Marker or mechanism? Dysnatraemia and outcomes in the perioperative period

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In the last issue of the BJ/A, Cecconi and colleagues report that in patients presenting for major surgery, preoperative abnormalities of serum sodium concentration were common (present in 38.7% of patients with measurements), and that severe hypernatraemia was common (present in 7.2% of patients presenting for major surgery, preoperative abnormal results, the lack of clarity in published literature regarding the significance of abnormal sodium concentrations is perhaps surprising. The association of abnormal serum sodium concentrations with increased morbidity and mortality has previously been reported in a variety of clinical situations, including medical and surgical patients, patients requiring intensive care, and in the perioperative period. However, whether abnormal

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serum sodium concentrations cause morbidity and mortality per se, or are simply indicators of severe illness leading to adverse outcomes in patients, is not clear. Previous studies have presented data which could support both hypotheses.3–5 The difference is important, because whether preoperative serum sodium concentrations may be used to reliably prognosticate for perioperative outcomes and, more importantly, whether intervention to correct dysnatraemia may improve outcomes, is therefore unclear.

Previous studies have reported associations between both hypernatraemia and hyponatraemia and mortality;6–7 however, Cecconi and colleagues report that after correction for comorbidities and confounding factors, only severe hypernatraemia (defined as serum sodium concentration ≥150 mmol litre−1) was independently associated with mortality. This finding alone would seem to support the hypothesis that abnormalities of serum sodium are markers of concomitant illness, and do not cause morbidity and mortality de novo, except in the most extreme of cases.

One possible explanation for the finding that only severe hypernatraemia was associated with mortality is that Cecconi’s study was not, unlike other reported series, a retrospective analysis from a generic database or registry, but a sub-study from the European Surgical Outcomes Study (EuSOS). EuSOS was a large prospective cohort study, that collected perioperative data on all patients presenting for inpatient non-cardiac and non-neurological surgery, in 498 participating centres throughout 28 countries in Europe, for an entire week. A total of 46 539 patients were included in the EuSOS study, of whom 816 (77%) had a serum sodium concentration measured in the 28 days before surgery. The relationship between in-hospital mortality to serum sodium and preoperative risk factors was analysed using univariate and multivariate logistic regression. To account for selection bias in measuring serum sodium, sensitivity testing was performed, which included a propensity score analysis. The strength of Cecconi’s findings is increased by the size and scope of the study. By analysing a large group of patients in this way, it is possible the authors have been better able to identify confounding factors than in previous studies. As a consequence, it is possible that hyponatraemia, while associated with adverse outcome in univariate analysis, was not identified as an independent predictor of mortality, as it is a surrogate for co-existing disease. This explanation seems physiologically plausible, in that no mechanism for mild or moderate dysnatraemia directly causing increased mortality has been previously described. In addition, even severe abnormalities of serum sodium do not usually directly cause adverse outcomes – although, clearly severe abnormalities of serum sodium concentrations can cause direct morbidity (such as seizures and coma with severe hyponatraemia) and mortality.

In this context, the finding that severe hypernatraemia was independently associated with mortality may imply a genuine adverse effect of elevated serum sodium concentration. Sodium chloride has been shown to induce helper T (T_h17) cells, which produce interleukin-17, and have a role in mediation of inflammation and autoimmunity. The induction of T_h17 cells occurs via a toxicity responsive element binding protein – which is produced in response to increased toxicity. Increased levels of T_h17 cells occur in animals exposed to high salt diets. It is possible that T_h17 cells are implicated in poor outcomes associated with hypernatraemia.3 Alternatively, there may yet be other unmeasured confounding factors, not identified in Cecconi’s analysis, that account for the association. Previous studies have consistently demonstrated worse outcomes with hypernatraemia compared with hyponatraemia,6–7 which is consistent with Cecconi’s findings. Another explanation for the finding that hypernatraemia, and not hyponatraemia, is associated with mortality is that the patients’ serum sodium concentrations at the time of surgery were not accurately captured. The preoperative serum sodium concentration used in the analysis was the most recent result available in the 28-days before surgery. The exact timing of the sodium measurement, whether the patient had corrective therapy for dysnatraemia, and the serum sodium concentration at the time of surgery were unknown. If a significant proportion of patients had normalized their serum sodium in the interval between last measurement and the day-of-surgery, it is likely that any morbidity or mortality associated with dysnatraemia would be more difficult to detect. Lack of a day-of-surgery serum sodium and data describing whether the patient had undergone any corrective treatments for dysnatraemia is a significant limitation of the study, recognized by the authors.

Serum sodium concentrations are controlled primarily by water balance, regulated by antidiuretic hormone (ADH), via the hypothalamic-pituitary axis. ADH is secreted in response to increases in osmolality or decreases in plasma volume, and causes decreased excretion of water via the kidney. However, regulation of serum sodium is complex, with other inputs including the renin-angiotensin-aldosterone system and the sympathetic nervous system, both of which promote sodium retention, and adrenal and thyroid function. During acute illness and surgery, factors that influence the secretion and action of ADH include anxiety, pain, nausea and vomiting, thirst, fluid restriction, drugs (e.g. opiates, amiodarone, non-steroidal anti-inflammatory drugs, antidepressants), i.v. fluid administration, and haemodynamic instability.10 Other drugs (e.g. diuretics) can alter water and sodium homeostasis via non-ADH mechanisms. Overall, the response to stress, illness and therapies may vary, and depends on the complex interplay of the various homeostatic mechanisms and concurrent therapies. It is perhaps not surprising then, that abnormal serum sodium concentrations are common in hospitalized patients, and that it is difficult to account for every possible confounding factor, and to delineate whether dysnatraemia itself causes adverse outcome. Correction of dysnatraemia may not always be easy or possible before surgery, particularly given the complex nature of the patients response to illness, and attempts to correct sodium abnormalities (such as administration of hypertonic or hypotonic fluids) are not without risk.11–12 Previously published studies lack data on what therapies were administered to patients with dysnatraemia – whether any attempt at investigation of cause, or correction of serum sodium concentrations was made, and whether attempts were successful. Similarly, this is not addressed by Cecconi and colleagues, but is an important question for future studies, both to examine the efficacy and safety of corrective therapies, and to examine the critical question as to whether correction of dysnatraemia improves outcomes.

The authors also discuss stratification of dysnatraemia into mild, moderate, and severe categories, and comment that this approach may have affected the study’s findings. It is certainly plausible given that the authors used a very narrow range to define normonatraemia (138–142 mmol litre−1). This narrow definition of normonatraemia may have resulted in patients categorized as having mild hyponatraemia or hypernatraemia, with serum sodium concentration just outside the normal range, having a normalizing effect on results, as the incidence of co-morbidities amongst these patients was low.

In previous studies, the use of hospital resources has also been shown to be increased in the presence of dysnatraemia,13 and this finding is confirmed by Cecconi and colleagues. The authors highlight the issue that whilst increased resources
were used in the dysnatraemic groups, the level of resource use still differed significantly within groups. The authors state that this may reflect a lack of recognition by clinicians that dysnatraemia is a marker of illness severity. However, the different use of resources may in fact be expected, given the breadth of the study and population – hospital environments in 28 different countries, hospitals of different sizes and types, and with different access to resources such as intensive care and invasive monitors – and may simply reflect these factors.

In the future, further studies are needed to answer these questions. Randomized trials assessing the efficacy and safety of correction of varying degrees of dysnatraemia in patients perioperatively, and whether correction of dysnatraemia improves outcomes are needed. However, whilst randomized controlled trials are the gold standard, they are not practical to answer every question – it would be ethically questionable to randomize healthy patients to induced severe hypernatraemia or hyponatraemia, or to randomize patients with dysnatraemia to non-correction for example. Importantly, whilst there is no doubt in-hospital mortality is an important outcome, it is relatively uncommon, and further patient-centred outcomes also warrant investigation in this setting. Finally, this study suggests clinicians can regard preoperative abnormalities of serum sodium as at least a marker of patient comorbidity and illness severity. It is possible that serum sodium concentration could be included as at least a marker of patient comorbidity and illness severity.

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References


Antagonism of neuromuscular block: all things are poison; only the dose makes a thing not a poison

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Kaufhold and colleagues1 present important new data on the efficacy of the low-dose encapsulating agent sugammadex to antagonize shallow neuromuscular block, with implications for patient safety. Their data, in conjunction with the observations of others indicating dose-dependent toxicity of antagonistic agents,2 3 remind us of the conclusion drawn by the physician Theophrastus Bombastus von Hohenheim, also known as Paracelsus (1493–1541): ‘All things are poison and nothing is without poison; only the dose makes a thing not a poison’.1 In addition, Kaufhold and colleagues1 remind us of the importance of thoughtful drug-effect modeling in order to arrive at valid effect estimates to be used in clinical practice.

Residual neuromuscular block at the end of surgery affects 20–50% of patients and translates to the inability of a patient...