---|
| Maintenance fluid with 35 mmol/L of sodium | 35 | 35 | 20 | 43 | Lactate; 20 |
| Maintenance fluid with 140 mmol/L of sodium | 140 | 115 | 4 | 5 | $Acetate^-$; 25, $Gluconate^-$; 3, $Citrate^{3-}$; 6 |

Table 2. Comparison of the demographics of patients.

| | Patients group using maintenance fluid with 35 mmol/L of sodium (n=87) | Patients group using maintenance fluid with 140 mmol/L of sodium (n=92) | p-value |
|---|---|---|---|
| Age (y.o) | 67 ± 10 | 67 ± 10 | 0.77 |
| Male n(%) | 63 (72%) | 72 (78%) | 0.39 |
| Body weight (kg) | 56.5 ± 12.8 | 57.5 ± 11.3 | 0.56 |
| BMI (kg/$m^2$) | 21.3 ± 4.3 | 21.5 ± 3.8 | 0.74 |
| ASA.PS | 2.0 ± 0.6 | 1.9 ± 0.5 | 0.21 |
| Operation time (min) | 664 ± 175 | 659 ± 143 | 0.82 |
| Operation categories | | | 0.99 |
| Esophageal cancer n(%) | 37 (43%) | 40 (44%) | |
| Head and neck cancer n(%) | 50 (58%) | 52 (57%) | |
| Serum creatinine level at ICU admission | 0.86 ± 0.58 | 0.85 ± 0.31 | 0.90 |
| APACHE II | 11 ± 4 | 12 ± 4 | 0.35 |
| Postoperative mortality (%) | 1(1.1%) | 1(1.1%) | 0.97 |
| 28 day ICU-free survival days (days) | 24.3 ± 2.8 | 23.8 ± 3.9 | 0.34 |

BMI: body mass index, ASA-PS: American Society of Anesthesiologists-physical status, APACHE: acute physiology and chronic health evaluation

Table 3: Comparison of transfusion, postoperative intravenous infusion and urine output.

| | Patients group using maintenance fluid with 35 mmol/L of sodium (n=87) | Patients group using maintenance fluid with 140 mmol/L of sodium (n=92) | p-value |
|---|---|---|---|
| Study period (hours) | 32.5 ± 2.4 | 32.9 ± 2.4 | 0.34 |
| Postoperative intravenous infusion during study period | | | |
| Volume of fluid received (mL) | 3337 ± 861 | 3291 ± 590 | 0.68 |
| Amount of sodium administered (mmol) | 243 ± 100 | 450 ± 94 | <0.001 |
| Amount of potassium administered (mmol) | 45.3 ± 15.0 | 14.5 ± 10.3 | <0.001 |
| Urine output during study period | 2491 ± 1156 | 2294 ± 719 | 0.18 |

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