Colloid Osmotic Pressure and the Formation of Posttraumatic Cerebral Edema

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 not cause edema of normal brain.3 That latter assertion is supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

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volume restoration with albumin or isotonnic crystalloid. Iso-
omolality was maintained in all animals, but COP was re-
duced 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 enthusi-
astic 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 moder-
ately severe category; witness the neurologic scores re-
ported 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.2 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 re-
ervation of brain turning a livid purple-black), the edema ob-
served is equivalent after administration of colloid and iso-
tonic 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 occur-
rence 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 pa-
ients 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 asso-
ciated 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
isosmotic 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 differ-
ences 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 investiga-
tion. The relevant studies might include the direct compar-
ison of albumin and starch (the latter ideally of a lower mo-
elscular weight and substitution ratio than that used in the
University of California, San Diego study), and a compari-
son of the effect of the two colloids on edema formation in
the face of both moderate and severe injuries (which would
invariably 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 syn-
drome as a derivative of fluid administration,12 and reports
of the benefits of fluid restriction in bowel surgery,13 pneu-
monecmytomy,14 and acute respiratory distress syndrome pre-
vention15 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 Cali-
ifornia, San Diego, San Diego, California, and Veterans Affairs
Medical Center, San Diego, California. jdrummond@ucsd.edu

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John C. Drummond