CORRESPONDENCE

Craniectomy for Traumatic Intracranial Hypertension

TO THE EDITOR: In the Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure (RESCUEicp) trial reported by Hutchinson and others (Sept. 22 issue),[1] mortality among patients with severe traumatic brain injury (TBI) and refractory intracranial hypertension who underwent decompressive craniectomy was lower than that among patients who received medical care. However, at 6 months, patients in the surgical group were more likely to have severe disability (as assessed with the use of the Extended Glasgow Outcome Scale [GOS-E][2]) than patients in the medical group. At 12 months, a higher percentage of patients in the surgical group than in the medical group had a favorable outcome.

Although most patients in the surgical group underwent a bifrontal decompressive craniectomy (63%), an analysis according to the type of surgery (i.e., bifrontal or unilateral craniectomy) was not performed. This analysis would be helpful given that in the United States, unilateral decompressive craniectomy is a more common surgical decompression procedure than bifrontal decompressive craniectomy.

This trial included children as young as 10 years of age. Since among patients with severe TBI, school-aged children generally tend to have better outcomes than adults,[3,4] these patients perhaps should be assessed with a pediatric version of the GOS-E in a separate subgroup analysis.[5]

Jimmy W. Huh, M.D.
Shih-Shan Lang, M.D.
Todd J. Kilbaugh, M.D.

Children's Hospital of Philadelphia
Philadelphia, PA
huh@email.chop.edu

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1. Hutchinson PJ, Kolias AG, Timofeev IS, et al. Trial of decompressive craniectomy for traumatic intracranial hypertension. N Engl J Med 2016;375:1119-30.
2. Jennett B, Snoek J, Bond MR, Brooks N. Disability after severe head injury: observations on the use of the Glasgow Outcome Scale. J Neurol Neurosurg Psychiatry 1981;44:285-93.
3. Coronado VG, Xu L, Basavaraju SV, et al. Surveillance for traumatic brain injury-related deaths — United States, 1997-2007. MMWR Surveill Summ 2011;60:1-32.
4. Emami P, Czorlich P, Fritzsche FS, et al. Impact of Glasgow Coma Scale score and pupil parameters on mortality rate and outcome in pediatric and adult severe traumatic brain injury: a retrospective, multicenter cohort study. J Neurosurg 2016 April 1 (Epub ahead of print).
5. Beers SR, Wisniewski SR, Garcia-Filion P, et al. Validity of a pediatric version of the Glasgow Outcome Scale-Extended. J Neurotrauma 2012;29:1126-39.

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TO THE EDITOR: The RESCUEicp trial showed that among patients with traumatic intracranial hypertension, decompressive craniectomy, as compared with medical therapy, reduced mortality and increased rates of vegetative state, lower severe disability, and upper severe disability. Can the authors indicate whether patients in the surgical group had already undergone cranioplasty (replacement of the bone flap over the defect) when functional outcome was assessed at 6 months? Cranioplasty improves cerebral perfusion and reverses abnormal physiological features of cerebrospinal fluid caused by decompressive craniectomy,[1,2]

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and in clinical practice it is often associated with improvement in neurologic status.[3]

If patients in the surgical group did not undergo cranioplasty before the outcome assessment at 6 months, the benefit of decompressive craniectomy may have been underestimated. Would the authors consider reporting the rate of cranioplasty at 6 months among patients in the surgical group? Also, would they consider performing a post hoc subgroup analysis to shed light on whether cranioplasty changes the effect of initial decompressive surgery on functional outcome at 6 months?

Thomas Gaberel, M.D., Ph.D.
University Hospital of Caen
Caen, France
thomas.gaberel@hotmail.fr

Sherry H.Y. Chou, M.D.
University of Pittsburgh
Pittsburgh, PA

Clement Gakuba, M.D., Ph.D.
Harvard Medical School
Boston, MA

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

1. Winkler PA, Stummer W, Linke R, Krishnan KG, Tatsch K. Influence of cranioplasty on postural blood flow regulation, cerebrovascular reserve capacity, and cerebral glucose metabolism. J Neurosurg 2000;93:53-61.
2. Nalbach SV, Ropper AE, Dunn IF, Gormley WB. Craniectomy-associated Progressive Extra-Axial Collections with Treated Hydrocephalus (CAPECTH): redefining a common complication of decompressive craniectomy. J Clin Neurosci 2012;19:1222-7.
3. Bender A, Heulin S, Röhrer S, et al. Early cranioplasty may improve outcome in neurological patients with decompressive craniectomy. Brain Inj 2013;27:1073-9.

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TO THE EDITOR: In the RESCUEicp trial, the dichotomization of "favorable outcomes" in the patients depends on the definition of a "favorable" outcome. The conventional definition in patients with TBI is full independence at 6 months (moderate disability or better).[1] In the RESCUEicp trial, the proportion of patients with these favorable outcomes was just 26.6% in the medical group and 27.4% in the surgical group, as compared with the reported "favorable outcomes" (34.6% in the medical group and 42.8% in the surgical group; P=0.12). Figure 2 of the article may not precisely reflect this result. In the surgical group, all "22 more survivors" described were in a vegetative state or were severely disabled. None were independent (a favorable outcome according to the conventional definition).

Furthermore, the increased rate of survival at 6 months may relate to high mortality among patients in the medical group (48.9%), as compared with 18% mortality among patients in the medical group of the Decompressive Craniectomy (DECRA)[2] trial. In both the DECRA and RESCUEicp trials, decompressive craniectomy was a last-tier intervention, and the proportion of patients with conventional favorable outcomes after craniectomy in the DECRA trial (30%) was similar to that in the RESCUEicp trial. In both trials, decompressive craniectomy increased disability and did not increase full independence in survivors.

D. James Cooper, M.D.
Alistair Nichol, Ph.D.
Carol Hodgson, Ph.D.
Australian and New Zealand Intensive Care Research Centre
Melbourne, VIC, Australia
jamie.cooper@monash.edu

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

1. Roozenbeek B, Lingsma HF, Perel P, et al. The added value of ordinal analysis in clinical trials: an example in traumatic brain injury. Crit Care 2011;15:R127.
2. Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive craniectomy in diffuse traumatic brain injury. N Engl J Med 2011; 364:1493-502.

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TO THE EDITOR: The RESCUEicp trial showed a significant superiority of decompressive craniectomy over medical management in preventing death among patients with TBI and refractory intracranial hypertension. These results appear to be contrary to the results of the DECRA trial. In addition, mortality among patients in the medical group of the RESCUEicp trial was 48.9%, as compared with 18% among patients in the medical group in the DECRA trial.

Another point that merits mention is that 37.2% of the patients in the medical group in the RESCUEicp trial underwent decompressive craniectomy because of clinical deterioration. Therefore, it is reasonable to speculate that the medical therapy received after randomization may not have been adequate in the medical group. Although treatment with barbiturates is often regarded as a final-tier treatment, their efficacy in controlling refractory elevation of intracranial pressure is controversial.[1] It may be necessary to increase the intensity of medical treatment to manage uncontrolled intracranial pressure. Further explanation of this aspect of the trial would be appreciated.

Shen Hu, M.D
Daming Wang, M.D.

Beijing Hospital
Beijing, China
379882975@qq.com

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

1. Roberts I, Sydenham E. Barbiturates for acute traumatic brain injury. Cochrane Database Syst Rev 2012;12:CD000033.

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TO THE EDITOR: In the RESCUEicp trial involving patients with refractory traumatic intracranial hypertension, decompressive craniectomy resulted in lower mortality than mortality among patients who received medical care. However, survivors tended to cluster in the GOS-E category of upper severe disability. Whether this degree of disability is acceptable will depend on the patient, his or her family, and societal influences.

This trial further showed that decreasing intracranial pressure does not treat primary brain injury. Mediation of the secondary injuries (herniation and ischemia) resulting from traumatic intracranial hypertension does not directly address the variable underlying pathophysiological processes. Thus, the degree of injury in the "rescued" patients in the RESCUEicp trial manifested itself as severe disability.

The RESCUEicp trial joins a large and growing body of "failed" randomized, controlled trials involving treatment of patients with TBI and intracranial pressure,[1-4] and the best consequence of this trial would be to end the era of focusing on intracranial pressure alone and of applying one management algorithm to all manifestations of intracranial hypertension. Until clinicians and clinical researchers begin to target the various pathophysiological processes underlying elevated intracranial pressure, the list of large, negative trials is likely to continue to grow.

Randall M. Chesnut, M.D.

University of Washington
Seattle, WA
chesnutr@uw.edu

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1. Andrews PJD, Harris BA, Murray GD. Hypothermia for intracranial hypertension after traumatic brain injury. N Engl J Med 2016;374:1385.
2. Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive craniectomy in diffuse traumatic brain injury. N Engl J Med 2011;364:1493-502.
3. Wright DW, Yeatts SD, Silbergleit R, et al. Very early administration of progesterone for acute traumatic brain injury. N Engl J Med 2014;371:2457-66.
4. 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.

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THE AUTHORS REPLY: In reply to Huh et al. and Gaberel and colleagues: exploratory analyses to evaluate craniectomy sites and pediatric outcomes, both of which are important issues, are ongoing. Also, the timing of cranioplasty may affect outcomes after TBI. The initiation of a prospective registry for cranioplasties in the United Kingdom is under way.[1]

With regard to the comments by Cooper et al. and Hu and Wang, the contrasting results of the DECRA and RESCUEicp trials are due to different hypotheses, inclusion criteria, and therapeutic protocols. The DECRA trial, as compared with the RESCUEicp trial, enrolled patients with a lower intracranial-pressure threshold (20 mm Hg vs. 25 mm Hg) for shorter intervals (15 minutes vs. 1 to 12 hours), after lower intensities of therapy (stage 1 interventions vs. stage 1 and 2 interventions), and within a shorter interval after injury (all patients enrolled within 72 hours after injury vs. 44% of patients enrolled >72 hours after injury). Patients with intracranial hematomas were enrolled in the RESCUEicp trial, but they were not enrolled in the DECRA trial. At enrollment, the populations also differed with respect to expected outcome; the requirement for stage 2 interventions increases the relative risk of death by 60%.[2] Hence, at 6 months, the pooled mortality of 37.5% in the RESCUEicp trial versus 18.7% in the DECRA trial is unsurprising.

In addition, our primary analysis showed a significant between-group difference in the GOS-E distribution and a substantial reduction in mortality with surgery; this finding differed from that of the DECRA trial, in which mortality was similar in the two groups. The severity of injury in the RESCUEicp trial underpinned dichotomization in the prespecified sensitivity analysis at upper severe disability (independent at home) or better. Given the high expectation of a poor outcome, the use of a "conventional" dichotomy would be as inappropriate as the use of it in populations with mild TBI (in whom disability-free survival is often attainable). This approach is concordant with recent recommendations.[3] Up-

Table 1. Definitions of Severe Disability According to the Extended Glasgow Outcome Scale and the Modified Rankin Scale.

Scale and Category	Definition
Extended Glasgow Outcome Scale	
Upper severe disability	Patient does not require assistance at home (or can be left alone for at least 8 hr) but requires assistance outside the home
Lower severe disability	Patient is dependent on others for care
Modified Rankin scale*	
Moderately severe disability (a score of 4)	Patient is unable to walk without assistance and unable to attend to his or her own bodily needs without assistance
Severe disability (a score of 5)	Patient is bedridden, incontinent, and requires constant nursing care and attention

* Scores on the modified Rankin scale, which assesses the degree of disability or dependence in daily activities, range from 0 (no symptoms) to 6 (death).

per severe disability is a better outcome than a modified Rankin score of 4 (on a scale from 0 [no symptoms] to 6 [death]), the threshold that has driven the use of craniectomy in patients with ischemic stroke (Table 1).[4]

Also, barbiturates were an option in patients in the medical group after randomization. The fact that 37.2% of patients in the medical group eventually underwent a craniectomy, whereas 9.4% of patients in the surgical group required barbiturates, indicates that the failure to control intracranial pressure was greater in the medical group.

We agree with Chesnut about the acceptability of disability but question the statement regarding "failed" trials. The DECRA trial and the European Study of Therapeutic Hypothermia (32°C–35°C) for Intracranial Pressure Reduction after Traumatic Brain Injury (the Eurotherm3235 Trial) were valuable because they showed that craniectomy and hypothermia, respectively, are not beneficial as stage 2 interventions. The progesterone trial by Wright et al., which was cited by Chesnut as a failed trial, did not address intracranial hypertension. We think that the treatment of intracranial hypertension will remain important, since it is a driver of increased mortality.[5] Integration of intracranial-pressure waveform analysis (in order to characterize autoregulation) with multimodality monitoring (microdialysis, brain oxygenation, and electrocorticography) can identify pathophysiological subgroups and may allow targeted treatment after TBI.

Peter J. Hutchinson, Ph.D., F.R.C.S. (SN)
Angelos G. Kolias, Ph.D., M.R.C.S.
David K. Menon, F.Med.Sci.
University of Cambridge
Cambridge, United Kingdom
pjah2@cam.ac.uk

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

1. Kolias AG, Bulters DO, Cowie CJ, et al. Proposal for establishment of the UK Cranial Reconstruction Registry (UKCRR). Br J Neurosurg 2014;28:310-4.
2. Stocchetti N, Zanaboni C, Colombo A, et al. Refractory intracranial hypertension and "second-tier" therapies in traumatic brain injury. Intensive Care Med 2008;34:461-7.
3. Maas AI, Murray GD, Roozenbeek B, et al. Advancing care for traumatic brain injury: findings from the IMPACT studies and perspectives on future research. Lancet Neurol 2013;12:1200-10.
4. Vahedi K, Hofmeijer J, Juettler E, et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. Lancet Neurol 2007;6:215-22.
5. Hutchinson PJ, Kolias AG, Czosnyka M, Kirkpatrick PJ, Pickard JD, Menon DK. Intracranial pressure monitoring in severe traumatic brain injury. BMJ 2013;346:f1000.

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Dietary Sodium and Cardiovascular Disease Risk

TO THE EDITOR: Cogswell et al. (Aug. 11 issue)[1] argue that the reported association between low sodium intake and increased cardiovascular risk does not fulfill the criteria for causality, and they therefore conclude that low sodium intake should be recommended. We wish to call attention to several issues in their assessment of the available data.

First, the criticism by Cogswell et al. with regard to fasting urinary sodium estimates of