

CLINICAL THERAPEUTICS

Hyperosmolar Therapy for Raised Intracranial Pressure

Allan H. Ropper, M.D.

This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author's clinical recommendations.

A 49-year-old female passenger was thrown against the doorframe during an automobile accident. After being pulled from the car, she opened her eyes intermittently, moaned, and had flexion withdrawal of her limbs (Glasgow Coma Scale score, 8). Her pupils were 5 mm in diameter and reactive to light. Her blood pressure was 165/85 mm Hg, her heart rate 112 beats per minute, and her breathing regular. After her spine was stabilized, she was conveyed to an intensive care unit (ICU). In the ICU, she no longer opened her eyes, had flexion posturing of her arms, and made no verbal responses (Glasgow Coma Scale score, 5). There was a contusion on her right frontal scalp but no sign of other organ injury. Computed tomography showed large regions of frontal brain contusion with surrounding edema (Fig. 1). The patient was intubated, and an external ventricular drain was placed in order to measure intracranial pressure, which was 29 mm Hg with periodic elevations to 36 mm Hg. After drainage of cerebrospinal fluid, the intracranial pressure transiently decreased to 26 mm Hg. The serum sodium concentration was 139 mmol per liter. The neurointensivist recommended an intravenous bolus infusion of 23% saline to reduce intracranial pressure and attain a serum sodium concentration of 150 mmol per liter. The patient's weight was 55 kg.

THE CLINICAL PROBLEM

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N Engl J Med 2012;367:746-52.

DOI: 10.1056/NEJMct1206321

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Almost all acute and catastrophic brain diseases raise the intracranial pressure. Traumatic brain injury, intracerebral and extracerebral hematoma, cerebral infarction with brain swelling, and the generalized brain swelling of acute liver failure are among the disorders causing this physiological disturbance. Elevated intracranial pressure has consistently been associated with a poor outcome. In a review of studies of traumatic brain injury, the rate of death was 18.4% for patients with an intracranial pressure of less than 20 mm Hg but 55.6% for those with an intracranial pressure of more than 40 mm Hg.¹

Estimates of the proportion of in-hospital deaths that are due to brain death range from 2.3 to 11%,^{2,3} but patients with elevated intracranial pressure from severe brain injury more often survive with various degrees of disability. For example, 10 to 15% of traumatic brain injuries are severe,⁴ and most of these cases are associated with raised intracranial pressure. Each year, approximately 80,000 persons in the United States sustain disabling head injuries,⁵ with an estimated financial burden of \$60 billion annually for their ongoing care.

In all the above-mentioned types of acute cerebral lesions, raised intracranial pressure has a proximate relationship to survival and is often the only remediable

element of the disease. The prevention of secondary brain damage from raised intracranial pressure is therefore a central focus of neurologic intensive care.

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

Because the cranium is essentially a fixed vault, any increase in the volume of the brain results in an increase in intracranial pressure. Expansion of one of the intracranial components of the brain, intravascular blood, and cerebrospinal fluid must be at the expense of a reduction in another component (the Monro-Kellie hypothesis^{6,7}). In response to an increase in brain volume, cerebrospinal fluid is initially forced from the cranial subarachnoid spaces and lateral ventricles into the spinal subarachnoid space. As this compensatory mechanism is exhausted, pliable blood vessels are compressed and cerebral blood flow is reduced. As intracranial pressure reaches 50 to 60 mm Hg, it approaches arterial pressure in the vessels of the circle of Willis and brings about global brain ischemia, the end result of which is brain death.

The pressure-volume relationship within the cranium approximates an exponential curve, with the inflection point in adults generally ranging from 20 to 25 mm Hg; the range is lower in children because of their higher ratio of brain volume to intracranial volume (Fig. 2). This range roughly coincides with the transition from the flat portion of the elastance curve to its steep portion, where small increments in volume result in large elevations in pressure. On the basis of the studies in the aforementioned review,¹ the goal of care has been to keep the intracranial pressure below these levels.

The fact that hyperosmolarity reduces brain volume has been known since the serendipitous observation in 1919 that the rapid intravenous administration of hypertonic salt solution and glucose caused a marked drop in cerebrospinal fluid pressure in cats.⁸ The brain parenchyma is 80% water, higher than in other organs, making brain volume very responsive to changes in water content. The effectiveness of an osmolar agent in creating a gradient for water egress depends on the extent to which the solute is excluded by the blood-brain barrier. This is summarized as the reflection coefficient of the substance, with

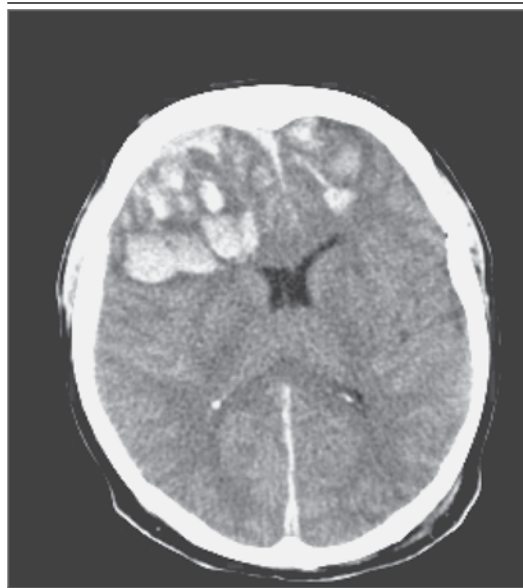


Figure 1. Computed Tomographic Image in a Patient with Increased Intracranial Pressure after a Traumatic Brain Injury.

Shown are large regions of heterogeneous bifrontal contusions that are causing distortion of adjacent tissue and compression of the ventricles (mass effect).

values ranging from 0 (indicating complete permeability) to 1 (indicating complete impermeability). The reflection coefficient for sodium approaches 1.0, making it an ideal agent for inducing an osmotic gradient between blood and brain tissue. Mannitol, which has a reflection coefficient of 0.9, is also highly effective in reducing brain water content, and it has an added effect on its first pass through the brain of lowering blood viscosity and causing a reactive constriction of cerebral conductance vessels, which reduces intracerebral blood volume and intracranial pressure.⁹

The beneficial effect of hyperosmolar therapy requires that the blood-brain barrier be intact. In regions of brain-tissue damage, as in traumatic contusion, the barrier is disrupted and allows equilibration of molecules between blood and the interstitial fluid of the brain. Thus, hyperosmolar agents exert their effect largely by removing water from the remaining normal brain tissue. It follows that hyperosmolarity reduces intracranial pressure in proportion to the volume of undamaged brain tissue and has a limited effect on brain edema surrounding a mass lesion.¹⁰

Most of the reduction of brain volume occurs

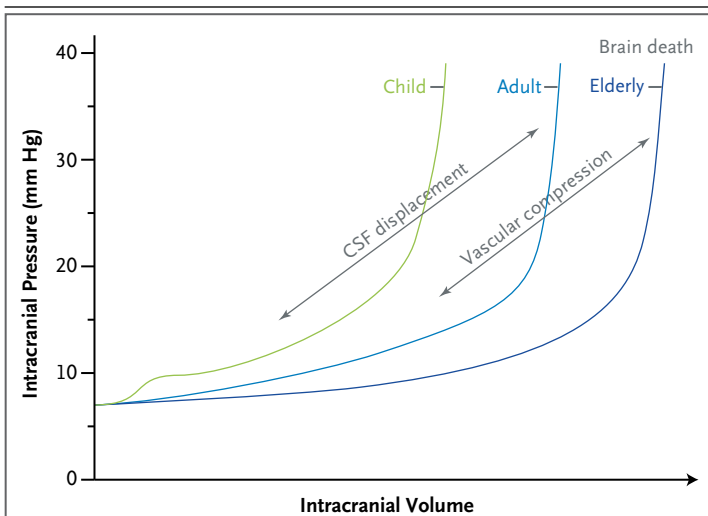


Figure 2. Relationship between Pressure and Volume within the Cranium.

A theoretical intracranial compliance curve shows that small increments in intracranial volume result in large changes in intracranial pressure at the right side of the curve. Initially, increases in intracranial volume result in the displacement of cerebrospinal fluid (CSF). With further increases in volume, blood vessels are compressed, ultimately reducing cerebral blood flow. Pressure increases more rapidly in children and less rapidly in the elderly because of the corresponding higher and lower ratios of brain volume to intracranial volume.

during and soon after the period of maximal osmolarity induced by the infusion of a hyperosmolar agent, but sustaining the reduction in intracranial pressure depends on maintaining serum hyperosmolarity. The brain slowly accommodates to serum hyperosmolarity by raising intracellular solute concentrations through a number of means, most of which are not clearly understood. The notion of “idiogenic osmoles” was introduced 50 years ago to account for this recuperation of brain osmolarity. In response to a decrease in brain water content, astrocytes elaborate polyols, amino acids, and methylamines, thereby raising osmolarity and returning brain water to a normal volume.^{11,12} Neurons similarly manufacture and accumulate small protein molecules that raise intracellular osmolarity. For this reason, once a state of serum hyperosmolarity has been attained, that level must be sustained until the underlying mass decreases in size or another intervention reduces intracranial pressure. Otherwise, the gradient for water transfer is reversed, allowing a rebound increase in intracranial volume and pressure.

CLINICAL EVIDENCE

The first case series in which hyperosmolar therapy (in the form of urea) was used to reduce intracranial pressure was reported in the 1950s.¹³ A decade later, mannitol was introduced for this purpose,¹⁴ and the clinical use of hypertonic saline was described in the 1990s.¹⁵ The effect of hyperosmolar therapy is indicated by a visible reduction in brain volume during craniotomy or by a drop in intracranial pressure within minutes after the infusion of a hypertonic solution at the bedside; reversal of the signs of transtentorial herniation may also be observed.¹⁶

The main treatment to reduce intracranial pressure that can be compared with hyperosmolar treatment is acute forced hyperventilation (see the Clinical Use section). The effects of hyperosmolar therapy are more consistent and longer lasting than the effects of hyperventilation. In a comparison between hyperosmolar agents, one small randomized trial used equimolar doses of mannitol and hypertonic saline in 20 patients in stable condition with a sustained intracranial pressure above 20 mm Hg after either traumatic brain injury or stroke.¹⁷ At 60 minutes after the start of the infusion, intracranial pressure was reduced by a mean of 14 mm Hg in the mannitol group and 10 mm Hg in the hypertonic-saline group. The findings in another small trial suggested that hypertonic saline is more effective than an equivalent volume of mannitol in reducing intracranial pressure in patients with traumatic brain injury,¹⁸ and repeated boluses of hypertonic saline have been effective when mannitol has failed.¹⁹ However, the small differences between the two agents in these studies are not adequate to direct a choice between them.

There have been limited studies of hyperosmolar therapy in children with traumatic brain injury. In one small trial, children receiving hypertonic saline required less frequent infusions and had fewer complications than did those receiving lactated Ringer's solution, though the survival rate and duration of the hospital stay were similar in the two groups.²⁰

CLINICAL USE

Raised intracranial pressure should be treated promptly. However, for patients with cranial trauma, raised intracranial pressure may be only

one aspect of an acute clinical condition that can include visceral-organ injury, shock, respiratory failure, and hypotension.

For patients who have a mass lesion, such as a large subdural hematoma, that can be removed, surgical evacuation or resection is the most expedient way to reduce intracranial pressure. When the increase in brain volume is the result of a cerebral contusion, diffuse cerebral edema, or some other condition that is unresectable, as in the case described in the vignette, surgery is generally not undertaken. Attempts to decompress the cranial contents by removing parts of the skull after traumatic brain injury have lowered intracranial pressure but have not improved the outcome, as compared with standard care.²¹

Several other interventions, in addition to hyperosmolar therapy, may be useful in the management of raised intracranial pressure, depending on the circumstances. Attention should first be directed at avoiding serum hyposmolality. This requires that intravenous solutions for resuscitation and for infusion of medications have at least the effective osmolality of normal saline (290 mOsm per liter). Solutions such as 5% dextrose in water, 5% dextrose in half-normal saline, and lactated Ringer's solution (calculated osmolality, 273 mOsm per liter) are not desirable. A rapid but limited reduction in intracranial pressure can be effected by hyperventilation, which causes cerebral vasoconstriction through reduced carbon dioxide tension and alkalosis of the blood and cerebrospinal fluid. However, therapeutic hyperventilation is effective only for minutes to an hour and is largely a bridge to more durable therapy. The removal of cerebrospinal fluid through an external ventricular drain lowers intracranial pressure quickly, although the benefit depends on the amount of cerebrospinal fluid remaining in the ventricles and the effect may be of short duration. Placement of a ventricular drain is an invasive procedure that is associated with a small risk of infection but that has the advantage of allowing direct measurement of intracranial pressure. Glucocorticoids lower intracranial pressure almost exclusively by reducing edema surrounding a brain tumor but are ineffective in other conditions, such as traumatic brain injury.²² Induced hypothermia and high-dose barbiturates also lower intracranial pressure but do not improve the outcome; hypothermia is associated with

cerebral edema during rewarming, and barbiturates cause systemic hypotension at the doses required for a therapeutic effect on intracranial pressure. The mainstay of intracranial-pressure reduction is therefore the rudimentary approach of shrinking the brain by exposing it to the dehydrating effects of serum hyperosmolality.

The effect of a hyperosmolar agent on brain volume is ideally assessed by measuring intracranial pressure with one of a number of devices, such as an intraventricular catheter or intraparenchymal transducer, and adjusting the amount of infused solution to maintain the desired level of intracranial or cerebral perfusion pressure (calculated as mean blood pressure minus intracranial pressure). The target intracranial pressure is typically less than 20 mm Hg, with maintenance of cerebral perfusion pressure at 50 to 70 mm Hg.

The serum osmolality can be used as a surrogate measure of the effect of therapy with either mannitol or hypertonic saline. The initial target is an osmolality of 300 to 320 mOsm per liter, with adjustment as the clinical circumstances and the intracranial pressure require. The osmolality can be calculated from the levels of sodium, glucose, and blood urea nitrogen (with sodium measured in millimoles per liter and glucose and blood urea nitrogen measured in milligrams per deciliter), according to the following formula:

$$\text{osmolality} = (2 \times \text{sodium}) + (\text{glucose} \div 18) + (\text{blood urea nitrogen} \div 3).$$

The clinical laboratory can also provide a measurement of serum osmolality, which is assumed to be essentially equivalent to osmolality. The effect of either mannitol or hypertonic saline can also be assessed by measuring the serum sodium level; a value of 145 to 150 mmol per liter typically coincides with the desired effect.

Mannitol is a sugar alcohol that acts as an osmotic diuretic, causing sustained hyperosmolality by dehydration. It can be administered through a peripheral or central venous catheter. In patients with traumatic brain injury, a single dose of mannitol reduces intracranial pressure within 10 to 15 minutes, with a maximal effect of cutting the initial pressure approximately in half within 20 to 60 minutes.²³ Mannitol is given in a 20% solution in boluses of 0.25 to 1.0 g per kilogram of body weight at intervals of 2 to 4 or more hours. The highest dose is used in

emergency situations, and the lowest dose is administered as a maintenance regimen. Increasing doses at shorter intervals are often required over a period of days to maintain a reduction in intracranial pressure. When elevated intracranial pressure abates, the dose of mannitol can be reduced in graduated steps.

To assess the effect of mannitol, solute and osmolarity measurements should generally be obtained 20 minutes or more after an infusion. A discrepancy between the measured and calculated serum osmolarity (osmolar gap) reflects the circulation of molecules of mannitol and indicates that the blood sample was obtained too soon after an infusion to be useful in gauging the sustained effect of mannitol as an osmotic diuretic.

Hypertonic saline increases serum osmolarity directly rather than by inducing osmotic diuresis. It is used in a 3% solution (513 mmol per liter) in boluses of approximately 150 ml, in a 7.5% solution (1283 mmol per liter) in 75-ml boluses, or in a 23.4% solution (4008 mmol per liter, which is routinely available in hospital pharmacies for intravenous solution admixture and referred to as "23%") in 30-ml boluses. Continuous infusion of 3% saline has a modest initial effect on intracranial pressure, but the effect is transient and results in systemic fluid overload. Concentrations of more than 3% should be administered through a central venous catheter.

The amount of hypertonic saline that is required to reach a target serum sodium concentration can be approximated from the following formula:

$$\frac{\text{sodium requirement in millimoles} = (\text{lean body weight in kilograms} \times \text{the proportion of weight that is water, which is 0.5 for a woman and 0.6 for a man}) \times (\text{desired sodium} - \text{current sodium in millimoles per liter})}{\text{desired sodium} - \text{current sodium in millimoles per liter}}$$

The required volume in milliliters is then calculated as the sodium requirement divided by the sodium concentration of the chosen solution.

ADVERSE EFFECTS

High doses of mannitol can cause acute renal failure. The mechanism of this effect is not established but may involve intrarenal vasoconstriction combined with intravascular volume depletion. Renal failure usually resolves after re-

moval of mannitol by means of dialysis. The limited available data suggest that acute renal injury occurs only in patients receiving more than 200 g of mannitol daily.²⁴

Mannitol typically induces a hypokalemic, hyponatremic alkalosis associated with volume contraction and diuresis. These changes are ameliorated if normal saline is used as a replacement fluid and a euvolemic hypernatremic state is maintained. Hypertonic saline, in contrast, causes intravascular volume expansion, which may lead to congestive heart failure. Furosemide has been administered concurrently to mitigate this risk. The expected changes in the serum with hypertonic saline include mild acidosis, hyperchloremia, and hypokalemia.

As a result of mannitol infusion, and less often after infusion of hypertonic saline, elderly patients, those with diabetes, and those receiving glucocorticoids are at risk for a hyperglycemic hyperosmolar state that causes seizures, hemiparesis, or confusion. In a patient with a rapidly rising glucose level or an unexplained seizure, this diagnosis should be considered and insulin should be administered.

The potential for a rebound increase in intracranial pressure after the administration of mannitol has been discussed for decades but has proved to be difficult to detect if serum hyperosmolarity is maintained.²⁵ The therapeutic reduction in water content occurs only in undamaged regions of the brain, so there has also been concern that hyperosmolar treatment could exaggerate pressure gradients within the cranium and cause herniation. These displacements are slight, and although they can sometimes be detected with imaging techniques, they have little clinical effect.

Hypertonic solutions cause considerable skin sloughing if they infiltrate the subcutaneous tissues, and surveillance of intravenous catheters should be undertaken to avoid this problem.

AREAS OF UNCERTAINTY

The question of whether control of intracranial pressure has a beneficial effect on survival and clinical outcome has tentatively been answered affirmatively.²⁶ Similarly, hyperosmolar therapy is assumed to be beneficial on the basis of its ability to lower intracranial pressure, but no trials have been carried out in which hyperosmolar

therapy has been omitted from the treatment regimen. Monitoring of intracranial pressure, which requires the insertion of a device into the cranial cavity, has not been validated as a method for improving the outcome, as compared with treatment that is based on a fixed regimen of hyperosmolar therapy. However, gauging the dose and interval for hyperosmolar therapy is difficult without monitoring of intracranial pressure and poses a risk of either overtreatment or undertreatment.

The ideal osmotic agent and method of administration have not been established. The patient's blood pressure, cardiac output, and renal function often determine the choice between a dehydrating osmotic agent such as mannitol and a volume-expanding solution of sodium. The maximum serum sodium level and osmolarity that can be tolerated without causing hypotension or renal failure have not been established and depend on the patient's initial renal function, age, and medical status. A serum osmolarity of 320 mmol per liter has been stated to be the upper limit for safety, but particularly with respect to the risk of renal failure, this limit has been challenged and has been safely exceeded in practice.²⁷

GUIDELINES

According to the guidelines of the Brain Trauma Foundation, in cooperation with three neurosurgical societies, there is level II evidence for the effectiveness of mannitol, at doses of 0.25 to 1.0 g per kilogram of body weight, in reducing intracranial pressure.²⁸ The guidelines state that no direction can be given regarding the use of hypertonic saline or the interval of administration of any hyperosmolar agent. A consortium of pediatric societies has adopted similar guidelines for the treatment of children with

traumatic brain injury, but its members were unable to find adequate studies on the use of mannitol in children for their analysis and, as a result, could endorse only the use of hypertonic saline.²⁹

RECOMMENDATIONS

The deteriorating clinical state of the patient in the vignette, along with the large cerebral contusions and intracranial hypertension, makes further and fatal elevations of intracranial pressure likely. In such a precarious situation, the rapid induction of hyperosmolarity by repeated boluses of hypertonic saline or mannitol is appropriate. If hypertonic saline with a concentration of more than 3% is chosen, a central venous catheter should be inserted. To attain the target sodium concentration of approximately 150 mmol per liter desired by the intensivist (using the above-mentioned formula on the basis of the patient's weight of 55 kg and initial sodium concentration of 139 mmol per liter) requires the addition of 302 mmol of sodium and thus 589 ml of 3% saline or 75 ml of 23% saline solution. This can be achieved in a single infusion or in several more routine doses (e.g., 30 ml of 23% saline). Approximately 30 g (0.5 g per kilogram) of 20% mannitol is an alternative. Subsequent infusions should be adjusted to keep intracranial pressure below approximately 20 mm Hg. The levels of serum sodium or serum osmolarity, blood urea nitrogen, and serum creatinine should be measured at regular intervals, perhaps during each 8-hour nursing shift. Extreme hyperosmolarity, as reflected by a serum sodium concentration of more than 160 mmol per liter, is unlikely to have further benefit in reducing intracranial pressure.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

REFERENCES

1. Treggiari MM, Schutz N, Yanez ND, Romand J-A. Role of intracranial pressure values and patterns in predicting outcome of traumatic brain injury: a systematic review. *Neurocrit Care* 2007;6:104-12.
2. Palo J, Viitala S. Diagnosis and frequency of brain death. *Lancet* 1999;354:1909-10.
3. Baker A, Beed S, Fenwick J, et al. Number of deaths by neurological criteria, and organ and tissue donation rates at three critical care centres in Canada. *Can J Anaesth* 2006;53:722-6.
4. Langlois JA, Rutland-Brown W, Thomas KE. Traumatic brain injury in the United States: emergency department visits, hospitalizations and deaths 2002-2006. Atlanta: National Center for Injury Prevention and Control, 2006 (http://www.cdc.gov/traumaticbraininjury/pdf/blue_book.pdf).
5. Thurman DJ, Alverson C, Dunn KA, Guerrero J, Snieszek JE. Traumatic brain injury in the United States: a public health perspective. *J Head Trauma Rehabil* 1999;14:602-15.
6. Monro A. Observations on the structure and function of the nervous system. Edinburgh: Creech and Johnson, 1835:5.
7. Kellie G. An account of the appearances observed in the dissection of two of three individuals presumed to have perished in the storm of the 3rd, and whose

- bodies were discovered in the vicinity of Leith on the morning of the 4th November 1821 with some reflections on the pathology of the brain. *Trans Med Chir Sci Edinb* 1824;1:84-169.
8. Weed LH, McKibbin PS. Pressure changes in the cerebrospinal fluid following intravenous injection of solutions of various concentrations. *Am J Physiol* 1919; 48:512-30.
 9. Muizelaar JP, Wei EP, Kontos HA, Becker DP. Mannitol causes compensatory cerebral vasoconstriction in response to blood viscosity changes. *J Neurosurg* 1983;59:822-8.
 10. Videen TO, Zazulia AR, Manno EM, et al. Mannitol bolus preferentially shrinks non-infarcted brain in patients with ischemic stroke. *Neurology* 2001;57:2120-2.
 11. McDowell ME, Wolf AV, Steer A. Osmotic volumes of distribution: idiogenic changes in osmotic pressure associated with administration of hypertonic solutions. *Am J Physiol* 1955;180:545-58.
 12. Adrogue HJ, Madias NE. Hypernatremia. *N Engl J Med* 2000;342:1493-9.
 13. Javid M, Settlege P. Effect of urea on cerebrospinal fluid pressure in human subjects: preliminary report. *JAMA* 1956; 160:943-9.
 14. Wise BL, Chater N. The value of hypertonic mannitol solution in decreasing brain mass and lowering cerebro-spinal-fluid pressure. *J Neurosurg* 1962;19:1038-43.
 15. Fisher B, Thomas D, Peterson B. Hypertonic saline lowers raised intracranial pressure in children after head trauma. *J Neurosurg Anesthesiol* 1992;4:4-10.
 16. Koenig MA, Bryan M, Lewin JL III, Mirski MA, Geocadin RG, Stevens RD. Reversal of transtentorial herniation with hypertonic saline. *Neurology* 2008;70: 1023-9.
 17. Francony G, Fauvage B, Falcon D, et al. Equimolar doses of mannitol and hypertonic saline in the treatment of increased intracranial pressure. *Crit Care Med* 2008;36:795-800.
 18. Viallet R, Albanèse J, Thomachot L, et al. Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol. *Crit Care Med* 2003;31:1683-7.
 19. Horn P, Münch E, Vajkoczy P, et al. Hypertonic saline solution for control of elevated intracranial pressure in patients with exhausted response to mannitol and barbiturates. *Neurol Res* 1999;21:758-64.
 20. Simma B, Burger R, Falk M, Sacher P, Fanconi S. A prospective, randomized, and controlled study of fluid management in children with severe head injury: lactated Ringer's solution versus hypertonic saline. *Crit Care Med* 1998;26:1265-70.
 21. Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med* 2011;364:1493-502. [Erratum, *N Engl J Med* 2011;365:2040.]
 22. CRASH Trial Collaborators. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet* 2004;364:1321-8.
 23. James HE, Langfitt TW, Kumar VS, Ghostine SY. Treatment of intracranial hypertension: analysis of 105 consecutive continuous recordings of intracranial pressure. *Acta Neurochir (Wien)* 1977;36: 189-200.
 24. Better OS, Rubinstein I, Winaver JM, Knochel JP. Mannitol therapy revisited (1940-1997). *Kidney Int* 1997;52:886-94.
 25. Paczynski RP. Osmotherapy: basic concepts and controversies. *Crit Care Clin* 1997;13:105-29.
 26. Juul N, Morris GF, Marshall SB, Marshall LF. Intracranial hypertension and cerebral perfusion pressure: influence on neurological deterioration and outcome in severe head injury. *J Neurosurg* 2000; 92:1-6.
 27. Dinger MN, Zazulia AR. Osmotic therapy: fact and fiction. *Neurocrit Care* 2004;1:219-33.
 28. Bullock MR, Povlishock JT. Guidelines for the management of severe traumatic brain injury. II. Hyperosmolar therapy. *J Neurotrauma* 2007;24:Suppl 1: S14-S20. [Erratum, *J Neurotrauma* 2008; 25:276-8.]
 29. Kochanek PM, Carney N, Adelson PD, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents — second edition. *Pediatr Crit Care Med* 2012;13:Suppl 1:S1-S82. [Erratum, *Pediatr Crit Care Med* 2012;13:252.]

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durable control of recurrent respiratory papillomatosis.^{4,5} Whether these pathways were also disrupted in the lung tumors of the patient described by Yuan and colleagues was not reported. Yuan et al. describe a cell-culture technique that was used to identify specific treatment for recurrent respiratory papillomatosis, but other agents may also be effective, and caution is advised before broadly using histone deacetylase inhibitors for recurrent respiratory papillomatosis.

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

1. Yuan H, Myers S, Wang J, et al. Use of reprogrammed cells to identify therapy for respiratory papillomatosis. *N Engl J Med* 2012;367:1220-7.
2. Johnston D, Hall H, DiLorenzo TP, Steinberg BM. Elevation of the epidermal growth factor receptor and dependent signaling in human papillomavirus-infected laryngeal papillomas. *Cancer Res* 1999;59:968-74.
3. Wu R, Abramson AL, Shikowitz MJ, Dannenberg AJ, Steinberg BM. Epidermal growth factor-induced cyclooxygenase-2 expression is mediated through phosphatidylinositol-3 kinase, not mitogen-activated protein/extracellular signal-regulated kinase kinase, in recurrent respiratory papillomas. *Clin Cancer Res* 2005;11:6155-61.
4. Limsukon A, Susanto I, Soo Hoo GW, Dubinett SM, Batra RK. Regression of recurrent respiratory papillomatosis with celecoxib and erlotinib combination therapy. *Chest* 2009;136:924-6.
5. Lucs AV, Wu R, Mullooly V, Abramson AL, Steinberg BM. Constitutive overexpression of the oncogene Rac1 in the airway of recurrent respiratory papillomatosis patients is a targetable host-susceptibility factor. *Mol Med* 2012;18:244-9.

DOI: 10.1056/NEJMc1212926

THE AUTHORS REPLY: Batra and Soo Hoo support our personalized cell technique that helped us to

identify a therapy for progressive recurrent respiratory papillomatosis. Although we found that vorinostat was cytotoxic in vitro and clinically effective in vivo, we agree with their comment that there may be additional therapeutic agents that our approach might be able to validate. Indeed, we are currently expanding our studies to explore such possibilities as well as applying our approach to nonviral neoplasia. However, we do not agree with their postulate that a “hit-and-run” mechanism was operative in the patient we described. Our polymerase-chain-reaction (PCR), reverse-transcriptase PCR, and cloning experiments indicate that wild-type and mutant HPV type 11 genomes were present in the laryngeal tumor and lung tumor, respectively. These findings are consistent with the well-documented role of HPV in virtually all cases of recurrent respiratory papillomatosis.¹⁻³

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Since publication of their article, the authors report no further potential conflict of interest.

1. Smith EM, Pignatari SS, Gray SD, Haugen TH, Turek LP. Human papillomavirus infection in papillomas and nondiseased respiratory sites of patients with recurrent respiratory papillomatosis using the polymerase chain reaction. *Arch Otolaryngol Head Neck Surg* 1993;119:554-7.
2. Draganov P, Todorov S, Todorov I, Karchev T, Kalvatchev Z. Identification of HPV DNA in patients with juvenile-onset recurrent respiratory papillomatosis using SYBR Green realtime PCR. *Int J Pediatr Otorhinolaryngol* 2006;70:469-73.
3. Donne AJ, Hampson L, Homer JJ, Hampson IN. The role of HPV type in recurrent respiratory papillomatosis. *Int J Pediatr Otorhinolaryngol* 2010;74:7-14.

DOI: 10.1056/NEJMc1212926

Hyperosmolar Therapy for Raised Intracranial Pressure

TO THE EDITOR: Ropper (Aug. 23 issue)¹ recommends the use of mannitol at intervals of 2 to 4 or more hours to reduce intracranial pressure. Mannitol has been used for four decades to reduce intracranial pressure without solid evidence of benefit. In a randomized, controlled trial involving patients with intracerebral hemorrhage, mannitol improved neither the mortality nor the outcomes at 3 months.² Mannitol also did not improve cerebral blood flow as compared with saline in patients with intracerebral hemorrhage.³

In a study involving 6 patients with large hemispheric infarctions, mannitol boluses were associated with a clinically significant reduction of brain volume, which was most marked in the normal hemisphere.⁴ In another blinded study, mannitol administered in a 20% solution in boluses of 1.5 g per kilogram of body weight resulted in clinical improvement for 30 to 60 minutes in 5 of 12 patients with intracerebral hemorrhage, without a significant change in horizontal or vertical shift on magnetic resonance imaging.⁵ Fre-

quent and large doses of mannitol result in formation of idiogenic osmoles, leading to a reduction in efficacy and even to rebound brain edema. We therefore think that mannitol should be used cautiously in patients with raised intracranial pressure.

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

1. Ropper AH. Hyperosmolar therapy for raised intracranial pressure. *N Engl J Med* 2012;367:746-52.
2. Misra UK, Kalita J, Ranjan P, Mandal SK. Mannitol in intracerebral hemorrhage: a randomized controlled study. *J Neurol Sci* 2005;234:41-5.
3. Kalita J, Misra UK, Ranjan P, Pradhan PK, Das BK. Effect of mannitol on regional cerebral blood flow in patients with intracerebral hemorrhage. *J Neurol Sci* 2004;224:19-22.
4. Videen TO, Zazulia AR, Manno EM, et al. Mannitol bolus preferentially shrinks non-infarcted brain in patients with ischemic stroke. *Neurology* 2001;57:2120-2.
5. Misra UK, Kalita J, Vajpayee A, Phadke RV, Hadique A, Savlani V. Effect of single mannitol bolus in intracerebral hemorrhage. *Eur J Neurol* 2007;14:1118-23.

DOI: 10.1056/NEJMc1212351

TO THE EDITOR: Hypertonic saline has been associated with clinically significant renal insufficiency or acute renal failure in pediatric patients being treated for intracranial hypertension. In one study, 2 of 10 children being treated with mannitol and hypertonic saline for intracranial hypertension after traumatic brain injury required hemodialysis for renal failure.¹ In our study, we observed an increase in the serum creatinine level that was two to three times as high as the baseline level; this increase correlated with an increase in the serum sodium level above 160 mmol per liter (serum osmolality, >320 mOsm per liter) with the use of hypertonic saline (without mannitol) in pediatric patients with intracranial hypertension and maintenance of a euolemic hyperosmolar state.² As a result, our pediatric intensive care practitioners will attempt to avoid increasing the serum sodium level above 160 mmol per liter (serum osmolality, >320 mOsm per liter) when administering hypertonic saline for treating intracranial hypertension in pediatric patients.

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

1. Khanna S, Davis D, Peterson B, et al. Use of hypertonic saline in the treatment of severe refractory posttraumatic intracranial hypertension in pediatric traumatic brain injury. *Crit Care Med* 2000;28:1144-51.
2. Dominguez TE, Priestley MA, Huh JW. Caution should be exercised when maintaining a serum sodium level >160 meq/L. *Crit Care Med* 2004;32:1438-9.

DOI: 10.1056/NEJMc1212351

TO THE EDITOR: Ropper does not mention hyponatremic encephalopathy as a cause of raised intracranial pressure.¹ An equation for estimating the amount of hypertonic saline necessary to increase the serum sodium level is provided, and it is recommended that biochemical measurements (levels of serum sodium or serum osmolality, blood urea nitrogen, and serum creatinine) be checked every 8 hours. It is not mentioned that conditions associated with raised intracranial pressure are frequently associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and cerebral salt wasting.² Patients with SIADH and cerebral salt wasting can have hypertonic urine, with a combined urinary sodium and potassium concentration greater than that of plasma. The use of normal saline could actually result in a decrease in the serum sodium level, and the use of 3% saline could fail to raise the serum sodium level as much as calculated.³ A continuous infusion of both normal saline and 3% saline will probably be required to maintain hyperosmolality, and the serum sodium level should be checked at least every 4 hours.² A new class of drugs, vasopressin antagonists, may have a role in achieving and maintaining hyperosmolality in patients with raised intracranial pressure.⁴

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Drs. Moritz and Ayus report serving as consultants to Otsuka Pharmaceuticals. No other potential conflict of interest relevant to this letter was reported.

1. Moritz ML, Ayus JC. The pathophysiology and treatment of hyponatremic encephalopathy: an update. *Nephrol Dial Transplant* 2003;18:2486-91.
2. Moritz ML. Syndrome of inappropriate antidiuresis and cerebral salt wasting syndrome: are they different and does it matter? *Pediatr Nephrol* 2012;27:689-93.

3. Musch W, Decaux G. Treating the syndrome of inappropriate ADH secretion with isotonic saline. *QJM* 1998;91:749-53.
4. Galton C, Deem S, Yanez ND, et al. Open-label randomized trial of the safety and efficacy of a single dose conivaptan to raise serum sodium in patients with traumatic brain injury. *Neurocrit Care* 2011;14:354-60.

DOI: 10.1056/NEJMc1212351

TO THE EDITOR: Important details regarding mannitol were omitted from Ropper's article regarding management of elevated intracranial pressure. Ropper asserts that mannitol causes an osmotic diuresis, therefore increasing the serum sodium concentration, which leads to water shifting out of the brain due to an osmotic gradient. The article suggests that kidney function is necessary for mannitol to reduce intracranial pressure. However, in our practice, my colleagues and I have used mannitol (0.25 to 1.0 g per kilogram of body weight intravenously) to control intracranial pressure in patients with anuric renal failure who are receiving long-term intermittent hemodialysis. In this clinical situation, we have observed rapid, sustained decreases in intracranial pressure with the administration of mannitol. It is likely that the action of mannitol is due to increased plasma osmolarity after administration, causing water to shift out of the brain (for which renal function is not required).¹ Other possible mechanisms for the reduction of intracranial pressure associated with mannitol include an increase in cerebral perfusion,² causing cerebral vasoconstriction,³ and decreased production of cerebrospinal fluid.⁴ Other physicians may find, as we have, that the use of mannitol even in patients with chronic renal failure and elevated intracranial pressure is beneficial.

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

1. Winkler SR, Munoz-Ruiz L. Mechanism of action of mannitol. *Surg Neurol* 1995;43:59.
2. Rosner MJ, Coley I. Cerebral perfusion pressure: a hemodynamic mechanism of mannitol and the post-mannitol hemogram. *Neurosurgery* 1987;21:147-56.
3. Hartwell RC, Sutton LN. Mannitol, intracranial pressure, and vasogenic edema. *Neurosurgery* 1993;32:444-50.
4. Donato T, Shapira Y, Artru A, Powers K. Effect of mannitol on cerebrospinal fluid dynamics and brain tissue edema. *Anesth Analg* 1994;78:58-66.

DOI: 10.1056/NEJMc1212351

THE AUTHOR REPLIES: Misra and colleagues eschew the use of mannitol for raised intracranial pressure. This view may have merit, but they cite their own randomized trial¹ that involved approximately 60 patients, a third of whom had a cerebral hemorrhage smaller than 20 ml in volume and a third of whom had a cerebral hemorrhage larger than 40 ml in volume. As I discuss in my editorial² on the article by Chesnut et al.³ in this issue of the *Journal*, patients with small masses may not need treatment for intracranial pressure at all, and there may be a limited benefit to treating those with large lesions, so I am uncertain whether Misra's study settles the question of the usefulness of mannitol. If Misra and colleagues are questioning entirely the need to reduce intracranial pressure in cerebral hemorrhage, that is an interesting but separate polemic.

The risks of excessive dehydration in children are well noted by Huh and colleagues, and I commented in my article that serum sodium levels over 160 mmol per liter, arbitrarily stated by others to be the upper limit for safety, have been safely exceeded in adults.

Hyponatremic encephalopathy is an interesting entity, but in my experience it has not been obligatorily tied to brain swelling, especially when the cause is the natriuretic Nelson's syndrome. The other points made by Moritz and Ayus are worth noting, and vasopressin antagonists that cause hyperosmolarity are a new prospect as treatment for raised intracranial pressure. An additional issue regarding the correction of hyponatremia is the risk of "osmotic demyelination" (formerly called "central pontine myelinolysis") if the level of sodium is made to rise too rapidly.

In response to the point made by Benardete about mannitol being effective even in patients with renal failure: my article indicates that a "sustained" reduction of intracranial pressure requires osmotic diuresis. I accept that the continued circulation of mannitol in patients with renal failure might allow a prolonged hyperosmolar effect until the sugar is metabolized, but repeat dosing would be required to sustain hyperosmolarity, and chronic renal failure of a degree that prevents an osmotic diuresis is not typical in circumstances of raised intracranial pressure. Benardete is probably aware that the other oft-cited effects of mannitol on intracranial pres-

sure have been minor or transient in clinical studies.

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Since publication of his article, the author reports no further potential conflict of interest.

1. Misra UK, Kalita J, Ranjan P, Mandal SK. Mannitol in intracerebral hemorrhage: a randomized controlled study. *J Neurol Sci* 2005;234:41-5.
2. Ropper AH. Brain in a box. *N Engl J Med* 2012;367:2539-41.
3. Chesnut RM, Temkin N, Carney N, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med* 2012;367:2471-81.

DOI: 10.1056/NEJMc1212351

Missing Data in Clinical Trials

TO THE EDITOR: Little et al. (Oct. 4 issue)¹ mention limiting “the burden and inconvenience of data collection on the participants” as one of several ideas for limiting missing data in the conduct of clinical trials. Actually, this idea should be a design feature, and it is also important in limiting the burden on the investigator (a critical factor in successful data retrieval as well as patient accrual). Prominent trialists have long championed simple randomized trials for these and other reasons.² Simple, minimal data collection must be one of the most effective strategies for the prevention of missing data.

This concept is sometimes difficult to sell to investigators who may envision ancillary studies and additional publications ensuing from more data. However, quality trumps quantity, and perhaps this should be made clearer in criteria for academic promotion.

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

1. Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. *N Engl J Med* 2012; 367:1355-60.
2. Yusuf S, Collins R, Peto R. Why do we need some large, simple randomized trials? *Stat Med* 1984;3:409-22.

DOI: 10.1056/NEJMc1213388

TO THE EDITOR: Little and colleagues correctly point out that missing data are often the result of study designs that mandate study discontinuation when treatment is discontinued.¹ Intention-to-treat inference based on randomization requires that patient data be collected regardless of treatment status. However, an issue requires further clarification. When following patients who are

off treatment, and methods are used to address data that are missing at random, the goal is to recreate a result that would have been obtained if patients who discontinued treatment had been followed after discontinuing treatment. The use of patients who are receiving treatment to impute the results for those who have discontinued treatment would seem to be problematic. In addition, if the common practice of no longer considering data on patients after treatment discontinuation is not altered, methods to address missing data that are based on statistical models will have no similar patients from whom to model the missing data. How do the authors suggest that we deal with this conundrum?

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

1. Flyer P, Hirman J. Missing data in confirmatory clinical trials. *J Biopharm Stat* 2009;19:969-79.

DOI: 10.1056/NEJMc1213388

THE AUTHORS REPLY: We agree with Lewis that limiting the burden on participants and investigators is important in the design of a study. Excessive data collection not only creates more opportunities for missing data, but it can distract attention from the collection of critical data. That said, covariate data, auxiliary data, and secondary-outcome data can serve valuable purposes, including improving the ability to understand and model the missing data.

Hirman and Flyer raise the important issue of the appropriate intention-to-treat analysis when patients go off the treatment protocol. We see three broad options, the relative usefulness of