Brain Injury Management: *Quo Vadis?*

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At the 2005 CNS meeting, this paper was part of a session devoted to current management strategies and neurosurgical treatment algorithms derived from both clinical experience and evidence-based medicine. The overall theme of the meeting was "Quo Vadis?," or "Where are you going?," a theme that emphasized future developments in neurosurgery. This chapter will integrate the specific session's focus on current management strategies with the meeting's overall theme of where neurosurgery is going.

THREE BASIC PRINCIPLES

It is worthwhile to remember three basic principles before embarking on a discussion of current and future therapies (*Table 33.1*). These principles reflect lessons learned from long and painful experience and also inform future work in this area.

Individualization of Management

The first principle is the growing awareness that the ideal treatment for a brain-injured patient should be tailored to that patient's particular circumstances. For decades, we have been following the same basic algorithm for all patients. This uniform approach has been largely necessitated by our limited ability to investigate and characterize an individual patient's physiological picture. It is now possible to try a more targeted approach. For example, patients who are known to have a high cerebral blood flow (CBF) may tolerate hyperventilation and may be good candidates for barbiturate treatment. On the other hand, those with low blood flows may require artificial elevation of their blood pressure to levels that are higher than those targeted in most other patients. Individuals who seem to have large amounts of parenchymal edema may benefit most from mannitol or hypertonic saline (HTS). Although monitoring techniques to identify some of these physiologic patterns are commercially available, they are not used in many centers for various reasons, which may include expense, difficulty of use, and lack of clear correlation with improved outcome.

In addition to the targeting of interventions to a patient's specific physiological profile, other investigations are just beginning to evaluate targeting of treatments to a patient's genetic makeup. For example, patients who are found to possess a variant of the nitric oxide synthase gene could conceivably benefit from supplementation with L-arginine, which is a nitric oxide donor that may help to raise levels of nitric oxide and thereby improve CBF.[1]

Dangers of Prophylaxis against Intracranial Hypertension

The second basic principle is that therapeutic measures to lower elevated intracranial pressure (ICP) do not work if they are given prophylactically. In fact, they may actually worsen outcome. Class I and II data suggest that prophylactically hyperventilating all patients,[10] prophylactically placing all severe traumatic brain injury (TBI) patients in barbiturate coma,[19] routinely administrating pharmacological paralytics to all patients,[6] and routinely treating all patients with hypothermia do not help.[3] In fact, most of these treatments may worsen outcome when given to prevent intracranial hypertension rather than to treat ICP elevations promptly when they occur. Aggressive elevation of blood pressure to maintain a high cerebral perfusion pressure (CPP) in all patients also falls into this category.[15] Currently, prophylactic decompressive craniectomy in severe TBI patients is a common practice for many neurosurgeons, but a good clinical study is needed to answer the question of whether or not this practice really improves outcome.

For these and other treatments, neurosurgeons must temper their instincts to be aggressive and to intervene before problems develop by realizing that such well-intentioned efforts might do more harm than good. We are not yet at the stage where we can play offense; all we can do is play defense and react when intracranial hypertension develops, but react as quickly as possible.

Regional versus Global Cerebral Metabolism

The third basic principle is increasing awareness of the possibility that regional heterogeneity of metabolism may exist in the injured brain. The brain is not a uniform black box in which all parts are identical to the whole in terms of their metabolic patterns. Instead, those parts of the brain that underlie an acute subdural hematoma or that border a contusion or infarction may behave very differently than normal tissue. The distinction between regional versus global metab-

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TABLE 33.1. Basic principles of traumatic brain injury management

1. Patients are different. They may require individualized management. What works in one patient may not work in another.
2. Aggressive interventions to prevent intracranial hypertension may do more harm than good.
3. Different parts of the brain may have very different patterns of metabolism.

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olism is important if one is to accurately interpret data obtained from cerebral monitoring devices. ICP is a global indicator of the state of cerebral metabolism, but invasive monitors that track cerebral oxygenation, measure CBF, or collect cerebral microdialysate measure only the very small volume of brain around the functional portion of the catheter. If these monitors lie in normal-appearing tissue, then they probably measure global metabolism. However, if they are adjacent to a hematoma or contusion, then they may reflect the status of marginally surviving tissue that may live or die depending on the patient's clinical course and subsequent management.

ALGORITHMS

Many algorithms are available for the management of basic problems and concerns in severe TBI patients. With few exceptions, these are based on expert opinion and on institutional preferences. This emphasis on local circumstances does not make these algorithms any less valuable. In fact, if one considers that the very best type of evidence-based medicine integrates a thorough review of available scientific evidence with an individual patient's condition, with the physician's judgment and experience, and with the circumstances in which care is rendered, local protocols may represent the very best type of practice algorithms. For example, a 10-year-old boy with a medium-sized acute epidural hematoma without neurological deficits may be managed with careful observation in a dedicated pediatric intensive care unit in a large teaching hospital, especially if that patient is injured on the morning of a typical working day. However, it might be best to operate on that same patient immediately if he arrives in a small, outlying hospital late on a Friday evening. The likelihood of early detection of neurological injury and the speed with which the patient can be taken to the operating room are probably different in these two institutions. Thus, the same clinical problem may be handled in very different ways.

Algorithms for the management of intracranial hypertension in severe TBI patients are no different than algorithms for managing any other clinical problem. They are all influenced by expert opinion, but the most useful algorithms are based, at least in part, on the medical literature. An example of one such algorithm is shown in *Figure 33.1*.

It is obvious that the pathway shown in *Figure 33.1* refers to the "one size fits all" approach outlined in the first basic principle described earlier. In some cases, it might be
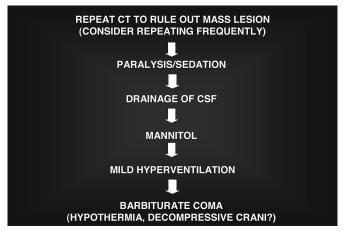

FIGURE 33.1 Basic sequence of steps to control intracranial hypertension after brain injury.

perfectly appropriate to deviate from this approach, e.g., to proceed immediately to mild hyperventilation if a patient's CBF and cerebral oxygenation suggest that the patient should be able to tolerate such an intervention with little risk of harm. However, as mentioned above, such detailed metabolic information is often not available. In these cases, it is reasonable to follow an algorithm that attempts to base its stepwise interventions on the principle of implementing those with the greatest likelihood of helping the largest number of patients while causing adverse effects in the fewest number of patients.

It should also be emphasized that interventions, such as moderate hypothermia and barbiturate coma, which failed to show benefit in trials that enrolled all TBI patients,[3,19] are undoubtedly helpful in particular subgroups of patients. Each of these treatments can be considered to be a key, and the challenge for clinicians is to identify the lock for which that key is a perfect fit. Answering these types of questions would require smaller, more focused clinical studies of specific types of patients, an approach which has not been employed in many clinical trials of TBI. Thus, the clinician must again resort to experience, judgment, and a professional opinion that is as informed as possible by scientific evidence.

THREE RECENT DEVELOPMENTS

As an illustration of the continually evolving status of recommendations about specific treatments in TBI, three specific therapies will be reviewed briefly below.

CPP-based Management

As neurosurgeons became aware of the deleterious effects of hypotension after brain injury, a large number of practitioners began to embrace the idea of elevation of CPP in these patients. Such management was thought to prevent increases in ICP. And, even if such increases did occur, it was felt that raising the CPP might help to offset the deleterious effects of an elevated ICP that cannot be reduced. However, such recommendations were based on Class III data.[16,17] Subsequent work suggested that a CBF-based management approach, as opposed to the traditional approach that focused primarily on ICP, did not improve outcome and actually caused a significant increase in the incidence of adult respiratory distress syndrome (ARDS).[15] The development of ARDS seemed to be directly related to some of the therapies that had been used to keep blood pressure elevated.[2] Subsequent work by other groups suggested that, as long as CPP remained at or above 60 mmHg, no additional benefit accrued from elevations beyond that level.[7] Thus, most researchers in this area now recommend that 60 mmHg be the default minimum value for CPP. However, as with all such recommendations, individual variability is important. Some patients may require elevation of CPP beyond this level, whereas in other cases, patients may be better left alone at a lower CPP if it seems that attempts to artificially elevate blood pressure may do more harm than good.

Steroids

In years past, steroids were routinely administered to brain-injured patients. It was assumed that steroids would be beneficial because of their obvious edema-reducing effect in brain tumors. However, a growing number of studies began questioning the value and wisdom of this practice. Late in 2004, the published results of the Corticosteroid Randomization After Significant Head Injury (CRASH) study showed an increase in mortality in patients who were administered steroids.[14] Patients enrolled in the study had to have a Glasgow Coma Scale (GCS) score of 14 or less. This study had planned to enroll 20,000 patients, but the external safety monitors halted it after 10,008 patients were enrolled because of the obvious difference in mortality between the two groups. In June 2005, the 6-month outcome data were published, with the same basic findings.[5] These studies send a strong message against the routine use of steroids in all head-injured patients.

At the same time, some individual practitioners use steroids in patients with high GCS scores who have moderately large hematomas or contusions that have not been evacuated if those patients complain of severe headaches. They place these patients on steroids in an attempt to decrease some of the swelling and inflammation from the hematoma. Anecdotally, they report great success with this approach.

How does one interpret such reports? It is difficult to perform studies on such a narrowly defined population of patients. Thus, proof of benefit of this focused application is difficult to demonstrate, but so is proof of harm. Again, this might be an example of a large overarching guideline (such as not giving steroids as a rule to all severe TBI patients) being too broad to address a specific subpopulation of patients.

Hypertonic Saline

HTS has long been recognized as a potentially useful osmotic agent for both prehospital resuscitation of trauma patients and treatment of intracranial hypertension. Clinical and laboratory work suggested that brain-injured patients might have better outcomes if they are resuscitated with HTS. The efficacy of prehospital resuscitation of hypotensive severe TBI patients with HTS was investigated in a prospective study reported in March 2004.[4] In that trial, 250 ml of 7.5% NaCl was administered to one group, whereas the other was randomized to 250 ml of Ringer's lactate. Both groups also received standard resuscitation fluids according to medically determined protocols. The end result is that there seemed to be no improvement of outcome with the use of HTS instead of Ringer's lactate as an initial resuscitation fluid. However, each group received the same prehospital volume of resuscitation fluid in addition to the study fluids and both groups demonstrated correction of hypotension before arrival at the hospital. Such features may have diluted the potential effects of HTS to such an extent that they became insignificant. Moreover, this study did not address the in-hospital use of HTS to control intracranial hypertension. As with so many questions in clinical neurosurgery, definitive answers require more good data.

FIVE UP-AND-COMING AREAS

In keeping with the "Quo Vadis?" theme of the 2005 Annual Meeting of the Congress of Neurological Surgeons, it is appropriate to conclude this discussion with an attempt to glimpse beyond the horizon to see what may be in store for us tomorrow (*Table 33.2*).

Better Understanding of Commonly Used Therapies

Most neurosurgeons are familiar with mannitol, decompressive craniectomy, CPP-based management, administra-

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TABLE 33.2. Areas of future development

1. Better understanding of common therapies
2. Information management
3. Genotype-specific therapies
4. Serum markers
5. Delivery of emergency neurosurgical care

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tion of steroids, and ordering of routine follow-up head computed tomographic scans. Many also have experience with the use of HTS. Despite the widespread use of these and other techniques, very little solid evidence is available to guide their application. Instead of devoting all of our research efforts to attempts to find new treatments, it might be wise to set aside a portion of those efforts to rigorously evaluate established therapies so that they can be employed as effectively as possible.

Information Management

The accelerating pace of computer technology makes it possible for many intensive care units to gather and store many channels of information on each patient several times per minute. Unfortunately, increasing the amount of information that we can store is not the same as increasing our knowledge and wisdom. There exists a huge need for advances in bioinformatics to help us analyze these mountains of physiological data. The ability to recognize deleterious trends as early as possible may represent the best type of defense that we can play.

Genotype-specific Therapies

As mentioned earlier, polymorphisms of certain genes may impact outcome after severe TBI. For several years, the apoE4 genotype has been associated with a worse outcome after TBI.[13,18] More recently, it has been shown that variants of the gene for nitric oxide synthase may be related to coronary artery spasm and myocardial infarction[11,12] and also to ischemia after brain injury and vasospasm after aneurysmal subarachnoid hemorrhage. If the effects of these and other polymorphisms continue to be as important in large trials as they are in preliminary studies, it may soon become important to perform a genotype analysis on all newly admitted TBI patients so that therapy can be tailored to their genetic profile.

Serum Markers

The identification of relevant serum markers revolutionized the diagnosis of myocardial infarction, just as various serum markers have become useful in the diagnosis and monitoring of certain cancers. Many investigators are pursuing the development of serum markers for brain injury. However, these efforts are still in their infancy. Some markers have been found to be sensitive, but not very specific, for brain injury. Efforts are now underway to identify other easily detectable compounds or patterns of appearance of compounds that reliably correlate with the presence of brain injury.

Systems for Delivery of Emergency Neurosurgical Care

Economic and regulatory forces have made it difficult, or even impossible, for many neurosurgeons to participate in their local and regional emergency medicine systems. The ongoing increases in demand for these services have far outpaced the supply of neurosurgeons. Some have advocated that non-neurosurgeons should assume a larger role in caring for these patients.[8,9] Others, however, have shown that the performance of emergency craniotomies by non-neurosurgeons is often fraught with so many problems that it is probably better to send the patient to a neurosurgeon rather than delay interhospital transfer for attempts at definitive treatment by a non-neurosurgeon.[20,21] Both in the operating room and at the bedside, it is difficult to care for neurotrauma patients without the expertise of neurosurgeons. A more realistic solution is to investigate creative ways for neurosurgeons to expand their reach in the intensive care unit. Such solutions might include a greater role for physician extenders who work for neurosurgeons, as well as greater collaboration with colleagues from related fields who often assist in the care of these patients. Finally, the possibilities of regionalization of neurotrauma care and special creation of regional centers of excellence in neurotrauma care deserve further exploration as other ways to optimize the care of those patients who are most in need of the skills of a neurosurgeon.

REFERENCES

1. Cherian L, Hlatky R, Robertson CS: Nitric oxide in traumatic brain injury. **Brain Pathol** 14:195–201, 2004.
2. Contant CF, Valadka AB, Gopinath SP, Hannay HJ, Robertson CS: Adult respiratory distress syndrome: A complication of induced hypertension after severe head injury. **J Neurosurg** 95:560–568, 2001.
3. Clifton GL, Miller ER, Choi SC, Levin HS, McCauley S, Smith KR Jr, Muizelaar JP, Wagner FC Jr, Marion DW, Luerssen TG, Chesnut RM, Schwartz M: Lack of effect of induction of hypothermia after acute brain injury. **N Engl J Med** 344:556–563, 2001.
4. Cooper DJ, Myles PS, McDermott FT, Murray LJ, Laidlaw J, Cooper G, Tremayne AB, Bernard SS, Ponsford J, HTS Study Investigators: Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: A randomized controlled trial. **JAMA** 291:1350–1357, 2004.
5. Edwards P, Arango M, Balica L, Cottingham R, El-Sayed H, Farrell B, Fernandes J, Gogichaisvili T, Golden N, Hartzenberg B, Husain M, Ulloa MI, Jerbi Z, Khamis H. Komolafe E, Laloe V, Lomas G, Ludwig S, Mazairac G, Munoz Sanchez Mde L, Nasi L, Olldashi F, Plunkett P, Roberts I, Sandercock P, Shakur H, Soler C, Stocker R, Svoboda P, Trenkler S, Venkataramana NK, Wasserberg J, Yates D, Yutthakasemsunt S, CRASH Trial Collaborators: Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury-outcomes at 6 months. **Lancet** 365:1957–1959, 2005.
6. Hsiang JK, Chesnut RM, Crisp CB, Klauber MR, Blunt BA, Marshall LF: Early, routine paralysis for intracranial pressure control in severe head injury: is it necessary? **Crit Care Med** 22:1471–1476, 1994.
7. Juul N, Morris GF, Marshall SB, Marshall LF: Intracranial hypertension and cerebral perfusion pressure: Influence on neurological deterioration and outcome in severe head injury. The Executive Committee of the International Selfotel Trial. **J Neurosurg** 92:1–6, 2000.
8. Kaups KL, Parks SN, Morris CL: Intracranial pressure monitor placement by midlevel practitioners. **J Trauma** 45:884–886, 1998.
9. Ko K, Conforti A: Training protocol for intracranial pressure monitor placement by nonneurosurgeons: 5-year experience. **J Trauma** 55:480–484, 2003.
10. Muizelaar JP, Marmarou A, Ward JD, Kontos HA, Choi SC, Becker DP, Gruemer H, Young HF: Adverse effects of prolonged hyperventilation in patients with severe head injury: A randomized clinical trial. **J Neurosurg** 75:731–739, 1991.

11. Nakayama M, Yasue H, Yoshimura M, Shimasaki Y, Kugiyama K, Ogawa H, Motoyama T, Saito Y, Ogawa Y, Miyamoto Y, Nakao K: T-786→C mutation in the 5′-flanking region of the endothelial nitric oxide synthase gene is associated with coronary spasm. **Circulation** 99:2864–2870, 1999.

12. Nakayama M, Yasue H, Yoshimura M, Shimasaki Y, Ogawa H, Kugiyama K, Mizuno Y, Harada E, Nakamura S, Ito T, Saito Y, Miyamoto Y, Ogawa Y, Nakao K: T-786→C mutation in the 5′-flanking region of the endothelial nitric oxide synthase gene is associated with myocardial infarction, especially without coronary organic stenosis. **Am J Cardiol** 86:628–634, 2000.

13. Nicoll JA, Roberts GW, Graham DI: Apolipoprotein E epsilon 4 allele is associated with deposition of amyloid beta-protein following head injury. **Nat Med** 2:135–137, 1995.

14. Roberts I, Yates D, Sandercock P, Farrell B, Wasserberg J, Lomas G, Cottingham R, Svoboda P, Brayley N, Mazairac G, Laloe V, Munoz-Sanchez A, Arango M, Hartzenberg B, Khamis H, Yutthakasemsunt S, Komolafe E, Olldashi F, Yadav Y, Murillo-Cabezas F, Shakur H, Edwards P, 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** 364:1321–1328, 2004.

15. Robertson CS, Valadka AB, Hannay HJ, Contant CF, Gopinath SP, Cormio M, Uzura M, Grossman RG: Prevention of secondary ischemic insults after severe head injury. **Crit Care Med** 27:2086–2095, 1999.

16. Rosner MJ, Daughton S: Cerebral perfusion pressure management in head injury. **J Trauma** 30:933–941, 1990.

17. Rosner MJ, Rosner SD, Johnson AH: Cerebral perfusion pressure: management protocol and clinical results. **J Neurosurg** 83:949–962, 1995.

18. Teasdale GM, Nicoll JA, Murray G, Fiddes M: Association of apolipoprotein E polymorphism with outcome after head injury. **Lancet** 350:1069–1071, 1997.

19. Ward JD, Becker DP, Miller JD, Choi SC, Marmarou A, Wood C, Newlon PG, Keenan R: Failure of prophylactic barbiturate coma in the treatment of severe head injury. **J Neurosurg** 62:383–388, 1985.

20. Wester K: Decompressive surgery for "pure" epidural hematomas: Does neurosurgical expertise improve the outcome? **Neurosurgery** 44:495–502, 1999.

21. Wester T, Fevang LT, Wester K: Decompressive surgery in acute head injuries: Where should it be performed? **J Trauma** 46:914–919, 1999.