Hypertonic saline and stroke*

Cytotoxic brain edema—swelling of nerve and glial cells—is among the very early pathophysiologic sequelae of focal cerebral ischemia. Once cell swelling has exhausted the cerebral compliance, intracranial pressure increases and, thereby, causes secondary ischemia. Hypertonic solutions, mannitol in particular, have long been used to reduce intracranial pressure. More recently, hypertonic saline has been used for treatment of increased intracranial pressure (1, 2), in particular because sodium chloride with a reflection coefficient of 1.0 is better excluded from brain with an intact blood-brain barrier than mannitol (reflection coefficient = 0.9). Hypertonic saline has been found to reduce intracranial pressure after experimental head injury (3). Hypotensive patients suffering from head injury and a Glasgow Coma Scale score ≤8 and treated with hypertonic saline had a significantly improved outcome (4, 5). For treatment of hemorrhagic shock, hypertonic saline has been used since 1980, when Velasco et al. (6) showed that a bolus injection of 7.5% NaCl (4 mL/kg) rapidly restored arterial pressure and cardiac output in hemorrhaged dogs. Volume expansion is achieved by the osmotic gradient shifting fluid from the intracellular to the intravascular compartment. A dilution by fluid shift is indicated by the average plasma Na^+ increase of only 15 mEq/L as opposed to the theoretically expected 25 mEq/L (7). Such fluid shifts can also be derived from a mathematical model based on thermodynamic transport equations and experimental data (8). From these equations it can be deduced that rapid hyperosmotic infusion goes along with a decreased capillary hydraulic resistance and, hence, an improved microcirculation. This effect is likely to be even more pronounced in tissues with swollen endothelial and glial cells, as typically seen after cerebral ischemia.

Hypertonic saline, in other words, can affect brain tissue via two mechanisms, a direct effect on edema and an improvement of the microcirculation via fluid shifts from swollen cells to the capillary lumen. Both effects depend on a rather steep osmogradient between the intracellular and the intravascular compartments, that is, on a bolus injection of hypertonic saline, which has been proven effective in focal venous ischemia in rats (9) or in intestinal ischemia in pigs (10). In both conditions, the bolus injection was followed by an improvement of microvascular flow. All pathophysiologic evidence suggests that an improvement of the microcirculation is most important for hypertonic solutions to be effective in ischemia. Especially in focal cerebral ischemia, a hypertonic bolus can reach tissue with critically low flow in the ischemic penumbra. Tissue can only be saved if flow surpasses the critical flow thresholds in this tissue at risk.

In the current issue of *Critical Care Medicine*, Dr. Toung and colleagues (11) describe a quite different approach by infusing rats after permanent middle cerebral artery occlusion continuously with hypertonic solutions (5% or 7.5% NaCl or 20% mannitol) beginning 6 hrs after stroke and ending after 2 days. It is not surprising that with such treatment, plasma osmolality increased to critical levels (e.g., 360 mOsm/L in the 7.5% NaCl group). The authors do not provide data on plasma sodium levels achieved, but it can be assumed that these were pathologically elevated. Interestingly enough, even with the osmotic gradient achievable by chronic infusion—far less steep but longer maintained than after bolus injection—survival improved as did brain edema and lung water, both of where were significantly reduced in the treated groups.

A shortcoming of this study, however, is the far too short observation time: Animals were killed immediately after the infusion protocol had ended. At that point, not only was the plasma osmolality increased but brain tissue osmolality must have been equally elevated. Brain tissue is thus hypertonic, and since water can freely enter the brain following the osmotic gradient, any free fluid entering the body will contribute to secondary swelling of brain tissue. Before chronic infusions of hypertonic saline can be tested in patients, such damaging "rebound" phenomena have to be excluded. In fact, the same research team found worsened outcomes after chronic infusion with hypertonic saline in a previous study (12) using a transient focal arterial occlusion model with an even shorter observation time (22 hrs), although these rats received only 0.9% saline as oral fluid after surgery in order to prevent influx of water into the hyperosmotic tissue.

Another often mentioned argument against a nonrestrictive use of hypertonic saline is the fear to induce pontine myelinolysis (7, 13, 14) and "cellular dehydration" (7). However, pontine myelinolysis is most frequent if hyponatremia is corrected by hypertonic saline infusion in cases with severe malnutrition or alcoholism. In >1,700 patients treated with hypertonic solutions, there has not been a single case of neurologic deterioration (5, 7, 15), and rats treated with chronic infusions of 7.5% saline (0.5 mL/hr) for 4 days did not show any histopathologic damage (12).

As a benefit of the current study (11), we may conclude that even with a far from optimal treatment regime (slow, chronic infusion), hypertonic saline can positively affect outcome from stroke. The authors are encouraged to compare chronic infusions and bolus injections of hypertonic saline after permanent middle cerebral artery occlusion with the aim of observing the beneficial effects of hypertonic treatment on outcome with less negative side effects such as hyperosmolality and hypernatremia.

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Early enteral nutrition vs. early parenteral nutrition: An irrelevant question for the critically ill?*

The debate over the optimal route of nutrition support has caught the attention of many clinicians and researchers over the last few years as illustrated by several reviews published on the use of enteral nutrition (EN) compared with parenteral nutrition (PN) (1–3). Most of these reviews have included heterogenous populations, making it difficult to draw conclusions that are specific to any disease state, including the critically ill patient. In an attempt to make inferences as how to best manage the nutrition support of critically ill patients, we recently reviewed the world's published literature on this topic and developed evidence-based, nationally endorsed clinical practice guidelines (4). In these guidelines, we strongly recommend the use of EN compared with PN in the "average" critically ill patient, and we recommend that EN be started within 24 to 48 hours of admission to the intensive-care unit (ICU). These recommendations are supported by metaanalyses of existing randomized trials in critically ill patients that demonstrate reduced morbidity associated with the use of EN compared to PN (4, 5) and with the use of early EN compared with delayed EN (4). Nowhere in this literature is there a suggestion that EN results in reduced mortality compared with PN.

Parenteral nutrition clearly has a role in the critically ill patient with an absolute contraindication to EN, but such patients are uncommon in the ICU. It is perhaps more common, at least in some European countries, to initiate PN at the same time as initiating EN in critically ill patients expected to have a prolonged ICU stay (6). The evidence demonstrating the positive effects of this practice on clinical outcomes are lacking (7), and thus this practice was not endorsed in our guidelines.

For those critically ill patients who do not tolerate adequate amounts of EN over the early course of their stay, PN may be used to supplement protein and calories to achieve desired amounts. Data to inform practitioners as to how much EN is inadequate and when PN should be initiated in this setting are also lacking. Consideration of the underlying state of nourishment (recent weight loss, recent decrease in oral intake, body mass index, visceral protein stores) and the nature of the underlying illness (degree of catabolism and expected duration of illness) can guide the individual practitioners in making decisions about when to start PN. We recommend that PN not be initiated until all efforts to maximize EN have been attempted (small bowel feedings and motility agents) (4). When PN is used, strategies that maximize the benefits and minimize the risks associated with PN should also be used (i.e., supplemental glutamine, withholding lipids, hypocaloric doses, and tight glycemic control) (4)

With this as background, it is difficult to understand the relevance of analyzing randomized, controlled trials comparing EN to PN when nutrition support was initiated early in the course of hospitalized patients. In this issue of *Critical Care Medicine*, Peter et al. (8) have performed a systematic review of the literature on this topic. To be included in the review, the trial had to start nutrition support within 96 hours. The use of this arbitrary timeframe is not justified and is in fact questionable. As mentioned here,