Intravenous fluid therapy in critically ill patients aims to treat hypovolaemia and dehydration, replace lost electrolytes, and act as a vehicle for the excretion of waste products and redundant metabolites. None of the existing crystalloid solutions perfectly suits all of these roles. In fact, since Thomas Latta and Robert Lewins first used intravenous saline solution in the 1830s, and Alexis Hartmann added lactate to Ringer’s solution in the 1930s, these substances have remained unchaged [1].

It is a well-publicized fact that 0.9% saline solution produces a metabolic acidosis when administered in sufficiently large quantities [2–4]. The term ‘dilutional acidosis’ represents an approximation to the model of dilution of plasma or extracellular volume with any electrolyte solution that is free of bicarbonate [5–7]. The concept of ‘hyperchloraemic acidosis’ is based upon the Stewart approach to acid–base chemistry [8]. Here the arterial partial pressure for carbon dioxide ($P_{CO_2}$), the strong ion difference (SID), $[\text{Na}^+] + [\text{K}^-] - [\text{Cl}^-] - [\text{Lactate}^-]$, and the sum of all anionic charges of weak plasma acid ($A_{an}$) are considered independent pH-regulating variables. The law of electroneutrality demands that a decrease in SID, e.g. as a result of hyperchloraemia or an increase in $A_{an}$, associated with an increase in serum albumin, results in a fall in the dependent variable, bicarbonate.

Both models explain some of the aspects of this type of metabolic acidosis without being entirely conclusive. Waters et al. [7] demonstrated a metabolic acidosis after infusion of saline and saline-based colloids during prolonged surgery, but plasma-volume expansion was absent in their patients. Prough and White [9] suggested that hypervolaemia was not necessary for the diagnosis of dilutional acidosis.

Whatever the aetiology of saline-related metabolic acidosis, only a demonstrable influence on true or surrogate outcome measures in randomized controlled trials involving patients will have an impact on clinical practice. Intuition suggests that in critically ill patients, a ‘mixed metabolic acidosis’ resulting from lactic plus hyperchloraemic acidosis would be undesirable. More than 30 years ago, Coran et al. [10] stated that in higher risk patients, any additional prolongation of acidosis might be detrimental. What is the current evidence for the clinical relevance of this phenomenon?

Williams et al. [3] observed a longer time to first urination in volunteers, a higher incidence of abdominal discomfort and more frequent subjective mental changes after infusion with saline compared with Ringer’s lactate. In a model of massive haemorrhage, survival was better after resuscitation with Ringer’s lactate than saline solution [11]. Acidosis in anaesthetized pigs was associated with impaired gastro-pyloric motility, suggesting a role in post-operative gastroparesis and vomiting [12]. Gastric mucosal perfusion was impaired in elderly surgical patients receiving saline and saline-based colloids compared with those receiving Hartmann’s solution and Hextend, a colloid with a more balanced glucose and electrolyte formulation [13]. Waters et al. [14] found that patients undergoing aortic reconstructive surgery required more blood products after saline than after lactated Ringer’s solution, although the differences in estimated blood loss were not significant. In this study [14], the urine output was larger in the saline group, but patients in this group also received larger total volumes of intravenous fluids. Gan et al. [15] demonstrated a favourable coagulation response and less blood loss in transfused patients after Hextend compared with hetastarch in saline. None of the studies so far have been powered to demonstrate a link between hyperchloraemic metabolic acidosis and survival, duration of hospital or critical care unit stay, or resource utilization, but the value of a reduced risk of post-operative nausea and vomiting to a surgical patient cannot be underestimated.

In this issue of Clinical Science, Reid and co-workers present a blinded volunteer study of biochemical and clinical responses to bolus administration of 2 litres of 0.9% saline versus Hartmann’s solution [16]. Their main findings were the expected retention of saline (56% of administered volume at 6 h) and the lower retention of Hartmann’s solution (30% at 6 h), a faster median time to first urination after Hartmann’s solution (70 min) than after saline (185 min), and a larger total urine volume after Hartmann’s solution (1000 ml) than after saline (450 ml). Surprisingly, despite the lower dose of sodium administered, total urine sodium content was higher after Hartmann’s solution (122 mmol) than after saline (73 mmol). It must be welcomed that the investigators not only examined urine volumes and time intervals from initiation of infusion to first urination, but also the quality of the urine produced.

This study by Reid et al. [16] represents another building block in our understanding of the physiological and physicochemical responses to large volume intravenous fluid administration. The effects of 0.9% saline solution on anti-diuretic hormone secretion and those of hyperchloraemia on renal blood flow and glomerular filtration rate have been documented [17], but an in-
fluence of hyperchloraemia on sodium retention remains speculative. In the present study [16], the authors demonstrated a 30% larger peak blood-volume expansion with saline compared with Hartmann’s solution, but 90% more of the saline administered was retained at 6 h. Haematocrit calculations suggested that the bulk of this volume remained in the interstitial space. This would lead to concerns about increased lactic acidosis from tissue oedema after repeat infusions, and the reduced availability of urine flow as a vehicle for metabolic acids.

Clearly, clinicians would wish to see the crystalloids they administered end up in the fourth space, i.e. the urinary tract.

The limitations to the use of Hartmann’s solution, such as in neonates, and patients with renal failure and who perhaps have undergone neurosurgery, are well known. In addition, the chloride content of Hartmann’s solution is still greater than that of plasma.

Is it time for a new solution? Without doubt, the manufacturing industry would be ready to provide a crystalloid that in clinical trials has been shown to be suitable for both the initial treatment of hypovolaemia and dehydration and for fluid maintenance during surgery, without exacerbating an existing metabolic acidosis. Do we have to wait for another 100 years to pass since Alexis Hartmann presented his solution in the 1930s?

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