Hyperchloremic Metabolic Acidosis: Is It Clinically Relevant?

Michael G. Mythen¹, Mark A. Hamilton²

¹Director of the Centre for Anaesthesia, Consultant in Anaesthesia and Intensive Care
²Research Fellow, Centre for Anaesthesia
The Middlesex Hospital
London, United Kingdom

Summary

"First, do no harm." These words have been the doctrine of medicine since its inception. The era of evidence-based medicine now compels us to provide scientific evidence that we indeed do no harm and that the treatments we prescribe have a beneficial effect. The colloid/crystalloid debate continues to evolve and is as hotly contested now as it was a decade ago. There may be some international differences in the use of colloids or crystalloids, but most of us continue to use both. Whatever our preferred choice of intravenous fluid for the treatment of hypovolemia, clinical outcome studies suggest that "when?" and "how much?" are probably more important questions than "what?". There are now a wide variety of fluids available to the clinician and most differ markedly in their composition. Aside from the gross classification of IV fluids into colloids and crystalloids, they may be subclassified into balanced or unbalanced categories, i.e., those that contain concentrations of electrolytes similar to those in the plasma and those that do not (see Table 1). The very fact that "normal" saline is unphysiological was recognized many years ago. This fact led Alexis Hartmann to develop Hartmann's solution in an attempt to produce an isotonic alkaliising solution. He recognized the need for proportionately more sodium than chloride¹, which led to a solution very similar to Ringer's original². The existence of hyperchloremic acidosis has been recognized in many areas for some time, e.g., diabetic ketoacidosis and ammonium chloride poisoning, and is generally termed a low-anion gap acidosis. There is now mounting evidence that the administration of intravenous saline and saline-based fluids is the commonest avoidable cause of clinically relevant hyperchloremic acidosis.

Key Words

- Volume replacement
- Colloids
- Crystalloids
- Hyperchloremic acidosis
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What is hyperchloremic metabolic acidosis?

Hyperchloremic metabolic acidosis is the clinical combination of a non-respiratory acidosis, i.e., metabolic acidosis caused by an increase in the plasma concentration of chloride to supraphysiological levels.

Pathogenesis of hyperchloremic metabolic acidosis

Currently, there are two explanations for the pathophysiology of hyperchloremic metabolic acidosis. The first is the physico-chemical approach pioneered by Dr. Stewart; the second, simply a dilutional explanation for a reduction in the plasma bicarbonate when non-bicarbonate containing fluids are infused intravenously. Recent studies, however, suggest that the dilutional theory may be less likely.

Conventional methods of interpreting acid-base balance focus on the Henderson-Hasselbach equation, which describes a ratio of carbon dioxide to bicarbonate to derive the pH. The respiratory component of the equation is easy to comprehend because CO$_2$ is part of the equation; the metabolic component, however, is less easy to understand. We use surrogate markers of metabolic disturbance such as base excess to quantify the degree of metabolic acidosis. There has been an increasing awareness that this model, which works clinically, fails to explain much of the associated pathophysiology, particularly the influence of electrolytes and proteins on acid-base balance. In 1979, Dr. Stewart adopted a physico-chemical approach to acid-base balance and devised a model, subsequently modified by Fencl, which explained many of these anomalies. Stewart maintained that for all aqueous systems there must be electrical neutrality and conservation of mass and that water will dissociate/associate to give/receive hydrogen ions if the balance of either is altered. He also stated that only three independent factors control acid-base balance, namely:

- PCO$_2$
- Strong ion difference (SID)
- Weak acids (albumin and phosphate)

All other variables such as hydrogen ions, hydroxide, bicarbonate, etc., change only if one or more of the three independent variables changes.

<table>
<thead>
<tr>
<th>Solution</th>
<th>Na$^+$ (mmol L$^{-1}$)</th>
<th>Cl$^-$ (mmol L$^{-1}$)</th>
<th>K$^+$ (mmol L$^{-1}$)</th>
<th>Ca$^{2+}$ (mmol L$^{-1}$)</th>
<th>HCO$_3$ (mmol L$^{-1}$)</th>
<th>Lactate (mmol L$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Chloride 0.9%</td>
<td>154</td>
<td>154</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hespan</td>
<td>154</td>
<td>154</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gelofusine</td>
<td>150</td>
<td>150</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EloHes 6%</td>
<td>150</td>
<td>150</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemaccel</td>
<td>145</td>
<td>145</td>
<td>5.1</td>
<td>6.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hartmann’s</td>
<td>131</td>
<td>111</td>
<td>5</td>
<td>2</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Plasmalyte B</td>
<td>140</td>
<td>98</td>
<td>5</td>
<td>2.5</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Hextend</td>
<td>143</td>
<td>124</td>
<td>3</td>
<td>2.5</td>
<td></td>
<td>28</td>
</tr>
</tbody>
</table>

Typical fluid electrolyte compositions

Table 1

Strong ions in a solution and is normally between 38 and 42 meq/L. Strong ions are those which in solution form are virtually fully dissociated, e.g., Na$^+$, Cl$^-$, K$^+$, Ca$^{2+}$, Mg$^{2+}$, and, for the purposes of the model, lactate. For example, if one adds NaCl to water, there is virtually complete dissociation. The only things that exist in the solution are Na$^+$, Cl$^-$, H$_2$O, H$^+$ and OH$^-$ ions; there are no “NaCl molecules”. If there is a change in the concentration of one of these ions, i.e., an increase in the Cl$^-$, the SID will be reduced and electrical neutrality has to be restored. The result is the dissociation of water, which produces hydrogen ions and decreases the pH of a solution. Therefore, increasing the chloride concentration makes the system more acidic. The increase in the hydrogen ion concentration, however, is only in the nanomolar range and does not restore electrical neutrality. The proteins restore the bulk of electrical neutrality.

Weak acids

Albumin and phosphate are the predominant weak acids. If the concentration of albumin decreases, the solution becomes more alkaline. This is a very common occurrence in the critical care patient.

What is the most common avoidable cause of hyperchloremic metabolic acidosis?

The most common avoidable cause of hyperchloremic metabolic acidosis is probably the administration of fluids containing supraphysiological concentrations of chloride in sufficient quantity, such as 0.9% saline. Sodium chloride has 154 mmol of sodium, which is compatible with that found in the extracellular space, and 154 mmol of chloride, which is supraphysiological (normal range 98-107 mmol/L). The explanation for the ensuing acidosis is given above, but it is essentially due to a decrease in the SID of the plasma.
Does hyperchloremic acidosis occur in humans?

Hyperchloremic acidosis following saline administration has been clearly demonstrated in animal models. There is also now good evidence to support its occurrence in humans as outlined below.

Healthy volunteers

Williams et al. administered 50 mL/kg of either normal saline or Ringer's lactate solution over 1 hour to 18 healthy volunteers in a blinded crossover study (i.e., all subjects received both fluids but on different days) and found that the saline-treated individuals developed a significant metabolic acidosis. In a more recent study by Waters et al., healthy volunteers were administered either 15 mL/kg of 6% hydroxyethyl starch (HES) or albumin. Both groups achieved the same volume expansion, but only the HES group had a significant decrease in base excess. It is particularly interesting to note that the albumin used in this study had a chloride concentration of 98 mmol/L rather than approximately 150 mmol/L, which is more common.

Gynecological/urological surgery

There have been numerous case reports of patients developing hyperchloremic acidosis as a result of ileal conduits. There are also case reports describing the development of hyperchloremic acidosis with large volume saline resuscitation, some with presumed detrimental effects. Scheingraber et al. randomized two groups of patients undergoing intra-abdominal gynecological surgery to receive normal saline or Ringer's lactate at an infusion rate of approximately 30 mL/kg/h. They observed a significant increase in chloride level in the saline-treated group and a significant decrease in pH to a mean of 7.28. The volumes infused in the first 2 hours were 71 mL/kg of saline vs. 67 mL/kg of Ringer's lactate. The investigators also conducted a study on the effect of irrigation fluid (containing ethanol, mannitol and sorbitol) absorption on acid-base balance in patients (n = 20) undergoing transurethral resection of the prostate (TURP). All patients received a background infusion of 15-20 mL/kg/h of Ringer's lactate solution and were divided into two groups depending on the amount of irrigation fluid absorption. The investigators observed a minimal, although significant, fall in pH from 7.41 to 7.37 and, not unsurprisingly, noted that the longer the surgery, the greater the amount of irrigation fluid absorption as well as a larger decrease in SID in the study group. The decrease in SID was multifactorial in origin and not simply due to the chloride of the irrigating solution.

Cardiac surgery

Cardiac surgery patients commonly experience a fall in pH at the end of cardiopulmonary bypass (CPB). There are a multitude of explanations to account for this phenomenon. Hayhoe et al. studied 10 patients on CPB and used a pump prime of 500 mL of Haemaccel® (Hoechst, Australia), a urea-linked polygeline solution with 145 mmol of sodium and chloride, with 900-1100 mL of Ringer's lactate. At the end of surgery, they observed a significant increase in chloride and a fall in the SID. These findings were enough to explain the drop in pH. They also observed an increase in the strong ion gap (SIG: difference between the observed and expected SID), which they postulate was due to the polygeline in the Haemaccel®. Lisaker et al. recently compared a combination of Haemaccel and Ringer's lactate versus Plasmalyte® 148 as pump primes in 22 patients. Both groups developed fluid-induced acidosis: the Haemaccel® group had hyperchloremic acidosis whereas the Plasmalyte® group had anion-gap acidosis. The investigators postulated that the Plasmalyte®-associated anion-gap acidosis was due to the acetate and gluconate in the Plasmalyte®. They also noted that the chloride acidosis resolved more quickly.

Is hyperchloremic metabolic acidosis clinically relevant?

There has been much discussion regarding the allegedly benign nature of hyperchloremic metabolic acidosis, but opinions still differ. It is unclear if the drop in pH itself is responsible for the associated clinical symptoms although it seems unlikely because the fall in pH is often mild and disproportionate to the symptoms and signs. It may be a chemical effect due to the supra-physiological quantities of chloride or, possibly, the result of interference with red cell structure and function. The evidence presented below may help to answer some—but not all—of these questions.

In an animal model of hemorrhage, resuscitation with Ringer's lactate was associated with improved survival when compared with normal saline. Similarly, Kellum et al. demonstrated improved survival in a rat endotoxemia model when animals were resuscitated to similar blood pressures using Hextend® as opposed to normal saline. In

General surgery

In an early study, McFarlane et al. randomized 30 patients undergoing hepatobiliary or pancreatic surgery to receive either 15 mL/kg/h of normal saline or Plasmalyte® and found that the saline group had a significant change in chloride, base excess and standard bicarbonate. Wilkes et al. randomized 47 patients into two groups, namely an unbalanced and balanced fluid group during major surgery. The unbalanced group received Hespan® (6% hydroxyethyl starch in N/saline) and N/saline; the balanced group received Hextend® (6% hydroxyethyl starch in a balanced electrolyte and dextrose injection) and Ringer's lactate. They observed a significant increase in chloride and a reduction in base excess in the unbalanced group. They also reported a 67% incidence of hyperchloremic acidosis in the unbalanced group versus 0% in the balanced group.
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In the healthy human volunteers that Williams et al. studied\(^1\), there were subjective mental changes only in the subjects who received normal saline. These ranged from minor inability to concentrate to significant inability to read or perform simple arithmetic. No changes occurred when Ringer’s lactate was infused. There were also subtle changes in the saline arm of the study carried out by Wilkes et al.\(^8\), in which 13 patients had difficulty with abstract thinking whereas none did in the Ringer’s lactate arm.

Cerebral function

In the healthy human volunteers that Williams et al. studied\(^1\), there were subjective mental changes only in the subjects who received normal saline. These ranged from minor inability to concentrate to significant inability to read or perform simple arithmetic. No changes occurred when Ringer’s lactate was infused. There were also subtle changes in the saline arm of the study carried out by Wilkes et al.\(^8\), in which 13 patients had difficulty with abstract thinking whereas none did in the Ringer’s lactate arm.

Renal function

It is interesting to speculate on the regulatory role of chloride in renal blood flow or urine production as did Wilcox\(^9\), who found that chloride caused renal vasoconstriction in greyhounds. Healthy volunteers often provide us with less complicated data on which to base our assumptions. Williams et al. administered 50 mL/kg of saline over 1 hour to 18 healthy volunteers, followed by the same amount of Ringer’s lactate solution at a later date\(^5\). There were significant pH differences between the groups with the saline-induced acidosis persisting for up to 1 hour. The most striking observation between the groups was the significant delay in time until first urination in the saline group (76 min vs. 106 min). The trend to delayed urination continues with the Scheingraber study on gynecological surgery patients showing decreased urine production in the saline group (717 vs. 1075)\(^7\). Wilkes et al. also observed a trend to decreased urine production in the saline-treated groups (balanced fluid group 1.68 ± 1.32 mL kg-1 hr-1 versus saline group 0.96 ± 0.7 mL kg-1 hr-1; \(p = 0.0787\))\(^14\). Bennett-Guerrero et al. provide us with further significant data\(^20\). They studied the effect of intraoperative fluid administration (Ringer’s lactate, Hextend\(^\circledR\), Hespan\(^\circledR\) or albumin) on cardiac surgery patients and observed a significant decrease in urine output and a significant increase in postoperative creatinine in the unbalanced fluid groups.

GI tract function

Wilkes et al. noted a significant increase in the tonometry CO₂ gap, indicating gut hypoperfusion in the unbalanced group\(^5\). Although the study was not powered to show a difference, there was also a significant trend towards increased nausea and vomiting in the unbalanced group and a greater core-to-peripheral temperature gradient. It is difficult to separate the effects per se of a lower pH or higher chloride levels on vascular reactivity. We do, however, know that there may be a link between gastric hypoperfusion and nausea and vomiting postoperatively. In the healthy volunteer study by Williams et al.,\(^1\) 10 patients in the saline group experienced abdominal discomfort compared with only one in the Ringer’s lactate group\(^1\).

Chloride may have the same vasoconstrictive effect on the splanchnic circulation as it does on the renal circulation. This effect may lead to nausea and vomiting or general gut discomfort, linked either to a genuine gut hypoperfusion effect or a chloride-specific effect.

Red cell function

There is evidence, however, to suggest that solutions with a high chloride load may cause red cell lysis in unphysiological situations, e.g., CPB\(^2\), and that natural colloids such as albumin may indeed be protective in that respect.

Coagulation

There is little direct evidence to suggest that hyperchloremic acidosis has detrimental effects on the clotting system. If, however, we extend this argument to say that unbalanced fluids cause hyperchloremic acidosis, the study conducted by Gan et al. in 1999 may provide us with some insight\(^22\). Patients undergoing major surgery were randomized to receive either Hespan\(^\circledR\) (unbalanced) or Hextend\(^\circledR\) (balanced). The balanced group had less blood loss and less time to clot formation. This observation may reflect the fact that the balanced group had a much lower requirement for calcium supplementation as acknowledged by the authors. The patients studied by Scheingraber et al. showed strong trends to a higher blood loss (962 vs. 704 mL) although this finding was not statistically significant\(^23\).

Respiratory function

One could hypothesize that in patients being weaned for extubation, even a mild acidosis may make the process more difficult as the respiratory system attempts to rectify the pH by excreting CO₂. Bellar et al.\(^23\) retrospectively looked at a small (n = 45) sample of post surgery ICU patients and found that although chloride levels significantly correlated with the fall in bicarbonate, as one would expect, the pH was well maintained and reflected adequate respiratory compensation. There was no obvious effect on extubation as a result.
CONCLUSION

Is hyperchloremic acidosis real? Yes. Is hyperchloremic acidosis clinically relevant? Probably. We know from numerous observational studies that the phenomenon exists. More recently, new approaches to acid-base theory have given us the ability to understand and predict the mechanisms responsible for the acidosis. We also know that even a mild degree of acidosis, coupled with acidosis from a different source, e.g., lactic acidosis from tissue hyperperfusion, may be enough to complicate the management of patient care. Although the data are still sparse, there is mounting evidence that the administration of unbalanced fluids in sufficient quantities may cause abdominal dysfunction, renal dysfunction and, possibly, clotting abnormalities. The solution to the problem may be easier to achieve with the advent of new balanced colloids and the appropriate use of physiologically balanced crystalloids.

Evidence supporting the clinical relevance of hyperchloremic acidosis is scanty and predominantly observational, but its mechanism is clear. In our opinion, there is enough evidence rendering the use of fluids high in chloride unwise, especially given the wide range of fluids available today.

REFERENCES