



## Fluid management in patients undergoing neurosurgery

Taeha Ryu

Department of Anesthesiology and Pain Medicine, Daegu Catholic University School of Medicine, Daegu, Korea

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### Corresponding author

Taeha Ryu, M.D.

Department of Anesthesiology and Pain Medicine, Daegu Catholic University School of Medicine, 33 Duryugongwon-ro 17-gil, Nam-gu, Daegu 42472, Korea

Tel: 82-53-650-4785

Fax: 82-53-650-4517

E-mail: [anesryu@cu.ac.kr](mailto:anesryu@cu.ac.kr)

Fluid management is an important component of perioperative care for patients undergoing neurosurgery. The primary goal of fluid management in neurosurgery is the maintenance of normovolemia and prevention of serum osmolarity reduction. To maintain normovolemia, it is important to administer fluids in appropriate amounts following appropriate methods, and to prevent a decrease in serum osmolarity, the choice of fluid is essential. There is considerable debate about the choice and optimal amounts of fluids administered in the perioperative period. However, there is little high-quality clinical research on fluid therapy for patients undergoing neurosurgery. This review will discuss the choice and optimal amounts of fluids in neurosurgical patients based on the literature, recent issues, and perioperative fluid management practices.

**Keywords:** Albumin; Colloids; Crystalloid solutions; Fluid therapy; Hemodynamics; Neurosurgery.

## INTRODUCTION

Fluid management is part of the basic care in many clinical situations. Perioperative fluid therapy in patients undergoing neurosurgery is a vital component of anesthetic practice and critical care. There is increasing evidence that intraoperative fluid therapy may influence postoperative outcomes [1-3].

The main purpose of fluid management in neurosurgical anesthesia is to prevent brain damage caused by inadequate cerebral perfusion and provide a good surgical environment. Therefore, it is essential to maintain hemodynamic stability and proper cerebral perfusion pressure during neurosurgery.

Hemodynamic alterations and electrolyte imbalances often occur during neurosurgery because of the frequent use of diuretics to relieve increased intracranial cerebral pressure and edema. In addition, depending on the type of sur-

gery, large amounts of fluids may need to be administered to correct preoperative hypovolemia and perioperative unstable hemodynamics, and prevent cerebral vasospasm.

An extensive debate about the choice and optimal dose of fluid for hemodynamic stability and improved outcomes exists. This review is intended to assist in the clinical applications and research on fluid therapy during neurosurgery by reviewing recent issues and literature on perioperative fluid therapy in various surgical fields, including neurosurgery.

## CHOICE OF FLUID IN NEUROSURGICAL PATIENTS

The general principle of fluid therapy for neurosurgery is to maintain normal blood volume and prevent a decrease in plasma osmolarity. In a normal blood-brain barrier (BBB), the movement of water between the plasma and brain is mainly influenced by the osmotic gradient. Therefore, in

neurosurgery, the osmolarity of the fluid is the most important factor to prevent cerebral edema.

A crystalloid fluid contains small molecular substances without high molecular substances, and it is classified as hypotonic, isotonic, or hypertonic according to its osmolarity. Lactated Ringer's solution (LR), a commonly used crystalloid, is hypotonic at 273 mOsm/L. Low plasma osmolarity can cause cerebral edema. Therefore, hypotonic solutions, such as LR, are avoided, while normal saline (NS) has traditionally been used as the main fluid in patients with neurosurgery [4].

Since a reduction in oncotic pressure without changing the osmolarity increases cerebral edema in animal models of brain injury [5], colloid solutions have been known to prevent the severe reduction of colloidal oncotic pressure when used appropriately. However, the European Society of Intensive Care Medicine (ESICM) task force recommended against the use of colloids in patients with brain injury [6], continuing the debate about the use of colloids in neurosurgery.

## Crystalloid solutions

Hypotonic solutions, such as the LR solution, are avoided in neurosurgical patients to minimize cerebral fluid accumulation. In contrast, NS, an isotonic crystalloid, has been widely used in neurosurgery because it is thought to reduce the risk of cerebral edema [7]. However, since NS has equal amounts of sodium and chloride (154 mEq/L), hyperchloremic metabolic acidosis occurs when a large amount of NS is administered because its chloride concentration is higher than the normal plasma chloride concentration (96–106 mEq/L).

Numerous laboratory and clinical studies have reported a dose-dependent association between hyperchloremia and the use of NS [8–10]. Hyperchloremic acidosis is associated with acute kidney injury (AKI) during abdominal surgery [9]. In a large, propensity-matched retrospective study of 22,851 patients who underwent a non-cardiac surgery, postoperative hyperchloremia resulted in acute metabolic acidosis, leading to increased 30-days mortality and length of hospital stay [10]. A large retrospective study on abdominal surgery showed that patients treated with balanced crystalloids had better outcomes, including mortality, postoperative infection, need for renal replacement therapy (RRT), need for transfusions, electrolyte imbalance, and acidosis than those treated with NS [9].

Meanwhile, the adverse outcomes of NS were not observed in a randomized control study of critically ill patients [11,12], non-critically ill patients [13], and postoperative patients who underwent neurosurgery [14]. In a recent meta-analysis, the balanced crystalloid solution was beneficial in significantly reducing postoperative hyperchloremia and metabolic acidosis, but the evidence was insufficient to compare the effects of buffered and non-buffered crystalloids on mortality and organ failure [15].

In contrast, balanced salt solutions (BSSs) replace chloride ions with lactate, acetate, and gluconate, which prevents the occurrence of hyperchloremic metabolic acidosis [16]. A BSS is the most common choice of resuscitation fluid in clinical practice [17]. In patients who underwent craniotomy, the NS group had higher sodium and chloride levels and had more patients with marked acidosis than in the BSS group [18].

However, though LR is a balanced crystalloid solution, it is hypotonic. A decrease of 1 mOsm/L in the plasma osmolarity results in an increase of 19 mmHg in the pressure of fluid movements across the BBB, and a 3% decrease in the plasma osmolarity results in cerebral edema with a 3% increase in the brain volume and 30% decrease in the intracranial blood cerebrospinal fluid volume [16,19]. Prehospital resuscitation with LR compared to NS was associated with increased mortality in patients with traumatic brain injuries (TBI) [20]. Therefore, LR is not suitable for neurosurgical patients. Instead, isotonic BSS, excluding hypotonic solutions, such as LR, has emerged as a fluid of choice for patients undergoing neurosurgery [21].

An isotonic balanced solution reduces the incidence of hyperchloremic metabolic acidosis and electrolyte imbalances in patients with brain injury, but the intracranial pressure is not different compared with NS [22]. Although a balanced solution has a clear benefit of reducing hyperchloremic metabolic acidosis, its advantage of reducing morbidity and mortality is not clear and requires evaluation.

High-quality data comparing NS and balanced solutions in perioperative and neurosurgical patients are not yet available. Based on the above evidence, although evidence is still lacking, an isotonic balanced solution is preferred over NS in neurosurgical patients because of the lower risk of metabolic acidosis and renal injury.

## Colloid solutions

Large insoluble molecules in colloid solutions increase

the intravascular oncotic pressure. In an animal model of brain injury, oncotic pressure reduction without changing the osmolarity increased cerebral edema [5]. Colloid solutions have commonly been used to decrease cerebral edema and improve hemodynamics during neurosurgery [23].

### 1. Hydroxyethyl starch (HES)

Several randomized trials have shown that HES has adverse effects on kidney function. The routine clinical application of HES in patients with severe sepsis in the VISEP study [24] was associated with higher rates of acute renal failure and RRT than LR. Similarly, two large trials comparing colloids and crystalloids in patients with severe sepsis, the 6S trial [25] and CHEST trial [26], showed an increased incidence of AKI and need for RRT.

In contrast, there was no difference in the incidence of renal failure and mortality between saline and HES 130/0.4 in patients with severe sepsis in the CRYSTMAS trial [27]. Likewise, the CRISTAL study, a large, randomized trial, [28], compared the effects of colloids and crystalloids in critically ill patients with hypovolemia and found no significant differences in the 28-day mortality and need for RRT.

Due to the conflicting results, a systematic review and meta-analysis that included the above trials concluded that HES significantly increased the risk of mortality and AKI in critically ill patients [29]. The ESICM task force on colloid volume therapy in critically ill patients recommended against the use of 6% HES 130 in patients with severe sepsis or at risk of AKI. They also recommended not to use colloids in patients with head injuries [6]. Based on accumulating evidence, the European Medicines Agency has restricted the use of HES in critically ill patients, and the United States Food and Drug Administration has added a black box warning. A recent meta-analysis comparing colloids versus crystalloids for fluid resuscitation in critically ill patients showed little or no difference in mortality with moderate-certainty evidence, though starches slightly increased the need for blood transfusion and RRT [30]. However, the heterogeneity of protocols and results in the aforementioned research continues to cause controversy on the recommendations on HES restrictions.

There is some opposing evidence on the restricted use of HES in patients with neurosurgery.

Some animal models and *in vitro* studies have shown protective effects of HES on the BBB [31–33]. Two early randomized control trials comparing HES with crystalloid solutions in patients with ischemic stroke reported no differences in

the safety, hemodynamic efficacy, and complication rates [34,35].

HES has been sometimes used to maintain an optimal volume status to prevent delayed cerebral ischemia (DCI) due to cerebral vasospasm following a subarachnoid hemorrhage (SAH) as a component of the triple H-therapy. Compared to the standard therapy group, the goal-directed fluid therapy (GDFT) with a HES bolus group showed reduced frequencies of vasospasm and cardiopulmonary complications [36]. A recent retrospective study compared SAH patients who received HES with those who received crystalloids and found no significant difference in RRT [37]. Another retrospective study showed no positive correlation between the cumulative doses of HES and serum creatinine in SAH patients who had a normal renal function and concluded that the administration of HES 6% 130/0.4 is safe in SAH patients without pre-existing renal insufficiency. However, caution is warranted in the period of repetitive administration of contrast media [38]. It is noteworthy that the incidence of AKI did not increase despite the substantial amount of HES used in the above trials.

However, there is still no evidence of the superiority of the use of HES in patients undergoing neurosurgery. The possible negative effects, such as renal injury and coagulopathy, should be considered, and HES should be used with caution in neurosurgical patients, in line with the do not harm principle.

### 2. Albumin

In animal studies, high-concentration albumin therapy improved local cerebral blood flow (CBF), reduced infarct size and brain swelling, and improved neurological function [39–41]. In a retrospective study of patients with SAH, there was a higher proportion of patients with good outcomes at 3 months in the albumin group than in the non-albumin group, although there was no significant difference in the incidence of symptomatic vasospasm [42].

However, the SAFE trial, a multicenter, randomized, double-blinded trial, compared 4% albumin and NS in critically ill patients and showed no significant difference in the outcomes, such as mortality, proportions of organ failures, duration of intensive care unit (ICU) stay, duration of hospital stay, duration of mechanical ventilation, and duration of RRT [43]. However, in the subgroup analysis, the relative risk (RR) of death of trauma patients in the albumin group compared to the saline group (RR = 1.36) was higher than that in the patients without trauma (RR = 0.96). This difference in

the RR of death was because more brain injury patients were assigned to the albumin group than to the saline group.

A post-hoc analysis of a subgroup of patients with TBI in the SAFE trial, the SAFE-TBI study, showed that the 2-year mortality of patients with severe brain injury was significantly higher in the albumin group than in the saline group [44]. A post-hoc follow-up analysis of severe TBI suggested that increased intracranial pressure may have contributed to the high mortality in the albumin group [7]. The results of the SAFE trial and post-hoc analysis continue to influence albumin use in patients with TBI [45].

However, these results should be considered with caution. The SAFE-TBI trial has its own limitations in post hoc subgroup analysis. The mortality of TBI patients was not the primary endpoint of the SAFE trial, and the trial design was not randomized for TBI analysis. Furthermore, the 4% human albumin used in the SAFE study is a hypo-osmolar solution that may potentially increase the intracranial pressure and cause cerebral edema [46].

Experimental SAH models on animals have demonstrated the beneficial effects of albumin [39,47,48], and there has been some evidence on the beneficial effects of albumin in SAH patients [49,50].

The ALISAH trial [49], designed to determine the feasibility and safety of albumin administration in SAH patients, was terminated as two serious complications of pulmonary edema were reported. Patients receiving 1.25 g/kg/d of 25% albumin for 7 days demonstrated better neurological outcomes than those receiving a lower dose. Follow-up analysis of the ALISAH trial showed that higher doses of albumin were associated with a lower incidence of vasospasm, DCI, and cerebral infarction [50]. However, these results should be interpreted with caution. The said trial had an inadequate sample size and insufficient power because it was not designed to study the beneficial effects of albumin.

The ALIAS pilot trial suggested that high-dose albumin therapy has potential neuroprotective effects after ischemic stroke [51]. However, the ALIAS part 1 trial was suspended after safety analysis revealed an increased incidence of pulmonary edema and mortality [52]. The ALIAS part 2 trial, which was modified by adding exclusion criteria and safety measures, was also suspended because of the high incidence of pulmonary edema in the albumin group [53]. The pooled analysis of the data from the ALIAS part 1 and 2 trials showed no difference in the 90-day neurological outcomes and mortality between the 25% albumin and saline groups. However, there was an increased risk of pulmonary edema

and intracerebral hemorrhage in the patients administered with albumin 25% at 2 g/kg [54]. Based on this evidence, the ESICM recommends against the use of high-dose albumin in patients with acute ischemic stroke and the use of low-(4%) or high-dose (20–25%) albumin in neurointensive care patients [55].

Although controversies still exist based on the above evidence, the use of albumin in the perioperative period of neurosurgery remains questionable. The potential risks and benefits of albumin administration should be assessed on a case-by-case basis.

## HOW TO ADMINISTER THE OPTIMAL AMOUNT OF FLUIDS IN NEUROSURGICAL PATIENTS

The primary goal of perioperative fluid management during neurosurgery is to maintain hemodynamic stability and an adequate CBF. There is a growing body of evidence that intraoperative fluid therapy influences postoperative outcomes [1–3].

### Restrictive versus liberal fluid therapy in major surgeries

Traditional intraoperative fluid regimens, which include preoperative dehydration, third space loss, and insensible loss, tend to induce a positive fluid balance that is related to postoperative complications [1].

In the recent decade, several randomized controlled studies have compared restricted fluid therapy with liberal fluid therapy in patients undergoing major abdominal surgeries. Brandstrup et al. [2] showed that patients in the liberal group gained body weight and had more complications than the restrictive group.

After this trial, numerous studies on abdominal surgery showed positive results for restricted fluid therapy, leading to a gradual shift to the trend of using fluid restriction during surgery with the concept of zero-balance. However, in two large observational studies, the zero-balance concept has been concerning due to the possibility of worse outcomes, including AKI associated with excessive restriction [56,57].

Recently, RELIEF trial compared restrictive fluid therapy while maintaining perioperative zero balance with liberal fluid therapy [3]. The results showed that the patients in the restriction group had increased rates of surgical site infection and high risks of AKI.

Based on this recent evidence, worse perioperative outcomes have been observed in patients with both overhydration and excessive fluid restriction. Therefore, fluid optimization is essential for perioperative fluid management. It should also be noted that the amounts of administered volume in the liberal and restricted volume therapies were inconsistent and slightly different for each study [58]. In particular, the postoperative weight gain of the restrictive group in an earlier study by Brandstrup et al. [2] was comparable to the liberal group of the RELIEF study [3]. As such, an excessive restriction can result in worse outcomes, such as AKI.

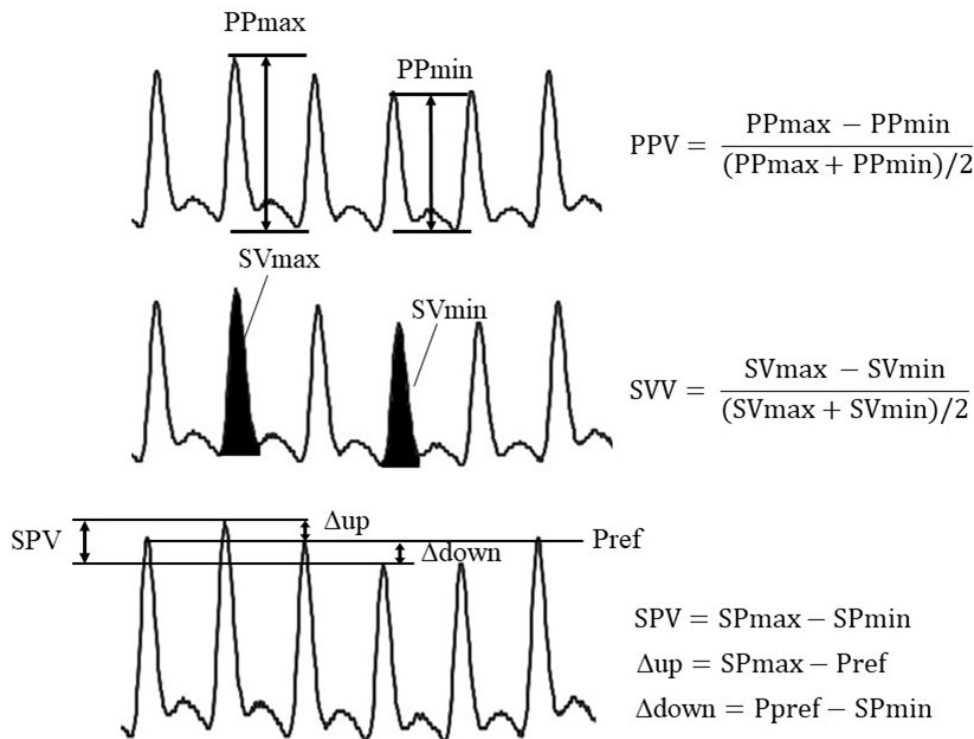
### GDFT based on dynamic parameters

To achieve the optimal fluid volume status, it is essential to avoid overhydration and excessive restriction and develop individually optimized fluid regimens using objective parameters. These objective parameters should be targeted preoperatively and measured perioperatively.

GDFT, a recently emerging fluid regimen, is a type of fluid

administration that optimizes pre-defined targets based on directly measured hemodynamic parameters (Fig. 1), such as the cardiac output, stroke volume (SV), stroke volume variation (SVV), pulse pressure variation (PPV), systolic pressure variation (SPV), pleth variability index (PVI), and other factors [1].

Favorable outcomes and decreased costs have been shown for patients who underwent GDFT during a major abdominal surgery [59–61]. Although the certainty of the evidence was very low, a meta-analysis comparing GDFT and restrictive fluid therapy in major non-cardiac surgeries showed that the mortality was slightly low in the GDFT group, and there were no differences between the two groups in the complication rate and length of hospital stay [1]. Unlike other studies, including this meta-analysis, one study [62] found that the total infused volume was higher in the restrictive group (basal crystalloid infusion ranging from 4 to 10 ml/kg/h) than in the GDFT group. A limitation of this meta-analysis was the lack of a definition of restrictive fluid therapy. GDFT consists of a given basal infusion and repeat-



**Fig. 1.** Dynamic parameters derived from the arterial pressure wave. Mechanical ventilation induces periodic changes in the arterial waveform. Various parameters are derived from this periodic change. Pulse pressure (PP) is the difference between the systolic and diastolic pressures. The area under curve of the arterial pressure wave represents the stroke volume (SV). Systolic pressure variation (SPV) is the difference between the maximum and minimal systolic pressures. SPV consists of two components, delta up ( $\Delta_{up}$ ) and delta down ( $\Delta_{down}$ ), by reference pressure (Pref). Pref is the systolic pressure measured at the end of expiration or during apnea. PPV: pulse pressure variation, SVV: stroke volume variation.

ed boluses of fluids (usually colloids) to achieve a predefined target. The basal infusion rate is particularly important to compare GDFT with other fluid regimens.

## GDFT during neurosurgery

In two retrospective studies of patients with SAH, a positive net fluid balance was independently associated with poor outcomes [63,64]. However, as it is difficult to compare restrictive and liberal fluid therapies in neurosurgical patients who must maintain euvolemia, recent studies on GDFT have been conducted. There have been some studies to optimize fluid administration using continuously measured dynamic parameters, such as SVV, PPV, and PVI for patients undergoing neurosurgery.

The SVV is a sensitive predictor of fluid responsiveness before and during brain surgery [65–67]. After the induction of anesthesia and before the start of the surgical procedure, the SVV more sensitively predicted an increase of more than 10% in the SV by LR solution infusion compared to the mean arterial pressure, heart rate, cardiac output, and central venous pressure (CVP) in neurosurgical patients [65]. An SVV of 9.5% was concluded as the optimal threshold (sensitivity: 78.6%, specificity: 93%) for predicting a > 5% increase in the SV after a 100-ml colloid solution infusion [66]. The target of the SVV of GDFT can affect clinical outcomes for supratentorial brain tumor resection [67]. Comparing two GDFT regimens for supratentorial tumor resection (with threshold SVV values set at 10 for the low SVV group and at 18 for the high SVV group), the low SVV group had lower postoperative serum lactate levels, shorter length of ICU stay, and a lower incidence of postoperative neurologic events than the high SVV group [67]. Comparing the GDFT group managed fluid by hemodynamic parameters including the SVV with the control group managed fluid by the therapeutic decision of the attending anesthesiologist, the former had less administered fluids, shorter length of ICU stay, lower ICU costs, and lower lactate levels than the control group [68].

The PPV and PVI have also been reported to be good predictors of fluid reactivity during brain surgery [69–72]. Between the CVP group, which maintained a CVP of 5–10 cm-H<sub>2</sub>O, and the PPV group, which maintained a PPV below 13%, in patients undergoing a brain tumor surgery, the latter had better postoperative hemodynamic stability and less postoperative fluid requirement [69]. The PPV-guided GDFT during supratentorial tumor resection had a comparable brain relaxation scale, low serum lactate levels, more intra-

operative fluids, and higher urine output than the standard care group [70]. In the sitting position for neurosurgery, measuring the PPV and PVI with an ear sensor predicted fluid responsiveness well, but the PVI could not be predicted with a finger sensor. However, the PVI measured with an ear sensor was limited by an unreliable signal in 26% of the patients [71].

A study on children undergoing neurosurgery showed different results. Comparing the PVI,  $\Delta V_{\text{peak}}$  (respiratory variations in aortic blood flow peak velocity), arterial pressure, CVP, heart rate, inferior vena cava diameter, SPV (including delta up [ $\Delta_{\text{up}}$ ] and delta down [ $\Delta_{\text{down}}$ ]), and PPV in pediatric patients undergoing neurosurgery, the PVI and  $\Delta V_{\text{peak}}$  predicted the fluid response well, but the PPV and other static and dynamic parameters were reported to be unpredictable [72].

Considering that hemodynamic changes are relatively common in neurosurgery, GDFT, which provides individualized optimal fluid status, is a promising fluid management strategy.

## CONCLUSION

Despite numerous studies on perioperative fluid management, there is insufficient evidence to draw definitive conclusions regarding fluid management in neurosurgical patients.

Although evidence is still lacking, isotonic balanced crystalloid solutions should be considered the first-choice fluid, while hypotonic solutions should be avoided. Furthermore, colloid solutions should be used with caution, and their potential risks and benefits should be considered.

To achieve an optimal fluid volume status while avoiding overhydration and excessive restriction, the amount and duration of fluid administration should be considered, and an individualized fluid strategy is recommended using GDFT based on dynamic fluid parameters.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

## DATA AVAILABILITY STATEMENT

Not applicable.

## ORCID

Taeha Ryu, <https://orcid.org/0000-0002-5973-7715>

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