

Colloid Osmotic Pressure and the Formation of Posttraumatic Cerebral Edema



This article has been selected for the ANESTHESIOLOGY CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

IN the beginning, it was “Run ’em dry for Neurosurgery.” It was the fervent (but empiric) belief of many clinicians that all crystalloid administration aggravated edema in injured brain, and, as a result, aggressive fluid restriction was commonly the standard. But then, the evolution of cerebral blood flow methodology begat the awareness that the common cerebral injury states, including traumatic brain injury (TBI), often entail regions of low cerebral blood flow that might become frankly ischemic in the event of hypotension; and careful maintenance of normovolemia (and sometimes hypervolemia) became the credo. Accordingly, with the increased fluid administration, we must again be concerned about whether crystalloids can aggravate brain edema. A carefully conducted preclinical investigation that appears in this issue of ANESTHESIOLOGY adds additional insights to that discussion.¹

First, let us review the facts to better evaluate all the fervor and speculation that has gone before. (1) Crystalloid administration that results in a reduction of serum osmolality will cause brain edema even in entirely normal brain²; accordingly, whatever fluid regimen is chosen it should not have sufficient free water to cause reduction in osmolality; (2) Reduction of colloid osmotic pressure (COP) in isolation will not cause edema of normal brain.³ That latter assertion is in contradistinction to what happens in most peripheral tissues, in which reduction of COP is associated with tissue swelling. The explanation for the difference resides largely in the properties of the endothelium of cerebral capillaries that are largely responsible for the so-called blood-brain barrier (BBB). In the majority of the capillary beds in the human body, the configuration of the desmosomes that connect endothelial cells creates an effective intercellular pore size of 60–70 Å; small electrolyte molecules pass freely; colloid molecules also pass but with difficulty. In the event of reduction of COP by dilution, a transmembrane osmotic pressure difference does occur. The gradient is small. For example, a

50% reduction in COP produces a transmembrane pressure gradient equivalent to an osmolality difference of less than 1 mOsm/l,⁴ but because small solvents move easily and the elastance ($\Delta P/\Delta V$) of the interstitium is usually modest, fluid moves extravascularly and edema forms. By contrast, the tight junctions of the capillary endothelium in the brain result in an almost continuous lipid barrier, with occasional pores of 5–7 Å. Lipid soluble materials pass by diffusion; small charged electrolyte molecules pass with difficulty, and the barrier is highly impermeable to all large hydrophilic molecules, for example, albumin and starches. In addition, the interstitial space of the brain is much “tighter.” With COP reduction, some transendothelial movement of water probably does occur, but dissolved solvent cannot follow and opposing osmolar and hydrostatic gradients develop immediately and measurable edema differences are prevented.

But all of that applies to normal brain. One of the sub-components of the seemingly endless crystalloid–colloid debate has been the issue of whether the administration of isotonic crystalloids, with the concomitant dilution of colloids and reduction of oncotic pressure, will aggravate edema in injured brain. Why might it? If TBI were to result in sufficient injury to the BBB to open it to an extent equivalent to that which occurs natively in most peripheral vascular beds, would the interstitium of the brain also develop edema as that occurs in the periphery? Although that edema might be less severe because of the “tighter” interstitial space in the brain, physiologic principles (and a prior investigation⁵) argue that it almost certainly will. And, the carefully conducted study by Jungner *et al.*¹ elsewhere in this issue reaffirms that expectation. In that study, after a 2.4 atm (moderately severe) fluid percussion injury, rats underwent hemorrhage and then

Accepted for publication February 5, 2010. The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

◆ This Editorial View accompanies the following article: Jungner M, Grande P-O, Mattiasson G, Bentzer P: Effects on brain edema of crystalloid and albumin fluid resuscitation after brain trauma and hemorrhage in the rat. ANESTHESIOLOGY 2010; 112:1194–203.

volume restoration with albumin or isotonic crystalloid. Iso-osmolality was maintained in all animals, but COP was reduced by 35–40% in the crystalloid group; and, there was greater cortical edema in that latter group.

Does this study mean that we should all become enthusiastic users of albumin in head-injured patients? No. The first reason, apart from the fact that the supportive data are from investigations performed in rats, is that the result (less edema formation) may be specific to insults of a narrow range of severities. The impact used results in an injury in the moderately severe category; witness the neurologic scores reported by the authors and the high survival rate in animals that sustained fluid percussion injury without protection of airway patency or control of gas exchange. Some opening of the BBB occurred, as reflected by both the tracer transfer evaluations in this experiment,¹ and the modest Evan's blue leakage that was observed with the same 2.4 atm impact in the earlier study.⁵ In both these studies, the BBB damage was far less than the gross opening of the BBB that occurs after freeze lesion injuries and perhaps with more severe TBI. With a more severe injury, one might speculate that any fluid administered might enter the ECF space in the brain. After a freeze lesion (which devastates the endothelial barrier and after which Evan's blue administration results in a large region of brain turning a livid purple-black), the edema observed is equivalent after administration of colloid and isotonic crystalloid.⁶ Any fluid can pass the BBB. Might the edema associated with colloid administration in the face of more severe TBI ultimately be more difficult to clear and therefore more persistent?

Although there is no experimental support for the occurrence of more refractory edema, that speculation is at least consistent with the retrospective analysis of the subset of patients with TBI included in the Saline Albumin Fluid Evaluation (SAFE) trial.⁷ That analysis (the validity of which has been challenged) reported a higher mortality among patients with severe TBI (GCS 3–8) who received albumin and no difference (actually a minor, nonsignificant trend toward better survival) among those with a moderately severe head injury (GCS 9–13). If the occurrence of relatively refractory, albumin-related edema were a factor in these mortality data, an ICP correlate would be anticipated. Unfortunately, the report of the SAFE TBI substudy did not include ICP trend data for the various groups.

Other unanswered questions remain. If albumin is associated with the formation of less edema in TBI of some or all severities, is the result likely to be specific to albumin, or is it likely to be a class effect of colloids? I suspect a class effect. I draw that conclusion largely on the basis of the very similar isovolemic exchange experiment done by our group a decade ago in which edema formation after fluid percussion injury (also 2.4 atm) was less when COP was maintained with a starch (450, 0.7) than that in an iso-osmolar group with a 50% reduction in COP.⁵ Might there be differences in either edema formation or outcome if albumin and starch were compared “nose to nose”? Yes. A vascular “sealing” effect has

been reported in some situations for starches⁸ as have differences in the effects of various fluids on white cell–endothelial interactions.⁹ Might these phenomena further influence edema formation? Perhaps. On the flip side, ischemia is probably often part of the pathophysiology of adult TBI; and there is evolving evidence that albumin has a protective effect (mechanism undefined) in the setting of ischemia.^{10,11} Might that have an additive influence on outcome beyond any effect of albumin on edema formation? Perhaps.

These considerations invite further preclinical investigation. The relevant studies might include the direct comparison of albumin and starch (the latter ideally of a lower molecular weight and substitution ratio than that used in the University of California, San Diego study), and a comparison of the effect of the two colloids on edema formation in the face of both moderate and severe injuries (which would inevitably require airway protection). There is still more for the ambitious investigator. Edema is a surrogate, albeit an important surrogate, but still a surrogate. In particular, if one suspects that the benefits of albumin might go beyond the effects on edema then neurologic outcome is a relevant, though experimentally demanding, endpoint.

For emphasis, I ask again, do the current results justify a sea change in the direction of albumin use in patients with TBI? I repeat, on the basis of the considerations above, no. I say it emphatically because more liberal use of albumin in this context might feel like part of a drift that is already in progress elsewhere in operating room management. In my daily practice, I see increasing numbers “closet colloidists.” Anxieties about swollen airways, postoperative visual loss as a compartment syndrome, the abdominal compartment syndrome as a derivative of fluid administration,¹² and reports of the benefits of fluid restriction in bowel surgery,¹³ pneumonectomy,¹⁴ and acute respiratory distress syndrome prevention¹⁵ are all already nudging many clinicians in a “more colloid-less crystalloid” direction. Hoisting a spinnaker on a boat that is already running comfortably downwind is easy, but this is a sail that is not ready to be run aloft.

John C. Drummond, M.D., F.R.C.P.C., The University of California, San Diego, San Diego, California, and Veterans Affairs Medical Center, San Diego, California. jdrummond@ucsd.edu

References

1. Jungner M, Grande P-O, Mattiasson G, Bentzer P: Effects on brain edema of crystalloid and albumin fluid resuscitation after brain trauma and hemorrhage in the rat. *ANESTHESIOLOGY* 2010; 112:1194–203
2. Tommasino C, Moore S, Todd MM: Cerebral effects of isovolemic hemodilution with crystalloid or colloid solutions. *Crit Care Med* 1988; 16:862–8
3. Zornow MH, Todd MM, Moore SS: The acute cerebral effects of changes in plasma osmolality and oncotic pressure. *ANESTHESIOLOGY* 1987; 67:936–41
4. Guyton AC: The microcirculation and the lymphatic system: Capillary fluid exchange, interstitial fluid, and lymph flow, in *Textbook of Medical Physiology*, 10th edition. Philadelphia, W.B. Saunders, 2001
5. Drummond JC, Patel PM, Cole DJ, Kelly PJ: The effect of reduction of colloid oncotic pressure, with and without

- reduction of osmolality, on post traumatic cerebral edema. *ANESTHESIOLOGY* 1998; 88:993-1002
6. Kaieda R, Todd MM, Warner DS: Prolonged reduction in colloid oncotic pressure does not increase brain edema following cryogenic injury in rabbits. *ANESTHESIOLOGY* 1989; 71:554-60
 7. Myburgh J, Cooper DJ, Finfer S, Bellomo R, Norton R, Bishop N, Kai Lo S, Vallance S: Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med* 2007; 357:874-84
 8. Zikria BA, King TC, Stanford J, Freeman HP: A biophysical approach to capillary permeability. *Surgery* 1989; 105: 625-31
 9. Nohe B, Johannes T, Reutershan J, Rothmund A, Haeberle HA, Ploppa A, Schroeder TH, Dieterich HJ: Synthetic colloids attenuate leukocyte-endothelial interactions by inhibition of integrin function. *ANESTHESIOLOGY* 2005; 103: 759-67
 10. Palesch YY, Hill MD, Ryckborst KJ, Tamariz D, Ginsberg MD: The ALIAS Pilot Trial: A dose-escalation and safety study of albumin therapy for acute ischemic stroke: II. Neurologic outcome and efficacy analysis. *Stroke* 2006; 37:2107-14
 11. Shin DH, Moon GJ, Bang OY: Albumin therapy in acute stroke patients. *J Neurol* 2007; 254:870-8
 12. Madigan MC, Kemp CD, Johnson JC, Cotton BA: Secondary abdominal compartment syndrome after severe extremity injury: Are early, aggressive fluid resuscitation strategies to blame? *J Trauma* 2008; 64:280-5
 13. Brandstrup B, Tonnesen H, Beier-Holgersen R, Hjortso E, Ording H, Lindorff-Larsen K, Rasmussen MS, Lanng C, Wallin L, Iversen LH, Gramkow CS, Okholm M, Blemmer T, Svendsen PE, Rottensten HH, Thage B, Riis J, Jeppesen IS, Teilmann D, Christensen AM, Graungaard B, Pott F: Effects of intravenous fluid restriction on postoperative complications: Comparison of two perioperative fluid regimens: A randomized assessor-blinded multicenter trial. *Ann Surg* 2003; 238:641-8
 14. Fernandez-Perez ER, Keegan MT, Brown DR, Hubmayr RD, Gajic O: Intraoperative tidal volume as a risk factor for respiratory failure after pneumonectomy. *ANESTHESIOLOGY* 2006; 105:14-8
 15. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF Jr, Hite RD, Harabin AL: Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; 354:2564-75