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## **Editorial II**

#### Seven misconceptions regarding volume therapy strategies—and their correction

An appropriate intravascular volume replacement is a fundamental component of managing the critically ill surgical or intensive care unit (ICU) patient because the failure to treat hypovolaemia may progress to organ dysfunction or even death.<sup>1</sup> Although the importance of adequate volume replacement is widely accepted, there are still no unique accepted recommendations. Aside from different crystalloid solutions, the natural colloid human albumin (HA) and different non-protein (synthetic) colloids have been promoted to treat volume deficits. Over the recent years, some misconceptions or myths of volume replacement concepts have been established that need to be reconsidered and to be corrected when necessary.

# First misconception: saline is a physiological solution

Saline solution is an isotonic crystalloid that is still the dominating crystalloid worldwide. It has been termed 'physiological' or 'normal' saline, but when it is compared with the composition of plasma, one must wonder why it has ever been termed as 'physiological'. With its high sodium (154 mmol litre<sup>-1</sup>) and high chloride (154 mmol litre<sup>-1</sup>) concentrations, it is far from being a plasma-adapted solution. In the early 1990s, substantial alterations in acid–base status were described in patients in whom considerable amounts of saline solution were infused—this was defined as 'hyperchloraemic acidosis'.<sup>2</sup> As a low base excess (BE) may serve as a surrogate

marker to identify patients with underperfused tissues, producing (hyperchloraemic) acidosis by administering fluids of an unphysiological composition, we may mask the diagnosis of perfusion deficit or make inappropriate clinical interventions due to the erroneous presumption of ongoing tissue hypoxia secondary to hypovolaemia. In a study in ICU patients, the BE was shown to predict outcome.<sup>3</sup> BE may also be used to identify patients who have a high risk of mortality and thus should be admitted to the ICU. In patients undergoing cardiac surgery with cardiopulmonary bypass, BE measured during the first hour after surgery was correlated with the length of ICU stay.<sup>4</sup>

Aside from experimental studies showing negative effects of hyperchloraemic acidosis,<sup>5</sup> there is increasing evidence for negative effects in humans. In healthy volunteers in whom 50 ml kg<sup>-1</sup> of either normal saline (NS) or Ringer's lactate (RL) was infused, metabolic acidosis developed in the NS group and time to first passing urine was increased significantly.<sup>6</sup> In a study of patients undergoing elective lower abdominal gynaecologic surgery who received  $\sim 6$  litre of either NS or RL,<sup>7</sup> the NS-treated patients had a lower urine output. In patients undergoing abdominal aortic aneurysm repair given either RL (total dose: 6.8 litre) or NS (total dose: 7 litre) in a doubleblinded fashion,<sup>8</sup> only the NS-treated patients developed hyperchloraemic acidosis and they needed significantly more blood products. In patients undergoing kidney transplantation, either ~6 litre of NS or RL was given.9 NS was not recommended because of producing metabolic acidosis and significant hyperkalaemia.

Although the clinical importance of metabolic acidosis has been intensively discussed, there appears to be no good reasons to use saline solution to correct hypovolaemia. The *British Consensus Guidelines on Intravenous Therapy for Adult Surgical Patients*<sup>10</sup> recently recommended that '... balanced solutions... should replace 0.9% saline ... (Evidence level 1b)'.

### Second misconception: albumin is superior to other plasma substitutes

HA may be used either for correcting hypovolaemia or for correcting hypoalbuminaemia. HA is dissolved in saline solution that may result in acidosis, secondary to its high chloride content. The superiority of HA for volume replacement compared with other plasma substitutes has never been shown with regard to mortality or major side-effects such as bleeding.<sup>11</sup> In the Guidelines for Diagnosis and Therapy of Sepsis,<sup>12</sup> HA is not recommended for volume replacement. A *post hoc* follow-up analysis of data from the SAFE study showed a significantly increased mortality in patients with traumatic brain injury treated with HA.<sup>13</sup> An international prospective cohort study including 1013 ICU patients needing fluid resuscitation for shock showed that hyperoncotic HA 20% was significantly associated with renal dysfunction and increased overall ICU mortality.<sup>14</sup>

Beneficial effects of HA have also been reported, especially in patients with liver cirrhosis and spontaneous bacterial ascites, where the use of HA plus antibiotics compared with only antibiotics,<sup>15</sup> and diuretic plus HA compared with diuretics alone,<sup>16</sup> resulted in a significantly improved outcome. However, in both studies, the control patients (no HA) did not receive any additional volume replacement. It is likely that hypovolaemia was present in the non-albumin-treated groups and this is associated with negative haemodynamic consequences. Correction of hypovolaemia by other non-protein colloids may have avoided acute kidney injury and have advantages over HA.

Because of its high net charge, albumin possesses excellent binding capacities, and is also an important transport protein for bilirubin, hormones, and many drugs. No therapeutic indication is documented for administering HA to improve its transport function in clinical studies. Albumin is assumed to serve also as a free radical scavenger and to bind toxic substances (e.g. free fatty acids). Therefore, HA seems to be indicated in patients with sepsis because toxic oxygen radicals may play a role in pathogenesis and maintenance of sepsis. To date, there are no data confirming the benefits of HA on morbidity or mortality in humans secondary to its scavenging properties. It is uncertain whether HA preparations currently commercially available have the same properties as natural albumin or whether they are altered by the manufacturing process.

#### Third misconception: all colloids are the same

In most recommendations on volume therapy, 'colloids' were subsumed to one single group.<sup>17</sup> Colloids have to be distinguished with regard to their different physico-chemical properties that markedly influence their wanted and unwanted (side) effects. Besides HA, various non-protein, synthetic colloids [dextrans, gelatins, hydroxyethyl starch (HES) preparations] are available to treat volume deficits. Colloidal plasma substitutes widely vary with regard to their initial volume replacement efficacy and their duration of haemodynamic stabilization (Fig. 1).

As safety issues are increasingly relevant, side-effects of the different colloids have also to be considered. The differences in safety became most obvious when considering the different generations of HES. The available HES preparations are characterized by concentration (hypooncotic: 3%; isooncotic: 6%; and hyperoncotic: 10%), molar substitution (MS; low MS: 0.4-0.42; medium MS: 0.5; and high MS: 0.62 and 0.7), mean molecular weight (Mw; low molecular weight-HES: 70 kDa; medium-molecular 130–264 kDa; and high weight-HES: molecular weight-HES: >450 kDa), the origin (potato-derived vs maize-derived HES), and their solvent (balanced vs unbalanced HES preparations). Most important differences between the different HES preparations can be seen with regard to their effects on coagulation and renal function.

Although disturbances of coagulation occurred with the first-generation HES (Mw >500 kDa, MS >0.7), the most recent HES (Mw <200 kDa, MS <0.5) appear to be almost clear of negative effects on coagulation.<sup>17</sup> The safety of HES in haemostasis has been increased by dissolving it in a plasma-adapted solution containing calcium instead of a saline solution.<sup>18</sup>

A prospective, multicentre study of renal function in intensive care patients with sepsis and septic shock<sup>19</sup> demonstrated that using a hypertonic, second-generation HES preparation with a medium MS and a medium Mw (10% HES 200/0.5) without following exclusion criteria for serum creatinine (serum creatinine was >3.6, instead of  $>2.0 \text{ mg dl}^{-1}$ ) and dose limitations (20 ml kg<sup>-1</sup> day<sup>-1</sup>) resulted in a significantly higher incidence of late renal failure requiring renal replacement therapy than the use of RL for volume replacement. This leads to the recommendation of the British Consensus Guidelines on Intravenous Therapy for Adult Surgical Patients that '... hetastarch and pentstarch Mw >200 kDa should be avoided in patients with sepsis . . . . (Evidence level 1b)'.<sup>10</sup> Although there are no large clinical trials, newer isooncotic HES preparations with an Mw 130 kDa and an MS <0.5 may have improved the renal safety of HES.<sup>20</sup> This resulted in the conclusion that there is not enough convincing evidence against the reasonable use of 6% HES 130/0.4.<sup>21</sup>

Colloidal plasma substitutes may also possess effects on organ perfusion, microcirculation, tissue oxygenation, inflammation, endothelial activation, and capillary leakage Editorial II



Fig 1 Haemodynamic effects of different plasma substitutes.

that go beyond their simple volume replacing properties.<sup>22</sup> Non-oncotic effects of albumin (e.g. anti-inflammatory properties) have been shown in some experimental or animal studies.<sup>22</sup> At present, no convincing beneficial effects on perfusion, inflammation, tissue oedema, or organ function have been demonstrated in humans. Only few studies using dextrans and gelatins have been published on this issue.<sup>22</sup> In contrast, beneficial effects have been shown with HES in several animal and patient studies. The exact mechanisms remain to be elucidated: the HES molecule may exert direct, substance-specific effects on endothelial cells and leucocytes,<sup>23</sup> improved perfusion may also be responsible for some of the beneficial effects of HES.

In summary, colloids differ greatly with regard to their haemodynamic efficacy, their side-effects, and their additional non-volume replacing properties (Fig. 2).

# Fourth misconception: crystalloids are as effective as colloids

In the adult, isotonic crystalloid solutions distribute within the intravascular ( $\sim 20-25\%$ ) and interstitial ( $\sim 75-80\%$ ) space. The younger the patient, the less of the infused crystalloid remains in the intravascular space when compensating for hypovolaemia.<sup>24</sup> In contrast to colloids that primarily remain within the intravascular space and provide a colloid oncotic pressure (COP), crystalloids provide no COP or even reduce it by dilution. Thus, much more crystalloid than colloid is required to correct hypovolaemia and there is increasing risk of producing tissue oedema formation.<sup>25</sup> In spite of much lower haemodynamic efficacy and the risk of producing tissue oedema, most recommendations for treating the critically ill regarded crystalloids equal to colloids.

Even a massive crystalloid resuscitation is less likely to achieve adequate restoration of organ perfusion or microcirculatory blood flow.<sup>25 26</sup> In a septic animal experiment, less endothelial swelling and less parenchymal injury were shown with colloid infusion (pentastarch) than with RL.<sup>27</sup> In patients undergoing major abdominal surgery, the influence of HES 130/0.4 on tissue  $Po_2$  was compared with that in patients who received RL.<sup>26</sup> Systemic haemodynamics remained unchanged and were similar in both groups; tissue  $Po_2$  increased significantly in the HES-treated patients, but decreased significantly in the RL group. In addition to its less beneficial effects on macro- and microcirculation, experimental, animal, and human studies documented negative effects of crystalloids on inflammation, endothelial activation, capillary leakage, and oedema formation.<sup>22 23</sup>

# Fifth misconception: use of pressure-related monitoring variables to guide volume therapy

The aim of an appropriate monitoring is to avoid insufficient fluid infusion and fluid overload. Standard haemodynamic monitoring such as measuring arterial pressure and heart rate (HR) is often not accurate in detecting volume deficit or guiding volume therapy. Filling pressures (central venous pressure and pulmonary artery occlusion pressure) have been shown to be misleading surrogates for accurately assessing left ventricular preload.<sup>28</sup> Cardiac filling pressures are influenced by several factors other than volume load, including alterations in vascular or ventricular compliance. Measurement of intrathoracic blood volume (ITBV) has been reported to be a better method to monitor volume replacement.<sup>29</sup> A reduction in ICU and hospital stay was shown and mortality reduced when using ITBV monitoring. ITBV, however, is only a static surrogate measure of filling conditions and not of the dynamic process of blood flow and perfusion.

	Albumin	Gelatins	HES
Plasma volume supporting capacity persistence of macromolecules	+	+	++
<ul> <li>Modulating of cascade system activation anti-inflammatory potential</li> </ul>	(+)	_	+ +
<ul> <li>Influence on white blood cell– endothelial cell interactions</li> </ul>	_	_	+ +

Fig 2 Anti-inflammatory potential of colloids.

Occult hypovolaemia may be associated with the development of organ perfusion deficits and subsequently with organ dysfunction.<sup>30</sup> Monitoring of cardiac output (CO) and central venous oxygen saturation ( $Scv_{o_2}$ ) are regarded to be more reliable measures for assessing the adequacy of volume replacement therapy than simple pressure monitoring.<sup>31 32</sup> Individual goal-directed volume therapy using dynamic variables such as CO and  $Scv_{o_2}$  has shown significant improvement in patients' outcome.<sup>32</sup>

### Sixth misconception: mortality is the only variable that counts for assessing the quality of volume replacement strategies

It has to been questioned whether we can make a meaningful statement on comparative mortality with regard to different plasma substitutes. Mortality in most surgery is very low, thus it is rather unlikely that a specific volume replacement strategy would significantly influence mortality. Similarly, in intensive care, it would be impossible to prove that the choice of a plasma substitute was the single life-saving influence, in view of the complexity of the underlying disease of the ICU patient and the many different drugs the ICU patient receives. With different volume replacement strategies, mortality has never been shown to be the major outcome variable when assessing the value of different monitoring strategies, anaesthesia techniques, catecholaminergic regimes, etc. When assessing the value of different volume replacement methods, we have to look more closely at outcome variables such as patient comfort, organ function, circulatory improvement, inflammatory response, unwanted adverse effects, or costs.

# Seventh misconception: the myth of meta-analyses

In recent years, we appear to have become obsessed with meta-analyses. It has been questioned whether meta-

analyses are appropriate instruments for assessing the value of different volume replacement strategies. There are a number of problems with meta-analyses, including distinguishing between the different plasma substitutes, different patient groups (e.g. type of surgery, sepsis, age, and co-morbidity), the use of different end-points for and duration of volume administration, clear definitions of outcome and adverse effects, and the use of studies over 20 yr old, despite the management of the critically ill changing markedly over that time. It is my view that we do not need more meta-analyses, pooling old data, but well-controlled studies in specific, well-defined groups of patients (trauma, burns, sepsis, general surgery, and cardiac surgery) comparing different types of volume replacement strategies (crystalloids, albumin, gelatins, dextrans, and different HES preparations), using clear criteria for volume therapy, and using well-defined endpoints aside from mortality.

In conclusion, there is a continuing search for the ideal volume replacement therapy, with many new substances coming on the market. Adequate volume replacement represents one piece of the puzzle for optimizing the patient's management. In recent years, considerable progress has been made in our understanding, including more sophisticated monitoring techniques to identify volume deficits, laboratory methods to identify adverse effects, and the importance of distinguishing different patient populations. Adhering to tradition will not help to improve current volume replacement strategies. We should remember that a mind is like a parachute, it best works when it is open.

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