

# Hyperchloraemia: ready for the big time?

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Chloride is in many ways the forgotten electrolyte. Recent evidence suggests that hyperchloraemia results in metabolic acidosis, and is associated with renal dysfunction, increased mortality, coagulation disturbances, splanchnic ischaemia, and a proinflammatory state. The renal effects and the increased mortality are the best established and most concerning of these associations. The choice of intravenous fluids significantly influences the development of hyperchloraemia. Further studies are required to confirm or refute these associations. In the interim high-chloride fluids, most commonly 0.9% saline, should be avoided as resuscitation fluids.

**Keywords:** acute kidney injury, chloride, critical care, hyperchloraemia, mortality, perioperative

## Introduction

Chloride is a Cinderella electrolyte and is often viewed as a passive companion to sodium. A PubMed search (February 7, 2015) revealed 236 results for 'hyperchloraemia' and 3071 for 'hypernatraemia'. Emerging evidence suggests, however, that chloride is a powerful, biologically active electrolyte in its own right and that hyperchloraemia is associated with adverse outcomes.

## Basic science

Chloride is the major strong anion in plasma, accounting for two-thirds of all negative charges in plasma, and one-third of plasma tonicity<sup>1,2</sup>. These contributions are even greater in interstitial fluid as there is minimal anionic protein in this compartment. Normal plasma chloride is in the range of 97–107 mmol/l, with low intracellular concentrations of approximately 10 mmol/l<sup>1,2</sup>. Daily chloride intake is approximately 150 mmol, equivalent to a litre of 0.9% saline a day<sup>1</sup>.

Although beyond the scope of this review chloride channels are extensively distributed and are important for a range of biological effects from fluid secretion to cell volume regulation and neurological functioning<sup>1,2</sup>.

## Incidence

Hyperchloraemia is common in the perioperative and critical care setting. A recent large cohort study in unselected postoperative patients reported an incidence of acute postoperative hyperchloraemia of 22%<sup>3</sup>. This may rise to as high as 57.7% in selected surgical intensive care populations<sup>4</sup>. Severe hyperchloraemia was noted to occur in 6.2% of patients in a multidisciplinary intensive care unit (ICU)<sup>5</sup>.

## Aetiology

As Table 1 shows, hyperchloraemia has multiple potential causes and is often multifactorial.

The question of whether our choice of intravenous fluid really influences serum chloride is key to further discussions on this topic and warrants further exploration.

In a study comparing the effects of just two litres of 0.9% saline versus Plasma-Lyte on healthy volunteers, a rapid rise in serum chloride was seen in the saline group and chloride levels remained

significantly higher in the saline group than the Plasma-Lyte group for the four hours of the study<sup>6</sup>.

A Cochrane review of perioperative fluid therapy showed a significantly higher plasma chloride in patients receiving 0.9% saline versus those receiving a balanced salt solution (114.0 vs. 106.9 mmol/l  $p = 0.0001$ )<sup>7</sup>. Yunos demonstrated significantly higher mean chloride levels in a saline-based fluid group versus a balanced salt solution group<sup>5</sup>. A recent study in trauma patients resuscitated with either 0.9% saline or a balanced salt solution showed a significantly higher serum chloride in the saline group: 111 vs. 104; difference:  $-7$  (95% CI:  $-10$  to  $-3$ )<sup>8</sup>. It is clear, then, that our choice of fluid influences plasma chloride levels; in particular the use of 0.9% saline solutions increases plasma chloride and puts the patient at risk of hyperchloraemia.

## Does hyperchloraemia matter?

While it is now clear that hyperchloraemia is common and the incidence is influenced by our choice of intravenous fluid, does this hyperchloraemia have any adverse effects? The rest of the review will explore this question in further detail.

## Metabolic acidosis

Hyperchloraemia has been associated with a normal anion gap metabolic acidosis. Although beyond the scope of this review, this is elegantly explained conceptually by Stewart's hypothesis, whereby a relative increase in serum chloride reduces strong ion difference (SID), and to maintain electroneutrality the dissociation of water produces hydrogen ions. In this theory it is important to note that chloride is the driver of the acidosis and not a passive participant in exchange for bicarbonate as seen in more traditional explanations.

While theoretically attractive it must be questioned whether high-chloride fluids and hyperchloraemia lead to an acidosis clinically. Mathematical modelling, laboratory data and animal studies have shown that it is the relationship of the SID of the infused fluid to the patient's bicarbonate or SID that determines the effect of fluid infusion on the subject's acid-base status<sup>9,10</sup>. As a result of the high chloride content, the SID of 0.9% saline is less than that of plasma bicarbonate/SID and thus leads to an acidosis. A fluid with an SID equal to or higher than the bicarbonate/SID of plasma (e.g. Ringer's lactate) leads, respectively, to no change in pH or an alkalosis.

Table 1: Aetiology of hyperchloraemia

Cause	Examples	
Chloride infusion	Administration of chloride-rich fluids Total parenteral nutrition	e.g. 0.9% sodium chloride
Pure water loss	Skin  Renal	Fever  Hypermetabolic states Diuretics Central diabetes insipidus Nephrogenic diabetes insipidus
Water loss in excess of chloride loss	Extrarenal  Renal	Diarrhoea Burns Osmotic diuresis Post-obstructive diuresis Intrinsic renal disease
Definite or relative increase in tubular chloride reabsorption	Renal tubular acidosis Recovery of diabetic ketoacidosis Early renal failure Acetazolamide Ureteral diversion procedures Post-hypocapnia	

Note: Modified from Yunos et al.<sup>1</sup>

In terms of human clinical data, Scheingraber compared fluid therapy in two groups of patients undergoing major gynaecological surgery<sup>11</sup>. One group received isotonic saline at 30 ml/kg/h and the other received Ringer's lactate at the same rate. The saline group rapidly developed hyperchloraemia and an acidosis, which was not seen in the Ringer's group. At two hours the mean base excess had dropped from -0.4 to -6.7 mmol/l in the saline group, the pH from 7.41 to 7.28 and the chloride had risen from 104 to 115 mmol/l. These are extreme fluid volumes for elective surgery but they graphically illustrate the point. Waters et al. demonstrated that hyperchloraemia was significantly correlated with an increase in base deficit intraoperatively<sup>12</sup>. In the Yunos study alluded to earlier the investigators conducted a prospective before and after study where they collected baseline data in their ICU for six months and then phased out the use of saline-based fluids<sup>5</sup>. They then repeated their data collection for six months and compared the two sets of data. Saline use fell from 2411 l in the control group to 52 l in the intervention group and balanced salt solution use increased from 469 l to 3205 l. This change was associated with a significant reduction in severe hyperchloraemia and a concomitant reduction in severe metabolic acidosis and acidaemia. A study in septic paediatric patients further showed that there is a linear relationship between chloride load and base deficit — in other words there is a clear dose-response relationship between chloride-containing fluids and acidosis<sup>13</sup>. In the trauma study by Young et al. the base deficit normalised within 6 h in the balanced salt solution group and remained in the normal range for the duration of the study but remained abnormal (elevated) throughout the 24-h study period in the 0.9% saline group<sup>8</sup>.

It is thus clear that hyperchloraemia is associated with a metabolic acidosis and acidotic patients tend to have poorer clinical outcomes<sup>14–16</sup>. It is, however, unclear whether the acidosis per se leads to adverse clinical outcomes or whether it is the underlying physiological derangement that determines the clinical consequences. As an example, one of the commonly quoted adverse effects of acidosis is reduced myocardial contractility<sup>17,18</sup>. It appears that the type of acidosis may determine the degree of myocardial depression, with ketoacidotic patients even showing normal or increased

myocardial contractility in some studies<sup>19–21</sup>. In terms of mortality it has been shown that lactate and base deficit both predict mortality but there may be poor correlation between these variables, suggesting that the effect of the anion and the acidosis may be separate<sup>15,22</sup>. In addition Gunnerson et al. demonstrated a differential mortality according to type of acidosis in a retrospective cohort analysis of intensive care patients. The inpatient mortality rate was 56% for lactic acidosis, 39% for strong ion gap acidosis and 29% for hyperchloraemic acidosis ( $p < 0.001$ ), with the baseline mortality rate of the entire cohort being 14%<sup>14</sup>. The exact clinical effect of the acidosis associated with hyperchloraemia thus remains unclear, but hyperchloraemic acidosis can still confound clinical management, e.g. in a patient with diabetic ketoacidosis (DKA), receiving 0.9% saline, a worsening acidaemia may be due to inadequate fluid volume or hyperchloraemia, the two scenarios requiring conflicting fluid strategies. In addition emerging evidence suggests that hyperchloraemia itself may be problematic, beyond a simple acid-base effect. This will be explored further below.

### Renal dysfunction

As long ago as 1983, it was shown in a canine model that hyperchloraemia induces renal vasoconstriction and reduces glomerular filtration rate (GFR). This vasoconstrictive effect was specific to the renal vasculature<sup>23</sup>. Chowdhury showed in human volunteers that two litres of 0.9% saline reduced renal artery blood flow and renal cortical perfusion — an effect not seen with Plasma-Lyte<sup>6</sup>.

Chowdhury also recently reported that a starch in a balanced salt solution increased renal cortical perfusion versus a saline-based starch<sup>24</sup>. In another volunteer study, subjects given Hartmann's solution showed an earlier time to first micturition and a greater urine output over six hours than patients given 0.9% saline. This greater diuresis has been ascribed to the lower osmolality of Hartmann's solution causing reduced vasopressin secretion. This is unlikely to be the sole explanation though, as the Hartmann's group also had a greater sodium excretion which suggests a primarily renal effect — possibly due to the difference in chloride load<sup>25</sup>. In a follow-up paper to Yunos's initial study evaluating the biochemical effects of restricting chloride-rich fluids the investiga-

tors evaluated the effect of this change in fluid therapy on clinical outcomes. They reported a significant reduction in acute kidney injury (AKI) and renal replacement therapy (RRT) in the chloride-restrictive group<sup>26</sup>. While these are only observational data this is amongst the first evidence that changing our choice of fluid and restricting chloride-containing fluids can change clinical outcomes. A recently published observational study in liver transplant recipients identified the use of large volumes of chloride-rich fluids as an independent predictor of AKI<sup>27</sup>. In contrast, the Cochrane review mentioned above suggested no difference in renal dysfunction and RRT between the chloride-rich and balanced salt groups<sup>7</sup>. It evaluated randomised studies of buffered vs. non-buffered fluids for perioperative fluid resuscitation up to May 2011, and included data from 14 publications. Of these only three ( $n = 207$ ) reported on 'renal insufficiency requiring support', seven ( $n = 399$ ) reported intraoperative urine output, and three ( $n = 222$ ) reported postoperative creatinine clearance. In addition five studies reported various creatinine-based indices but there were only two studies per category ( $n = 113-151$ ). This review thus included small numbers and did not specifically evaluate the development of AKI using current standard definitions; therefore the results regarding renal dysfunction should be viewed with caution.

### Splanchnic circulation

Concerns have also been raised over the effects of hyperchloraemia on the splanchnic circulation. A volunteer crossover study raised initial concerns with an increased incidence of abdominal discomfort in the 0.9% saline versus the Ringer's lactate group<sup>28</sup>. A subsequent study on elderly surgical patients demonstrated a higher gastric tonometry CO<sub>2</sub> gap in the saline versus the balanced-salt group<sup>29</sup>. This suggests reduced gastric perfusion in the saline group. Interestingly abdominal symptoms are key features of ammonium chloride poisoning, suggesting a link between chloride and the above findings. While current evidence is limited, gut hypoperfusion and bacterial translocation may predispose patients to septic complications and this is thus an area of concern and should be a focus for future research<sup>30-33</sup>.

### Sepsis

There are also concerns about the effects of hyperchloraemia in sepsis, although the evidence is limited to laboratory data and animal studies. Studies in rat models of septic shock have shown a worse acid-base profile in animals receiving 0.9% saline as opposed to lower chloride solutions<sup>34</sup>. The same group also demonstrated a significant correlation between an increase in chloride levels and hypotension in their rat model<sup>35</sup>. Investigating the cause of these findings the researchers found that hyperchloraemic acidosis induced increased NF- $\kappa$ B DNA binding, increased nitric oxide release, and increased interleukin (IL) 6: IL 10 ratios in cell culture, suggesting a proinflammatory effect at the cellular level<sup>36</sup>. Further research on this in a rat model confirmed that hyperchloraemic acidosis was associated with an increased cytokine release as compared with controls resuscitated with Ringer's lactate<sup>37</sup>. While this animal research suggests that hyperchloraemia has adverse haemodynamic and inflammatory effects in sepsis we simply do not have human data to confirm or refute these findings.

### Haemostasis and haemorrhage

The effect of hyperchloraemic fluids on haemostasis and haemorrhage has also been investigated.

In a series of studies by Roche and James, saline-based starches appeared to impair coagulation to a greater degree than equivalent balanced salt solution starches and Ringer's lactate<sup>38,39</sup>. This appears not to be related to differences in calcium content between fluids,

which leaves us to hypothesise about the role of primary chloride or secondary acid-base differences being the driving factor<sup>40</sup>. In terms of clinical studies, Martin showed that in patients undergoing major surgery those who received a starch in saline had a hypocoagulable thromboelastograph (TEG) compared with those who received a starch in a balanced salt solution, whereas those who received Ringer's lactate tended to develop a hypercoagulable state<sup>41</sup>. In a trial involving patients undergoing major surgery, those who received a saline-based colloid had significant TEG abnormalities and increased blood loss compared with those receiving a balanced salt-solution colloid<sup>42</sup>. In a study involving patients undergoing abdominal aortic aneurysm repair, those who received 0.9% saline had greater blood loss and received more blood products than those who received Ringer's lactate<sup>43</sup>. In contrast to the above, there was no difference in the international normalised ratio and activated partial thromboplastin time in trauma patients resuscitated with either 0.9% saline or Plasma-Lyte A<sup>8</sup>. This study did not, however, use the TEG. The data are thus by no means conclusive but do raise a concern regarding the potential for chloride-rich fluids to impair coagulation. Further clinical studies, either removing the confounder of colloid-based fluids or using modern colloids, and using the TEG as a standardised assessment of coagulation, are warranted.

### Mortality

While the basic science, animal studies and human surrogate outcome/organ dysfunction studies have raised concerns about hyperchloraemia, is there any evidence of an effect on mortality in human studies?

The Cochrane review mentioned previously included only three trials that reported mortality outcomes and showed no difference in mortality in perioperative patients whether they received saline or a balanced salt solution<sup>7</sup>.

Yunos's study, which highlighted the effect of high-chloride fluids on AKI and RRT, also did not demonstrate a mortality difference<sup>26</sup>.

In contrast to this is a thought-provoking study from Brazil<sup>44</sup>. The authors prospectively evaluated major surgical patients who required postoperative intensive care. They recruited 393 patients and analysed their postoperative chloride levels. Instead of using standard definitions of hyperchloraemia they constructed a receiver operating characteristic curve of chloride levels and hospital mortality. This showed an optimal cut-off point of 114 mmol/l and a reasonable area under the curve (AUC) for predicting death of 0.76. Using this cut-off, 31.7% of the patients were hyperchloraemic. Comparing mortality between those above and below the cut-off they found a significantly higher mortality in the hyperchloraemic patients (19.3 vs. 7.4%;  $p = 0.001$ ). These patients, however, had significantly longer surgery and received more intraoperative saline. Based on this it cannot be said whether the hyperchloraemia is causative or merely a marker of increased risk but it does raise serious concerns regarding the potential risks of iatrogenic hyperchloraemia.

In another Brazilian study, Boniatti evaluated a number of acid-base and biochemical variables as predictors of mortality in ICU<sup>4</sup>. While many showed an association on univariate analysis, only chloride and albumin remained significant on multivariate analysis and improved the predictive ability of a multiple logistic regression model consisting of SOFA score and age, increasing the AUC from 0.72 to 0.8. Again we have hyperchloraemia as a significant marker of poor outcome but no clarity on cause and effect.

Most recently, McCluskey reported that acute postoperative hyperchloraemia was associated with an increased risk of 30-day mortality (3.4 vs. 1.3%;  $p < 0.01$ ). This was a large retrospective cohort study involving over 22 000 patients who underwent inpatient non-cardiac, non-transplant surgery. The study also included propensity matching of hyperchloraemic and non-hyperchloraemic patients. The excess mortality in hyperchloraemic patients was still seen in this propensity-matched cohort (3.0 vs. 1.9%;  $p < 0.01$ ). Hyperchloraemia was found to be an independent predictor of mortality in multiple logistic regression analysis (odds ratio = 2.049; 95% CI 1.619–2.592;  $p < 0.01$ ).

While not conclusive, this association with mortality raises serious concerns and needs to be explored further.

## Conclusion

Hyperchloraemia leads to the development of metabolic acidosis and is associated with adverse renal effects and increased mortality, amongst other adverse effects. It is also apparent that our choice of intravenous fluids influences the development of hyperchloraemia. From a research perspective we need to explore further the association between hyperchloraemia and adverse outcomes in different populations and attempt to elucidate whether the hyperchloraemia is indeed contributing to any associated adverse outcomes in the clinical setting. We also need to explore whether preventing or treating hyperchloraemia results in improved clinical outcomes. In the interim it is prudent to avoid the use of 0.9% saline as a resuscitation fluid, and to avoid often unconsidered sources of chloride where possible, e.g. the use of colloids in 0.9% saline and the use of 0.9% saline as a diluent for large-volume medication infusions.

**Conflict of interest** – The author declares that he has no financial or personal relationship(s) which may have inappropriately influenced him in writing this paper.

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