Hyperchloremia and postoperative acute kidney injury: a retrospective analysis of data from the surgical intensive care unit

Tak Kyu Oh\textsuperscript{1}, In-Ae Song\textsuperscript{1}*\textsuperscript{,} Se Joong Kim\textsuperscript{2}, Sung Yoon Lim\textsuperscript{2}, Sang-Hwan Do\textsuperscript{1}, Jung-Won Hwang\textsuperscript{1}, Jinhee Kim\textsuperscript{1} and Young-Tae Jeon\textsuperscript{1}

Abstract

\textbf{Background:} Whether perioperative hyperchloremia can induce postoperative acute kidney injury (AKI) is controversial. We investigated the association between perioperative hyperchloremia and postoperative AKI in patients admitted to the intensive care unit (ICU) after surgery.

\textbf{Methods:} We performed a retrospective observational study of patients admitted to the surgical ICU at a single tertiary care hospital between January 2011 and June 2016. Our primary objective was to determine whether hyperchloremia or an increase in serum chloride levels was associated with postoperative AKI. Perioperative hyperchloremia was defined as serum chloride levels $\geq$ 110 mmol·L$^{-1}$ during postoperative days (PODs) 0–3. The increase in serum chloride levels was defined as the difference between preoperative and maximum postoperative serum chloride levels during the first 3 days after surgery.

\textbf{Results:} Of the 7991 patients included in the final analysis, 1876 (23.5%) developed hyperchloremia during PODs 0–3, and 1187 (14.9%) developed postoperative AKI. Exposure to hyperchloremia during the first 3 days after surgery was not associated with postoperative AKI (odds ratio, 1.09; 95% confidence interval, 0.80–1.49; $P$ = 0.571). However, among patients with preoperative chronic kidney disease stage $\geq$ 3 (estimated glomerular filtration rate < 60 mL·min$^{-1}$·1.73·m$^{-2}$), the incidence of postoperative AKI was higher in patients with an increase $>$ 6 mmol·L$^{-1}$ in serum chloride levels than in patients with an increase $\leq$ 1 mmol·L$^{-1}$ (odds ratio, 1.42; 95% confidence interval, 1.09–1.84; $P$ = 0.009). In addition, the incidence of postoperative AKI stage $\geq$ 2 was not associated with exposure to hyperchloremia or with the increase in serum chloride levels during PODs 0–3, regardless of preoperative kidney function.

\textbf{Conclusions:} Exposure to perioperative hyperchloremia is not associated with postoperative AKI in surgical ICU patients. However, in patients with moderate-to-severe chronic kidney disease (stage $\geq$ 3), a substantial perioperative increase in serum chloride levels may reflect a higher risk of AKI.

\textbf{Keywords:} Acute kidney injury, Critical care, Hyperchloremia, Intensive care unit

* Correspondence: songoficu@outlook.kr

\textsuperscript{1}Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, 166, Gumi-ro, Bundang-gu, Seongnam 463-707, Republic of Korea

© The Author(s). 2018 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
Background

Acute kidney injury (AKI) is characterized by elevated serum creatinine and/or decreased urine output due to a sudden loss of renal function [1]. Critically ill patients are particularly at risk, accounting for 57% of AKI cases [2–4]. AKI that occurs during the perioperative period is associated with progression to chronic kidney disease (CKD), heart failure, stroke, and postoperative mortality [5].

Hyperchloremic acidosis is a potential risk factor for AKI after abdominal surgery [6], septic shock [7], and subarachnoid hemorrhage [8]. Perioperative hyperchloremia is also associated with postoperative mortality after non-cardiac surgery [9]. However, the association between hyperchloremia and AKI in patients who have undergone specific types of surgery remains unclear, as does the association between hyperchloremia and postoperative AKI in patients admitted to the surgical intensive care unit (ICU) postoperatively.

We investigated the association between perioperative hyperchloremia and AKI in patients admitted to the ICU postoperatively. We included all surgical patients, regardless of surgery type and of the presence of CKD preoperatively. We hypothesized that the incidence of postoperative AKI would be higher among patients with hyperchloremia.

The primary objective of this study was to determine whether perioperative hyperchloremia was associated with postoperative AKI. The secondary objective was to examine whether a perioperative increase in serum chloride (Cl\(^{-}\)) was associated with postoperative AKI. We also examined whether the presence of CKD affected the relationship between perioperative hyperchloremia and postoperative AKI.

Methods

Patients and study design

This retrospective observational study was approved by the Institutional Review Board (IRB) of the Seoul National University Bundang Hospital (SNUBH) (approval number B-1806/474-105). The requirement for written informed consent was waived by the IRB. The study included all adult patients (≥ 19 years old) admitted to SNUBH between 1 January 2011 and 30 June 2016, who were admitted to the surgical ICU after undergoing surgical procedures. If a patient was admitted to the surgical ICU more than once during the study period, only the last postoperative ICU admission was considered. The exclusion criteria were as follows: (1) lack of accurate records of main perioperative laboratory investigations; (2) death within 72 h of postoperative ICU admission; (3) preoperative AKI; or (4) receiving chronic renal replacement therapy before surgery.

As of August 2017, SNUBH is a 1360-bed tertiary care hospital with five ICUs (medical, surgical, neurologic, and emergency I and II). During the study period, surgical ICU admission was indicated according to the complexity of the surgery and the severity of the patient’s condition. The decision on ICU admission was made by the intensivist, who was the main researcher (IAS) in the present study.

Diagnosis of postoperative AKI

For the diagnosis of postoperative AKI, we employed the criteria and grading system laid out in the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [10] because the KDIGO classification is recognized as the most adequate tool for this purpose [11, 12]. Specifically, AKI diagnosis was based only on creatinine levels (Additional file 1). Creatinine levels were obtained by venous measurement; the most recent measurement obtained within 1 month before surgery was considered as the baseline value. Postoperative AKI was defined as AKI diagnosed within 3 days postoperatively. During the study period, postoperative AKI was diagnosed by certified nephrologists; for the purpose of this study, two certified intensivists (TKO and IAS) reviewed all AKI diagnoses to confirm postoperative AKI. If there were disagreements between the two certified intensivists, the final decision was made through consultation with the nephrologists.

Data collection and outcomes

Demographic, clinical characteristics, and laboratory test results were obtained by retrospective review of medical charts. At SNUBH, samples for measuring serum creatinine and electrolyte levels are collected during routine preoperative laboratory testing. For the purpose of this study, the baseline creatinine and electrolyte (chloride) levels were defined as the levels measured most recently in blood sampled from the vein within 1 month before surgery. For the diagnosis of postoperative AKI, creatinine levels were measured in samples collected on postoperative days (PODs) 0–3. To identify patients with CKD, we obtained the preoperative estimated glomerular filtration rate (eGFR, mL·min\(^{-1}\)·1.73-m\(^{-2}\)) using the Modification of Diet in Renal Disease formula [13]. We recorded information on perioperative fluid management, including the type and dosage of fluid infused: NaCl 0.9% (mL·kg\(^{-1}\)), NaCl 0.45% (mL·kg\(^{-1}\)), balanced electrolyte solution (Ringer’s lactate or Plasmalyte; mL·kg\(^{-1}\)), colloid (hydroxyethyl starch; mL·kg\(^{-1}\)), red blood cell infusion (packs), and free water-containing dextrose (mL·kg\(^{-1}\)). The use of relevant drugs during PODs 0–3 was also recorded: inotropes or vasopressors (norepinephrine, vasopressin, dopamine, dobutamine, epinephrine), diuretics (mannitol, furosemide), radiocontrast agents, nephrotoxic antibiotics (aminoglycoside, cephalosporin, vancomycin, and sulfonamide), and nonsteroidal anti-inflammatory drugs. Data on
Invasive and non-invasive measurement of intraoperative blood pressure were collected, and intraoperative hypotension was defined as intraoperative mean blood pressure < 60 mmHg for > 1 min. Intraoperative fluid balance (percent) was calculated using the following formula: [(total input fluid (L) – total output fluid (L)] × 100 × [weight on admission (kg)]^1.

As described previously [9], hyperchloremia was defined as postoperative Cl^- > 110 mmol·L^-1 measured at least once during PODs 0–3. Exposure to hyperchloremia on the day of surgery (POD 0) was recorded as an additional independent variable. The largest (maximum) value of Cl^- measured during PODs 0–3 was also retained. The increase in Cl^- was computed as follows the maximum Cl^- or sodium levels during PODs 0–3 minus the preoperative Cl^-.

Statistical analysis

Patients were stratified into four groups according to baseline eGFR (≥ 90, 60–89, 30–60, and < 30 mL·min^-1·1.73-m^-2), incidence of hyperchloremia during PODs 0–3, increase in serum Cl^- (quartiles Q1–Q4) during PODs 0–3, and incidence of AKI (yes/no) during PODs 0–3, as explained in detail subsequently. Continuous variables were analyzed using the t test, while categorical variables were analyzed using the chi-square test.

We tested the potential association between postoperative AKI and exposure to perioperative hyperchloremia and increase in Cl^-. Restricted cubic splines (RCS) were used to analyze the relationship between the probability of postoperative AKI and either maximum Cl^- or increase in Cl^- perioperatively. Since the relationship between the probability of occurrence of postoperative AKI and the increase in Cl^- was not linear and the third quartile (Q3) of the distribution of values for the increase in Cl^- was close to an inflection point where the slope of the RCS graph changed, the distribution of values of increase in Cl^- was divided into quartiles, and the increase in Cl^- was analyzed as a categorical variable.

Next, we performed univariable logistic regression analysis for occurrence of postoperative AKI during PODs 0–3. Only covariates with P < 0.2 on univariable analysis were included in the multivariable model, with two types of main independent variables (perioperative hyperchloremia as binary exposure; perioperative increase in Cl^- as continuous exposure).

We generated separate multivariable models for exposure to hyperchloremia and for increase in Cl^- during PODs 0–3 to avoid multi-collinearity between the two models.

Because CKD is a well-known risk factor for AKI [14], we investigated the interaction between preoperative eGFR (normal kidney function, > 90 mL·min^-1·1.73-m^-2; CKD stage 2, 60–89 mL·min^-1·1.73-m^-2; CKD stage 3, 30–60 mL·min^-1·1.73-m^-2; CKD stage 4 or 5, < 30 mL·min^-1·1.73-m^-2) and the two types of main independent variables (hyperchloremia as binary exposure; increase in Cl^- as continuous exposure). When interaction between preoperative eGFR and the main independent variables was noted, we performed three additional subgroup analyses. In these subgroup analyses, we performed Bonferroni correction to control type 1 error, and a Bonferroni-corrected P value < 0.013 was considered to indicate statistical significance. The same method of analysis as described above was applied for postoperative AKI stage ≥ 2 as a dependent variable. For all multivariable models, the goodness of fit was confirmed using the Hosmer-Lemeshow test.

Additionally, Pearson correlation analysis was performed to evaluate the simple relationship between Cl^- and infusion of various fluids during PODs 0–3. All analyses were performed using IBM SPSS (version 24.0; IBM Corp., Armonk, NY, USA) and R (version 3.3.3; various R packages: http://www.r-project.org), with statistical significance set at P < 0.05 for group analyses and at a Bonferroni-corrected P value < 0.013 for subgroup analyses.

Results

Patients

Between 1 January 2011 and 30 June 2016, 12,746 patients were admitted to the ICU following surgery. Of these, 3854 postoperative ICU admissions were excluded because they represented multiple admissions; only the last ICU admission was considered for each patient. Additionally, 182 patients were excluded due to incomplete medical records, 358 patients due to preoperative AKI, 195 patients due to death within 72 h of ICU admission, and 166 due to receiving chronic renal replacement therapy before surgery. In total, 7991 patients were included in the final analysis. Of these, 1187 patients (14.9%) were diagnosed with postoperative AKI, of whom 186 (2.3%) exhibited AKI of stage ≥ 2 (Fig. 1). Table 1 summarizes the differences between patients with hyperchloremia and those with non-hyperchloremia during PODs 0–3. The two groups did not differ significantly in the incidence of postoperative AKI (289/1876, 15.4% vs 898/6115, 14.7%; P = 0.443) or AKI of stage ≥ 2 (51/1876, 2.7% vs 135/6276, 2.2%; P = 0.199).

Exposure to hyperchloremia (Cl^- ≥ 110 mmol·L^-1) and postoperative AKI

The RCS describing the relationship between postoperative AKI and maximum Cl^- are provided in Additional file 2.
While the results of the univariable logistic regression analyses are presented in Additional files 3 and 4. The covariates with $P < 0.2$ on the univariable analysis were entered into the multivariable logistic regression model, and the results of multivariable analysis based on model 1 are provided in Table 2. In the overall sample (7991 patients), exposure to hyperchloremia was not associated with postoperative AKI (odds ratio (OR), 1.09; 95% confidence interval (CI), 0.80–1.49, $P = 0.571$; model 1) or with AKI of stage ≥ 2 (OR, 0.77; 95% CI 0.40–1.49; $P = 0.437$; model 2).

Increase in Cl⁻ and postoperative AKI

The RCS describing the relationship between postoperative AKI and increase in Cl⁻ are provided in Additional file 1 (panel B). Based on the shape of the RCS curve, the distribution of values for the increase in Cl⁻ was divided into quartiles: Q1, increase in Cl⁻ ≤ 1 mmol·L⁻¹, 2535 patients (31.7%); Q2, increase in Cl⁻ of 1–3 mmol·L⁻¹, 1593 patients (20.0%); Q3, increase in Cl⁻ of 3–6 mmol·L⁻¹, 2075 patients (26.0%); and Q4, increase in Cl⁻ > 6 mmol·L⁻¹, 1788 patients (22.4%).

The results of the multivariable regression analysis of increase in Cl⁻ are provided in Table 3. The overall $P$ value for the 4-level factor (Q1–Q4) was 0.756. However, there was interaction between perioperative Cl⁻ increase and preoperative kidney function (Q1 * eGFR ≥ 90 mL·min⁻¹·1.73·m⁻² and Q4 * eGFR < 30 mL·min⁻¹·1.73·m⁻²), and thus subgroup analyses were performed for each predefined eGFR threshold (≥ 90, < 90, < 60, and < 30 mL·min⁻¹·1.73·m⁻²). On subgroup analysis, a Cl⁻ increase > 6 mmol·L⁻¹ was associated with postoperative AKI in patients with CKD stage ≥ 3 (eGFR < 60 mL·min⁻¹·1.73·m⁻²) (OR, 1.42; 95% CI, 1.09–1.84; $P = 0.009$ vs a Cl⁻ increase ≤ 1 mmol·L⁻¹). In addition, there was no significant association between the increase in Cl⁻ and occurrence of postoperative AKI of stage ≥ 2, and there was no significant interaction for AKI stage ≥ 2 between perioperative Cl⁻ increase and preoperative kidney function (Table 4).

Discussion

In this retrospective review of 7991 patients, we found that exposure to hyperchloremia was not an independent risk factor for postoperative AKI in patients admitted to the ICU after surgery. This result is consistent with the findings of Yessayan et al. [15], who also observed no significant association between hyperchloremia and AKI within 72 h of ICU admission in patients with sepsis or septic shock. However, while Yessayan et al. excluded patients with CKD stage 5 [15], we did not exclude such patients from our analysis. However, we excluded 195 patients who died within 72 h after surgery, whereas Yessayan et al. included such patients. Our reason for excluding patients who died within 72 h was that such patients...
Table 1 Characteristics of patients with and without perioperative hyperchloremia ($\text{Cl}^- \geq 110$ mmol·L$^{-1}$)

| Variables                                      | Perioperative hyperchloremia ($n = 1876, 23.5\%$) | No perioperative hyperchloremia ($n = 6115, 76.5\%$) | $P$ value |
|------------------------------------------------|--------------------------------------------------|------------------------------------------------------|-----------|
| Preoperative characteristics                   |                                                  |                                                      |           |
| Male sex                                       | 1091 (58.2%)                                     | 3636 (59.5%)                                        | 0.315     |
| Age, years                                      | 58.0 (15.7)                                      | 62.1 (15.6)                                         | <0.001    |
| Body mass index, kg m$^{-2}$                    | 23.5 (3.6)                                       | 23.6 (3.8)                                          | 0.240     |
| Surgery time, min                              | 268.8 (150.9)                                    | 220.1 (147.6)                                       | <0.001    |
| ASA class                                      |                                                  |                                                      | <0.001    |
| 1                                              | 433 (23.1%)                                      | 975 (15.9%)                                         |           |
| 2                                              | 892 (47.5%)                                      | 3191 (52.2%)                                        |           |
| $\geq$ 3                                       | 551 (29.4%)                                      | 1949 (31.9%)                                        |           |
| Cancer                                         | 405 (21.6%)                                      | 1840 (30.1%)                                        | <0.001    |
| eGFR$^{*\text{a}}$, mL·min$^{-1}$·1.73·m$^{-2}$ |                                                  |                                                      | 0.313     |
| $\geq$ 90                                      | 841 (44.8%)                                      | 2596 (42.5%)                                        |           |
| 60–89                                          | 528 (28.1%)                                      | 1825 (29.8%)                                        |           |
| 30–60                                          | 310 (16.5%)                                      | 1029 (16.8%)                                        |           |
| < 30                                           | 197 (10.5%)                                      | 665 (10.9%)                                         |           |
| Intraoperative characteristics                 |                                                  |                                                      |           |
| Type of operation                              |                                                  |                                                      | <0.001    |
| Non-cardiovascular surgery                     | 1567 (83.5%)                                     | 4786 (78.3%)                                        |           |
| Cardiovascular surgery                         | 309 (16.5%)                                      | 1329 (21.7%)                                        |           |
| Emergency surgery                              | 329 (17.5%)                                      | 781 (12.8%)                                         | <0.001    |
| Intraoperative hypotension$^{b}$               | 455 (24.3%)                                      | 1659 (27.1%)                                        | 0.013     |
| Type of anesthesia                             |                                                  |                                                      | <0.001    |
| General anesthesia                             | 1823 (97.5%)                                     | 5474 (89.9%)                                        |           |
| Regional anesthesia                            | 23 (1.2%)                                        | 278 (4.6%)                                          |           |
| Monitored anesthesia care                      | 24 (1.3%)                                        | 335 (5.5%)                                          |           |
| Patient management (PODs 0–3)                  |                                                  |                                                      |           |
| NaCl 0.9% infused, mL kg$^{-1}$                | 12.3 (13.2)                                      | 8.4 (9.5)                                           | <0.001    |
| NaCl 0.45% infused, mL kg$^{-1}$               | 6.5 (20.3)                                       | 2.9 (12.9)                                          | <0.001    |
| Balanced electrolyte solution infused, mL kg$^{-1}$ | 41.9 (37.1)                                   | 49.7 (40.7)                                         | <0.001    |
| Free water containing dextrose, mL kg$^{-1}$   | 47.2 (62.5)                                      | 59.3 (56.9)                                         | <0.001    |
| Hydroxyethyl starch infused, mL kg$^{-1}$      | 22.1 (21.5)                                      | 13.4 (16.5)                                         | <0.001    |
| Intraoperative fluid balance, %$^{c}$          | 1.8 (3.6)                                        | 1.7 (2.8)                                           | 0.321     |
| RRT (without RRT history)                      | 51 (2.7%)                                        | 135 (2.2%)                                          | 0.199     |
| Use of inotropes/vasopressors$^{d}$            | 1635 (87.2%)                                     | 4286 (70.1%)                                        | <0.001    |
| Use of diuretics$^{e}$                         | 1300 (69.3%)                                     | 3423 (56.0%)                                        | <0.001    |
| Use of radioccontrast                          | 991 (52.8%)                                      | 1738 (28.4%)                                        | <0.001    |
| Use of nephrotoxic antibiotics$^{f}$           | 377 (20.1%)                                      | 1147 (18.8%)                                        | 0.197     |
| Use of NSAIDs                                  | 754 (40.2%)                                      | 2194 (35.9%)                                        | 0.001     |
| Postoperative laboratory (PODs 0–3) and clinical outcomes | | | |
might have AKI associated with another critical illness not related to perioperative hyperchloremia, such as multi-organ failure or massive bleeding. Yessayan et al. also noted that AKI was not associated with an increase in Cl− [15]. However, in the present study, we found that patients with CKD stage ≥ 3 who exhibit a Cl− increase > 6 mmol·L−1 during PODs 0–3 have higher risk of postoperative AKI. Our results suggest that the association between perioperative hyperchloremia and occurrence of postoperative AKI may depend in part on the presence of perioperative CKD.

Our findings are in contrast to previous observations that had suggested an association between hyperchloremia and AKI in non-cardiac surgery [9], subarachnoid hemorrhage [8], severe sepsis or septic shock [7], and abdominal surgery [6]. A 2018 trial of balanced salt solutions in critically ill patients also found that use of saline increased the composite outcome of death from any cause, new renal replacement

### Table 1
Characteristics of patients with and without perioperative hyperchloremia (Cl− ≥ 110 mmol·L−1) (Continued)

| Variables | Perioperative hyperchloremia (n = 1876, 23.5%) | No perioperative hyperchloremia (n = 6115, 76.5%) | P value |
|-----------|-----------------------------------------------|-------------------------------------------------|---------|
| AKI occurrence | 289 (15.4%) | 898 (14.7%) | 0.443 |
| AKI stage ≥ 2 occurrence | 51 (2.7%) | 135 (2.2%) | 0.199 |

Values are expressed as the mean (standard deviation) or number (percentage)

ASA American Society of Anesthesiologists classification, eGFR estimated glomerular filtration rate, RRT renal replacement therapy, POD postoperative day, NSAID nonsteroidal anti-inflammatory drug; AKI, acute kidney injury

*Laboratory values within 3 days after operation

**The increase in Cl− or serum sodium levels was calculated as the difference between the preoperative value and the maximum value noted during PODs 0–3

[eGFR (mL·min−1·1.73·m−2) = 186 × (Creatinine)−1.154 × (Age)−0.203 (× 0.742 if female)]

1Intraoperative hypotension was defined as mean blood pressure < 60 mmHg for > 1 min

2Intraoperative fluid balance (% = (Total input fluid (L) − Total output fluid (L)) × weight on admission−1 (kg)

3Nephrotoxic antibiotics include aminoglycoside, cephalosporin, vancomycin, and sulfonamide

4Diuretics include mannitol and furosemide

5Inotropic/vasopressors include norepinephrine, epinephrine, vasopressin, dobutamine, and dopamine

### Table 2
Multivariable logistic regression analyses of postoperative AKI according to hyperchloremia exposure during PODs 0–3

| Group | Variable | Multivariable model 1 | P value |
|-------|----------|-----------------------|---------|
| Entire sample (n = 7991) | Hyperchloremia* on POD 0 | 1.22 (0.94, 1.58) | 0.144 |
| | Hyperchloremia* on PODs 0–3 | 1.09 (0.80, 1.49) | 0.571 |
| | Interaction of hyperCl on POD 0–3 with eGFR | | |
| | ≥ 90 mL·min−1·1.73·m−2 | 1 | (0.425) |
| | 60–89 mL·min−1·1.73·m−2 | 0.91 (0.62, 1.34) | 0.629 |
| | 30–60 mL·min−1·1.73·m−2 | 0.96 (0.65, 1.43) | 0.840 |
| | < 30 mL·min−1·1.73·m−2 | 0.70 (0.45, 1.08) | 0.109 |
| | Multivariable model 2 | | |
| | ≥ Stage 2 AKI: OR (95% CI) | | |
| | Hyperchloremia* on POD 0 | 1.61 (0.89, 2.93) | 0.367 |
| | Hyperchloremia* on PODs 0–3 | 0.77 (0.40, 1.49) | 0.437 |
| | Interaction of hyperchloremia with eGFR | | |
| | ≥ 90 mL·min−1·1.73·m−2 | 1 | (0.468) |
| | 60–89 mL·min−1·1.73·m−2 | 1.40 (0.67, 2.94) | 0.367 |
| | 30–60 mL·min−1·1.73·m−2 | 0.64 (0.24, 1.69) | 0.363 |
| | < 30 mL·min−1·1.73·m−2 | 0.91 (0.17, 4.94) | 0.915 |

Covariates with P < 0.2 on univariable analysis (see also Additional file 3) were included in the final multivariable model to adjust for potential confounders.

Covariates for multivariable model 1 included preoperative American Society of Anesthesiologists (ASA) score, preoperative estimated glomerular filtration rate (eGFR), NaCl 0.9% and balanced crystalloid infused. Covariates for multivariable model 2 included preoperative ASA score, preoperative eGFR, cardiovascular surgery, NaCl 0.45% and hydroxyethyl starch infused. The Hosmer-Lemeshow goodness-of-fit test was performed to investigate the fitness of the multivariable logistic regression model, and revealed no indication of lack of fit (Model 1: Hosmer-Lemeshow statistic 7.09, P = 0.527; Model 2: Hosmer-Lemeshow statistic 6.287, P = 0.615)

AKI acute kidney injury, CI confidence interval, POD postoperative day

*Hyperchloremia was defined as serum chloride levels ≥ 110 mmol·L−1

**Preoperative eGFR (mL·min−1·1.73·m−2) was calculated using the Modification of Diet in Renal Disease formula: 186 × (preoperative serum Creatinine)−1.154 × (Age)−0.203 (× 0.742 if female)
Table 3 Multivariable logistic regression analyses for postoperative AKI according to increase in serum chloride levels (Cl−)

| Group | Increase in Cl−, mmol L−1* | Multivariable model 3 | P value** |
|-------|-----------------------------|-----------------------|-----------|
| Entire sample (n = 7991) | Increase in Cl−, mmol L−1 | Odds ratio (95% CI) | P value** |
| Q1: ≤ 1 mmol L−1 | 1 | (0.756) |
| Q2: 1–3 mmol L−1 | 0.84 (0.60, 1.18) | 0.316 |
| Q3: 3–6 mmol L−1 | 0.89 (0.66, 1.21) | 0.456 |
| Q4: > 6 mmol L−1 | 0.90 (0.66, 1.24) | 0.528 |

Interaction of increase in Cl− with eGFR

| Group | Increase in Cl−, mmol L−1 | Odds ratio (95% CI) | P value*** |
|-------|-----------------------------|---------------------|-----------|
| Entire sample (n = 7991) | Increase in Cl−: Q1 * eGFR ≥ 90 | 1 | (0.297) |
| | Increase in Cl−: Q2 * eGFR: 60–89 | 1.04 (0.64, 1.70) | 0.867 |
| | Increase in Cl−: Q2 * eGFR: 30–60 | 0.93 (0.60, 1.44) | 0.738 |
| | Increase in Cl−: Q2 * eGFR: < 30 | 0.99 (0.63, 1.57) | 0.973 |
| | Increase in Cl−: Q3 * eGFR: 60–89 | 1.02 (0.60, 1.75) | 0.934 |
| | Increase in Cl−: Q3 * eGFR: 30–60 | 0.93 (0.60, 1.44) | 0.738 |
| | Increase in Cl−: Q3 * eGFR: < 30 | 1.10 (0.67, 1.80) | 0.702 |
| | Increase in Cl−: Q4 * eGFR: 60–89 | 0.92 (0.58, 1.46) | 0.728 |
| | Increase in Cl−: Q4 * eGFR: 30–60 | 1.51 (0.95, 2.40) | 0.084 |
| | Increase in Cl−: Q4 * eGFR: < 30 | 1.67 (1.01, 2.77) | 0.045 |

Four subgroup analysis

| Group | Increase in Cl−, mmol L−1 | Odds ratio (95% CI) | P value*** |
|-------|-----------------------------|---------------------|-----------|
| eGFR ≥ 90 (n = 3437) | Increase in Cl−, mmol L−1 | 1 | (0.739) |
| | Q1: ≤ 1 mmol L−1 | 1 | (0.023) |
| | Q2: 1–3 mmol L−1 | 0.84 (0.60, 1.19) | 0.323 |
| | Q3: 3–6 mmol L−1 | 0.90 (0.66, 1.22) | 0.491 |
| | Q4: > 6 mmol L−1 | 0.90 (0.66, 1.24) | 0.529 |
| eGFR < 90 (n = 4554) | Increase in Cl−, mmol L−1 | 1 | (0.123) |
| | Q1: ≤ 1 mmol L−1 | 1 | (0.195) |
| | Q2: 1–3 mmol L−1 | 0.88 (0.72, 1.07) | 0.164 |
| | Q3: 3–6 mmol L−1 | 0.90 (0.70, 1.17) | 0.430 |
| | Q4: > 6 mmol L−1 | 1.16 (0.94, 1.41) | 0.009 |
| eGFR < 60 (n = 2201) | Increase in Cl−, mmol L−1 | 1 | (0.068) |
| | Q1: ≤ 1 mmol L−1 | 1 | (0.164) |
| | Q2: 1–3 mmol L−1 | 0.82 (0.61, 1.09) | 0.164 |
| | Q3: 3–6 mmol L−1 | 0.90 (0.70, 1.17) | 0.430 |
| | Q4: > 6 mmol L−1 | 1.42 (1.09, 1.84) | 0.009 |
| eGFR < 30 (n = 862) | Increase in Cl−, mmol L−1 | 1 | (0.042) |
| | Q1: ≤ 1 mmol L−1 | 1 | (0.775) |
| | Q2: 1–3 mmol L−1 | 0.85 (0.56, 1.28) | 0.428 |
| | Q3: 3–6 mmol L−1 | 0.94 (0.64, 1.40) | 0.775 |
| | Q4: > 6 mmol L−1 | 1.48 (1.00, 2.21) | 0.053 |

Covariates with P < 0.2 on univariable analysis (see also Additional file 3) were included in the final multivariable model to adjust for potential confounders. Covariates for multivariable model 3 included preoperative American Society of Anesthesiologists (ASA) score, preoperative estimated glomerular filtration rate (eGFR), NaCl 0.9% and balanced crystalloid infused. The Hosmer-Lemeshow goodness-of-fit test was performed to investigate the fitness of the multivariable logistic regression models, and revealed no indication of lack of fit. Specifically, the Hosmer-Lemeshow statistic and P value, respectively, were 4.38 and 0.821 for the entire sample; 4.44 and 0.823 for the group of patients with eGFR ≥ 90 mL·min−1·1.73·m−2; 10.98 and 0.203 for the group of patients with eGFR < 90 mL·min−1·1.73·m−2; 11.92 and 0.155 for the group of patients with eGFR < 60 mL·min−1·1.73·m−2; 5.29 and 0.726 for the group of patients with eGFR < 30 mL·min−1·1.73·m−2.

AKI acute kidney disease, CI confidence interval, Cl− serum chloride levels

*Preoperative eGFR (mL·min−1·1.73·m−2) was calculated using the Modification of Diet in Renal Disease formula: 186 × (preoperative serum Creatinine)−1.154 × (Age)−0.203 (× 0.742 if female)

**The increase in Cl− was calculated as the difference between the preoperative value and the maximum value noted during postoperative days (PODs) 0–3. The following quartiles were obtained: Q1, 2535 patients (31.7%); Q2, 1593 patients (20.0%); Q3, 2075 patients (26.0%); and Q4, 1788 patients (22.4%)

***P < 0.05 ****P < 0.012 (after Bonferroni correction) were considered to indicate statistical significance
therapy, or persistent renal dysfunction [16]. Two of the above-cited trials examined perioperative data. The study by McCluskey et al. found that hyperchloremia was an independent risk factor for renal dysfunction in non-cardiac surgery [9]. The 2013 study by McCluskey et al. [9] differed from our study in several aspects. First, patients with preoperative kidney dysfunction were excluded, whereas our study included all surgical patients, including those with preoperative CKD. Second, McCluskey et al. used the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria [17], whereas we used the KDIGO criteria to diagnose postoperative AKI. The KDIGO criteria have been shown to be more sensitive for diagnosing AKI and to have more predictive value for in-hospital mortality [18]. Last, McCluskey et al. did not evaluate the postoperative increase in Cl− due to lack of data on preoperative Cl−. However, since Cl− is routinely measured preoperatively in most tertiary care hospitals in South Korea, we could perform a detailed analysis of the influence of Cl− levels on AKI incidence. Other studies have also identified the increase in Cl− as an important factor for occurrence of AKI [8, 15, 19].

Our results also differ from the findings of a recent study by Toyonaga and Kikura, involving a small cohort of 206 patients admitted to the ICU after elective abdominal surgery [6]. Specifically, Toyonaga and Kikura reported that hyperchloremic acidosis was associated with an increased incidence of AKI; however, they excluded patients with preoperative CKD [6]. On the other hand, we included patients with preoperative CKD and adjusted for CKD in the multivariable logistic analysis. In addition, several studies that reported an association between hyperchloremia and AKI in patients with major trauma [20], subarachnoid hemorrhage [8], severe sepsis or septic shock [7], or intracerebral hemorrhage [21] included patients who received large volumes of NaCl 0.9%. Our study differs from those previous investigations in that we included patients who were admitted to the ICU after undergoing any type of surgery.

Unlike many prior studies of perioperative AKI [7, 8], ours included patients with preoperative CKD. It is currently recognized that preoperative CKD is itself a risk factor for postoperative AKI [22], may predispose to chronic renal insufficiency, and may be involved in the relationship between chloride homeostasis and perioperative AKI. Our study revealed a potential association between a perioperative Cl− increase > 6 mmol·L−1 and the risk of postoperative AKI in patients with CKD stage

---

Table 4 Multivariable logistic regression analyses for postoperative AKI stage ≥ 2 according to Cl− increase

| Group                  | Variable | Multivariable model 4 |
|------------------------|----------|-----------------------|
|                        |          | Odds ratio (95% CI)    | P value   |
| Entire sample (n = 8157) | Increase in Cl−, mmol·L−1* |                        |           |
|                        | Q1: ≤ 1 mmol·L−1 | 1                      | (0.802)   |
|                        | Q2: 1–3 mmol·L−1 | 1.22 (0.65, 2.28)      | 0.542     |
|                        | Q3: 3–6 mmol·L−1 | 0.86 (0.46, 1.62)      | 0.642     |
|                        | Q4: > 6 mmol·L−1 | 1.00 (0.53, 1.89)      | 0.992     |

Interaction of Cl− increase with eGFR:

| Group                  | Variable | Multivariable model 4 |
|------------------------|----------|-----------------------|
|                        |          | Odds ratio (95% CI)    | P value   |
| Increase in Cl−: Q1 * eGFR ≥ 90 | 1 |                           | (0.960)   |
| Increase in Cl−: Q2 * eGFR 60–89 | 0.62 (0.23, 1.67) | 0.348     |
| Increase in Cl−: Q3 * eGFR 30–60 | 1.01 (0.31, 3.30) | 0.990     |
| Increase in Cl−: Q4 * eGFR < 30 | 0.00 (0.00) | 0.996     |
| Increase in Cl−: Q3 * eGFR 60–89 | 1.14 (0.46, 2.79) | 0.780     |
| Increase in Cl−: Q4 * eGFR < 30 | 1.44 (0.48, 4.37) | 0.518     |
| Increase in Cl−: Q4 * eGFR 30–60 | 1.22 (0.65, 2.28) | 0.542     |
| Increase in Cl−: Q4 * eGFR < 30 | 1.00 (0.53, 1.89) | 0.992     |

Covariates with P < 0.2 on univariable analysis (see also Additional file 4) were included in the final multivariable model to adjust for potential confounders. Covariates for multivariable model 4 included preoperative American Society of Anesthesiologists (ASA) score, preoperative estimated glomerular filtration rate (eGFR), cardiovascular surgery, NaCl 0.45% and hydroxyethyl starch infused.

*The increase in Cl− was calculated as the difference between the preoperative value and the maximum value noted during postoperative days (PODs) 0–3. The following quartiles were obtained: Q1, 2535 patients (31.7%); Q2, 1593 patients (20.0%); Q3, 2075 patients (26.0%); and Q4, 1788 patients (22.4%). The Hosmer-Lemeshow goodness-of-fit test was performed to investigate the fitness of the multivariable logistic regression models, and revealed no indication of lack of fit.

For the entire sample, the Hosmer-Lemeshow statistic was 5.76 and the P value was 0.674.

AKI acute kidney injury, CI confidence interval, Cl− serum chloride level.

*Preoperative eGFR (mL·min−1·1.73-m−2) was calculated using the Modification of Diet in Renal Disease formula: 186 × (preoperative serum Creatinine)−1.154 × (Age)−0.203 × (sex 0.742 if female).
≥ 3. These data suggest that perioperative hyperchloremic acidosis may have a greater impact on postoperative renal function in patients already at risk.

Our study has several limitations. First, because of the retrospective design, we could not fully exclude selection bias, especially with respect to the choice of infusion fluid. However, we found no effect of hyperchloremia on postoperative AKI incidence, suggesting that any effect of selection bias was likely modest. Second, our study was conducted in a single center, which limits the generalizability of our findings. Third, postoperative Cl⁻ were measured once per day, but not always at the same time, mainly due to aspects related to the patient’s physical condition. Fourth, there is a possibility that AKI may have preceded the observed change in chloride levels, which would have induced some bias in our analysis.

In particular, because our study was retrospective in nature, we could not control the choice and dosage of infusion fluid during PODs 0–3. With the exception of balanced crystalloid and free water-containing dextrose, most types of infusion fluids correlated positively with the maximum Cl⁻ noted during PODs 0–3 (Additional file 5), suggesting that postoperative AKI incidence was affected not only by Cl⁻ but also by the choice of fluid therapy. The effect of fluid type on AKI incidence is unclear, with two very recent studies reporting an adverse effect of high-chloride solutions in critically ill patients but no effect in non-critically ill patients [16, 23].

Conclusions
Despite its limitations, this retrospective study of 7991 patients admitted to the ICU after surgery found that exposure to perioperative hyperchloremia is not significantly associated with postoperative AKI. However, in patients with moderate-to-severe chronic kidney disease (stage ≥ 3), a substantial increase in Cl⁻ (> 6 mmol·L⁻¹) was associated with an increased risk of postoperative AKI.

Additional files

Additional file 1: Staging of postoperative acute kidney injury. Brief overview of KDIGO-based staging criteria for acute kidney injury. (DOCX 29 kb)

Additional file 2: Probability of AKI during the stay in the surgical ICU. AKI probability according to maximum serum chloride levels (A) and according to the increase in serum chloride levels (B) during PODs 0–3. Representation based on restricted cubic splines. AKI, acute kidney injury; ICU, intensive care unit; POD, postoperative day. (ZIP 74 kb)

Additional file 3: Risk factors for AKI in the surgical ICU. Results of the univariable logistic regression analysis for occurrence of AKI after postoperative ICU admission. (DOCX 39 kb)

Additional file 4: Risk factors for AKI stage ≥ 2 in the surgical ICU. Results of the univariable logistic regression analysis for occurrence of AKI stage ≥ 2 after postoperative ICU admission. (DOCX 39 kb)

Additional file 5: Association of total fluid use with perioperative serum chloride levels in surgical ICU patients. Results of the Pearson correlation analysis between total fluid use and maximum serum chloride levels or increase in serum chloride levels during PODs 0–3. (DOCX 31 kb)

Acknowledgments
The authors thank the Medical Research Collaborating Center at Seoul National University Bundang Hospital for revision regarding statistical analyses. We are particularly grateful to Dr. Eunjeong Ji for her contribution to the statistical analysis.

Availability of data and materials
All data supporting the conclusions of this article are included within the article and its additional files.

Authors’ contributions
TKO contributed to the study design, analyzed the data, and drafted the first manuscript. IAS contributed to the study design and conducted a critical revision of the manuscript. SJK, SYL, SHD, JWH, JHK, JWH, and YTJ contributed to the acquisition of data and revised the manuscript critically for important intellectual content. All authors have given final approval for the version of the manuscript to be published.

Ethics approval and consent to participate
This study was approved by the Institutional Review Board of SNUBH (B-1704/390–104), which waived the need for informed consent on account of the retrospective study design.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details
1Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, 166, Gumi-ro, Bundang-gu, Seongnam 463-707, Republic of Korea. 2Division of Nephrology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea.

Received: 3 July 2018 Accepted: 3 October 2018
Published online: 30 October 2018

References
1. Waikar SS, Bonventre JV. Creatinine kinetics and the definition of acute kidney injury. J Am Soc Nephrol. 2009;20(3):672–9.
2. Bellomo R, Kellum JA, Ronco C. Acute kidney injury. Lancet. 2012;380(9843):756–66.
3. Lewington AJ, Cerda J, Mehta RL. Raising awareness of acute kidney injury: a global perspective of a silent killer. Kidney Int. 2013;84(3):457–67.
4. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. Am J Kidney Dis. 2002;39(5):930–6.
5. Palant CE, Amdur RL, Chawla LS. Long-term consequences of acute kidney injury in the perioperative setting. Curr Opin Anaesthesiol. 2017;30(1):100–4.
6. Toyonaga Y, Kitamura M. Hyperchloremic acidosis is associated with acute kidney injury after abdominal surgery. Nephrology (Carlton). 2017;22(9):720–7.
7. Suetrong B, Pitsikas C, Boyd JH, Russell JA, Walley KR. Hyperchloremia and moderate increase in serum chloride are associated with acute kidney injury in severe sepsis and septic shock patients. Crit Care. 2016;20(1):315.
8. Sadan O, Singbartl K, Kandiah PA, Martin KS, Samuels OB. Hyperchloremia is associated with acute kidney injury in patients with subarachnoid hemorrhage. Crit Care Med. 2017;45(8):1382–8.
9. McCluskey SA, Karkouti K, Wijeysundera D, Minkovich L, Tait G, Beattie WS. Hyperchloremia after noncardiac surgery is independently associated with increased morbidity and mortality: a propensity-matched cohort study. Anesth Analg. 2013;117(2):412–21.
10. Kellum JA, Lameire N, Group KAGW. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care. 2013;17(1):204.
11. Pan HC, Chien YS, Jenq CC, Tsai MH, Fan PC, Chang CH, Chang MY, Tian YC, Fang JT, Yang CW, et al. Acute Kidney Injury Classification for Critically Ill Cirrhotic Patients: a Comparison of the KDIGO, AKIN, and RIFLE Classifications. Sci Rep. 2016;6:23022.
12. Ulger F, Pehlivanlar Kucuk M, Kucuk AO, Ilkaya NK, Murat N, Bilgic B, Abanoz H. Evaluation of acute kidney injury (AKI) with RIFLE, AKIN, CKD, and KDIGO in critically ill trauma patients. Eur J Trauma Emerg Surg. 2018;44(4):597-605.
13. Kilbride HS, Stevens PE, Eaglestone G, Knight S, Carter J, Delaney MP, Farmer CK, Irving J, O’Riordan SE, Dalton RN, et al. Accuracy of the MDRD (Modification of Diet in Renal Disease) study and CKD-EPI (CKD Epidemiology Collaboration) equations for estimation of GFR in the elderly. Am J Kidney Dis. 2013;61(1):57–66.
14. Luo X, Jiang L, Du B, Wen Y, Wang M, Xi X, Beijing Acute Kidney Injury Trial Workgroup. A comparison of different diagnostic criteria of acute kidney injury in critically ill patients. Crit Care. 2018;22:277.