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Fluid management concepts for severe neurological illness: an overview

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Abstract

Purpose of review—The acute care of a patient with severe neurological injury is organized around one relatively straightforward goal: avoid brain ischemia. A coherent strategy for fluid management in these patients has been particularly elusive, and a well considered fluid management strategy is essential for patients with critical neurological illness.

Recent findings—In this review, several gaps in our collective knowledge are summarized, including a rigorous definition of volume status that can be practically measured; an understanding of how electrolyte derangements interact with therapy; a measurable endpoint against which we can titrate our patients' fluid balance; and agreement on the composition of fluid we should give in various clinical contexts.

Summary—As the possibility grows closer that we can monitor the physiological parameters with direct relevance for neurological outcomes and the various complications associated with neurocritical illness, we may finally move away from static therapy recommendations, and toward individualized, precise therapy. Although we believe therapy should ultimately be individualized rather than standardized, it is clear that the monitoring tools and analytical methods used ought to be standardized to facilitate appropriately powered, prospective clinical outcome trials.

Keywords

fluid management; hemodynamic monitoring; subarachnoid hemorrhage; traumatic brain injury; volume status

INTRODUCTION

The acute care of a patient with severe neurological injury is organized around one relatively straightforward goal: avoid brain ischemia. However (to paraphrase Leo Tolstoy), healthy brains are all alike; every unhealthy brain is unhealthy in its own way. Each class of brain injury has a unique pathophysiology, each patient's response to therapy may vary and must be optimized by some guiding principle. However, even for relatively common critical

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Conflicts of interest

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neurological conditions like traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), and ischemic stroke, widespread clinical practices are based on society guidelines derived from a small number of high-quality clinical trials.

A coherent strategy for fluid management in these patients has been particularly elusive. Volume status is a major determinant of the brain's perfusion and oxygenation, and a well considered fluid management strategy is essential for patients with critical neurological illness. Yet, several gaps in our collective knowledge challenges persist, including a rigorous definition of volume status that can be practically measured; an understanding of how electrolyte derangements interact with therapy; a measurable endpoint against which we can titrate our patients' fluid balance; and agreement on the composition of fluid we should give in various clinical contexts.

DEFINING VOLUME STATUS

The simplest quantifiable indicators of volume status – heart rate, blood pressure (BP), urine output – change in response to many patients factors and are nonspecific for hypovolemia in the critically ill patient. Central venous pressure (CVP) was at one time considered a promising index of preload, yet it has consistently been shown to be a poor predictor of blood volume and fluid responsiveness [1]. Arterial pulse pressure variation (PPV) is a promising predictor of fluid responsiveness, though its interpretation has so far been validated in patients who are mechanically ventilated with positive pressure, in sinus rhythm, at tidal volumes of at least 8 ml/kg, and closed chests [2]. Recent work quantifying the natural distribution of PPV provides a valuable starting point for evaluating PPV as an index of volume status and predictor of fluid response [3]. The value of PPV-guided therapy is strongly suggested in an observational study of acute SAH patients by Drevet *et al.* (2017), wherein a restrictive fluid management protocol guided by PPV and CVP resulted in fewer hypoxemic episodes versus weight-based liberal fluid management. Notably, the restrictive fluid group had comparable outcomes with respect kidney injury, incidence of vasospasm and mortality [4■].

Fluid-responsiveness itself would seem to be a reasonable dynamic measure of volume status. Yet, for several reasons nicely summarized by [5], the typical 250–500-ml fluid challenge is not simply limited to its effect on preload, nor does it predictably alter preload. Pathological changes in vascular permeability that often accompany critical illness likely contribute to the highly variable effect of a fluid challenge on blood volume [6]. These factors call into question the validity of clinical trials where patients are randomized into groups based on a fixed dosing regimen to compare 'normovolemia' and 'hypervolemia' (e.g., [7,8]). Illustrating this possibility, [9] found no clear relationship between the circulating blood volume, as measured by ¹³¹I-labeled albumin, and a prospectively assigned fluid dose over 5 days in critically ill patients. Similarly, in a prospective trial with SAH patients, cardiac output (*CO*) was no different in patients assigned to prophylactic hypervolemic therapy versus those who were not [10].

Monitoring volume status in a specific injury-prone compartment could emerge as a useful approach in monitoring for complications of treating SAH-associated vasospasm. Early

trials demonstrated the value of a ‘triple-H’ package: hypertension, hypervolemia, and hemodilution. Although hypertension has reliably emerged as an important therapeutic component [11], hypervolemia has been linked to increased complications, particularly pulmonary edema and cardiac failure, in this class of patients. Ref. [12] used the Pulse Contour Cardiac Output Catheter (PiCCO) monitoring system to track a lung fluid index, which was higher in patient diagnosed with pulmonary edema.

SODIUM HOMEOSTASIS

Assessing and correcting volume status in neuro-critically ill patients is further complicated by frequent concomitant abnormalities of sodium homeostasis. Plasma sodium derangements have been demonstrated, in some pathologic states, to be predictive of the extent of neurological injury and prognosis.

Subarachnoid hemorrhage

Patients suffering a SAH with hyponatremia due to any cause have increased rates of morbidity and mortality. They have been shown to have longer hospital stays, as much as double the length of stay as patients who do not develop hyponatremia [13]. One study found that a decrease in serum sodium levels occurred 1 day prior to symptomatic vasospasm, which could assist in identifying patients at risk of developing this complication [14]. The location of the aneurysm has no relationship to the development or cause of hyponatremia [15].

Current management guidelines have not established optimal management strategies for dysnatremia in patients with SAH. In fact, both hypernatremia and hyponatremia are linked to adverse neurological outcomes. Patients with SAH have been shown to be hypernatremic within the first 4 days, and that from days 6 to 12 patients were more likely to be hyponatremic [16]. Mineralocorticoid therapy, such as fludrocortisone, is a further controversial aspect of the management of patients with SAH, as proponents of its use believe it can treat and attenuate the deleterious effects of cerebral salt wasting (CSW) syndrome early on. A recent systematic review demonstrated that adding mineralocorticoids does not improve outcomes in this patient group. Despite this finding, there is a need for larger prospective randomized controlled trials [17].

Intracerebral hemorrhage

Up to 15% of patients who experience intracerebral hemorrhage (ICH) are hyponatremic on hospital admission [18]. Hyponatremia is associated with worse National Institutes of Health Stroke Scale (NIHSS) scores on hospital admission, and worsening NIHSS scores during hospitalization. Such patients have higher acute and long-term mortality rates. Hyponatremic patients also have a higher risk of comorbidities during hospitalization. A possible mechanism of this propensity for disability and poor outcomes in hyponatremic patients may be the osmotic changes produced by the hyponatremic state, resulting in cerebral edema and increased intracranial pressure (ICP) [19]. Studies to date have not, however, demonstrated whether hyponatremia in these patients was a chronic preexisting condition, or one that evolved at the onset of the ICH. Furthermore, there is no evidence that correction of the

hyponatremia has any clinically significant effect on decreasing the morbidity or mortality rate [18].

Traumatic brain injury

In patients with severe TBI, dysnatremia is encountered in up to 40% of patients and is the most common electrolyte derangement in this group. Development of hyponatremia strongly correlates with increased mortality rates, worsening Glasgow Coma Scale scores, the presence of cerebral edema, and the presence of a basal skull fracture [20]. The cause of hyponatremia, on the other hand, can be due to hyperosmolar therapy, hypovolemia, central diabetes insipidus, syndrome of inappropriate Anti-Diuretic Hormone secretion, and CSW [21]. Significantly, CSW has been described in patients having even minor head trauma [22]. Rajagopal *et al.* [23] provides an excellent management protocol for the hyponatremic patient with TBI.

TARGETING FLUID THERAPY

Outside the realm of neurocritically ill patients, there is convincing evidence that the amount of fluid given is less important than how it is guided. A meta-analysis by [24] underscores the value of hemodynamic goals to individualize therapy – despite finding no major difference in the amount of fluid administered to surgical patients in ‘goal-directed’ versus ‘liberal’ fluid strategies, goal-directed patient groups experienced fewer complications and had shorter lengths of stay following surgery. Notably, this meta-analysis considered a therapy to be goal-directed if it targeted hemodynamic measures other than urine output, arterial pressure, or CVP.

Subarachnoid hemorrhage

CO-guided fluid therapy appears to be particularly relevant to neurocritically ill patients with a high risk of cardiopulmonary complications. The pulmonary artery catheters’ use has fallen out of favor in recent years over concerns with its associated complications. Commercial solutions aiming to estimate *CO* noninvasively via arterial and plethysmographic waveform analysis have stepped into the breach with mixed success. A recent study showed limited accuracy and precision for two such products during orthotopic liver transplantation [25]. The PiCCO catheter system is an interesting intermediate (recently reviewed in [26]). A series of studies [12,27,28] have shown that PiCCO-derived global end diastolic index (GEDI) and *CO* were predictive of pulmonary edema and heart failure in SAH patients. These studies are a major step forward in establishing the predictive validity of the PiCCO monitoring system for SAH patients.

CO-based endpoints may ultimately be the most appropriate guide for improving neurological outcomes for SAH-associated delayed cerebral ischemia (DCI). Vasospasm, a major cause of DCI, can be assessed in a routine manner with transcranial Doppler studies, and therapy is primarily targeted at reversing the deficit in cerebral blood flow. Following on observational studies linking neurological outcomes to PiCCO-derived hemodynamic measures [28,29], a subsequent randomized non-blinded trial [30] used *CO* and GEDI to guide fluid therapy in these patients, showing that this approach produced measurable

benefits in length of stay and DCI. As of yet, results are not reported from a prospective randomized controlled trial evaluating PiCCO-derived hemodynamic indices to guide therapy in SAH patients. We look forward to reading the published results, particularly as they compare with another registered trial, Intensive Management of Blood Pressure or Volume Expansion in Subarachnoid Hemorrhage (IMPROVES) [31], which will prospectively randomize patients to normovolemia versus volume expansion, as well as to conventional versus augmented BP groups in a two-way factorial design. Notably, the IMPROVES trial defines fluid therapy based on fluid dosage (ml/kg/day) and targeted to CVP; as described above, both weight-based fluid dosage and CVP-targeting have an unclear relationship to intravascular volume.

Ischemic stroke

The idea of *CO*-based monitoring using the PiCCO system appears to have spread outside the realm of treating SAH: just as with treating vasospasm, the goal of therapy for ischemic stroke is to perfuse territory beyond flow-limited vessels. It seems evident that a blood-volume responsive measure like *CO*, rather than mean arterial pressure, would be superior in a situation in which avoiding secondary brain injury requires both avoiding hypoperfusion of penumbral tissue, and limiting edema related to ischemic necrosis from the primary insult. Pilot data from [32] strongly support the link between *CO* and cerebral perfusion, and are the basis for this group's recently reported clinical trial design [33], the results of which we eagerly await. Conversely, the risks of volume therapy without *CO* guidance are suggested by a secondary analysis of the Albumin in Acute Stroke Part 2 (ALIAS 2) trial [34]. This analysis found that larger strokes, and higher NIHSS scores, were associated with larger volumes of fluid. Although the ALIAS 2 trial data could not address the mechanism for this association, it is certainly worth pointing out that cardiopulmonary complications including pulmonary edema were a major concern for patients receiving 25% albumin [35], echoing findings discussed previously regarding triple-H therapy for vasospasm.

Traumatic brain injury

The pathophysiology of DCI in TBI is rather more complex than that of SAH. In addition to a component of TBI-triggered vasospasm, cerebral perfusion may be severely compromised by both trauma-related vasogenic edema and cytotoxic edema after diffuse axonal injury. Further compounding the resulting reduction of cerebral perfusion pressure (CPP) and impaired oxygen diffusion, TBI is associated with impaired autoregulation and a breakdown of the blood–brain barrier. The Brain Trauma Foundation (BTF) guidelines [36] prioritize a CPP between 60 and 70 mmHg and reduction of ICP via osmotic therapy with mannitol or decompressive intervention. However, the pathophysiology of TBI also suggests that, at some point, enhancing CPP in the context of impaired autoregulation can worsen edema and perfusion. Thus, an alternative approach to treating TBI, based on general physiological principles guiding ICP reduction, known as the Lund concept, encompasses several domains of therapy aimed at reducing trans-capillary pressure and oncotic gradients, including recommendations for using antihypertensive drugs, against the use of vasopressors for CPP augmentation, and against the use of osmotic therapies such as mannitol or hypertonic saline. The Lund concept recommendations, in fact, seem to directly contradict society guidelines. Although a full consideration of these two approaches is beyond the

scope of this review, it is very much worth reading [37^{■■■},38] for two well argued viewpoints on this ongoing controversy.

CPP is coupled to blood flow via an autoregulatory process that has significant variability even in healthy adults [39]. If uniform CPP targets may not be appropriate, individualizing therapy based on an index of cerebral autoregulation holds promise for guiding management of TBI patients. Functional autoregulation is inferred when an arterial BP (ABP) change is associated with an anticorrelated change in ICP, representing a reduction of flow and hence cerebral blood volume. The correlation coefficient between ABP and ICP is the pressure reactivity index (PRx); positive values indicate a passive response to ABP, associated with loss of autoregulation, while negative values suggest intact autoregulation (for a very concise expert review, refer to [40]). The CPP optimization strategy takes advantage of the 'U'-shaped relationship between PRx and CPP, in which the minimum PRx represents an optimal CPP (CPPopt). A prospective analysis by [41] suggests that CPPopt may be a better predictor of favorable neurological outcomes in TBI compared with the BTF's current recommendation of maintaining a CPP within a fixed range of 60–70 mmHg. As computational methods for estimating CPPopt in real-time improve and become standardized, we anticipate prospective trials using this strategy.

FLUID SELECTION

Regardless of the strategy a clinician uses to optimize therapy in a neurocritically ill patient, he or she must make a choice of which fluid to use. There is broad agreement based on convincing clinical and preclinical data that hypotonic and glucose containing solutions are associated with worse outcomes for several classes of neurologically injured patients (93–94 in Grande 2017). Clear differences in outcome for this group of patients have been more difficult to establish with respect to crystalloid versus colloid containing solutions, and normal saline (0.9% NaCl) versus 'balanced' crystalloid solutions.

The 2004 Saline versus Albumin Fluid Evaluation (SAFE) Study [42], and its 2007 subgroup post-hoc follow-up study focusing on TBI patients [43], continues to be broadly influential as indicated by the strong preference for crystalloid over albumin use in a recent survey of neurotrauma centers [44]. However, several important criticisms have been raised against this conclusion, in particular from those who favor the Lund concept of plasma oncotic reversal of cerebral edema with isotonic albumin. A particularly salient point raised by [37^{■■■}] is that the 4% albumin used in the SAFE trial was hypo-tonic (260 mOsm/kg), in contrast to the isotonic normal saline solution; furthermore, demographic imbalances in the subgroup analysis may have biased the risk of harm toward the group receiving albumin. It seems likely that the size of these trials, the high-profile publication of their results, and the possibility of albumin-related harm to patients have posed substantial barriers to conducting a proper prospective randomized trial to investigate the question of albumin safety.

On the question of normal saline versus balanced crystalloid, such as lactated ringer's solution or Plasma-Lyte A, there are still no high-quality data in neurocritically ill patients. However, a recent large prospective cluster-randomized trial addressed this issue in a broad population of critically ill patients [45^{■■■}], evaluating the frequency of major adverse kidney

events and 30 day in-hospital mortality. The investigators found small effect sizes bordering on statistical significance in both areas, favoring balanced solutions. A subgroup composed of TBI patients showed no clear differences based on type of therapy received, although this subgroup was likely underpowered for that purpose. Perhaps illustrative of the changing attitude toward more restrictive fluid therapy over a decade, the trial reported remarkably lower cumulative fluids administered compared with the SAFE trial – as well as a nearly two-fold reduction in 30-day mortality in comparison with the older study despite the roughly comparable patient populations being investigated.

CONCLUSION

As the possibility grows closer that we can monitor the physiological parameters with direct relevance for neurological outcomes and the various complications associated with neurocritical illness, we may finally move away from static therapy recommendations, and toward individualized, precise therapy. Although we believe therapy should ultimately be individualized rather than standardized, it is clear that the monitoring tools and analytical methods used ought to be standardized to facilitate appropriately powered, prospective clinical outcome trials. We anticipate that resolving issues around monitoring will ultimately give traction toward addressing many of the lingering questions regarding supportive care of this critically ill patient class.

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KEY POINTS

- A fluid management strategy is essential for patients with critical neurological illness.
- Monitoring of volume status is recommended.
- Fluid therapy should be individualized rather than standardized.