The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 21, 2011 VOL. 364 NO. 16

Decompressive Craniectomy in Diffuse Traumatic Brain Injury

D. James Cooper, M.D., Jeffrey V. Rosenfeld, M.D., Lynnette Murray, B.App.Sci., Yaseen M. Arabi, M.D., Andrew R. Davies, M.B., B.S., Paul D'Urso, Ph.D., Thomas Kossmann, M.D., Jennie Ponsford, Ph.D., Ian Seppelt, M.B., B.S., Peter Reilly, M.D., and Rory Wolfe, Ph.D., for the DECRA Trial Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group*

ABSTRACT

BACKGROUND

It is unclear whether decompressive craniectomy improves the functional outcome in patients with severe traumatic brain injury and refractory raised intracranial pressure.

METHODS

From December 2002 through April 2010, we randomly assigned 155 adults with severe diffuse traumatic brain injury and intracranial hypertension that was refractory to first-tier therapies to undergo either bifrontotemporoparietal decompressive craniectomy or standard care. The original primary outcome was an unfavorable outcome (a composite of death, vegetative state, or severe disability), as evaluated on the Extended Glasgow Outcome Scale 6 months after the injury. The final primary outcome was the score on the Extended Glasgow Outcome Scale at 6 months.

RESULTS

Patients in the craniectomy group, as compared with those in the standard-care group, had less time with intracranial pressures above the treatment threshold ($P<0.001$), fewer interventions for increased intracranial pressure ($P<0.02$ for all comparisons), and fewer days in the intensive care unit (ICU) ($P<0.001$). However, patients undergoing craniectomy had worse scores on the Extended Glasgow Outcome Scale than those receiving standard care (odds ratio for a worse score in the craniectomy group, 1.84; 95% confidence interval [CI], 1.05 to 3.24; $P=0.03$) and a greater risk of an unfavorable outcome (odds ratio, 2.21; 95% CI, 1.14 to 4.26; $P=0.02$). Rates of death at 6 months were similar in the craniectomy group (19%) and the standard-care group (18%).

CONCLUSIONS

In adults with severe diffuse traumatic brain injury and refractory intracranial hypertension, early bifrontotemporoparietal decompressive craniectomy decreased intracranial pressure and the length of stay in the ICU but was associated with more unfavorable outcomes. (Funded by the National Health and Medical Research Council of Australia and others; DECRA Australian Clinical Trials Registry number, ACTRN012605000009617.)

From the Departments of Intensive Care (D.J.C., L.M., A.R.D.) and Neurosurgery (J.V.R.), Alfred Hospital; the Departments of Epidemiology and Preventive Medicine (D.J.C., L.M., A.R.D., J.P., R.W.) and Surgery (J.V.R.), Monash University; the Neurosciences Clinical Institute (P.D.) and the Monash–Epworth Rehabilitation Research Centre (J.P.), Epworth Healthcare; and the Epworth Hospital (T.K.) — all in Melbourne, VIC; the Department of Intensive Care Medicine, Nepean Hospital, University of Sydney, Sydney, NSW (I.S.); and the Department of Neurosurgery, Royal Adelaide Hospital, Adelaide, SA (P.R.) — all in Australia; and the Intensive Care Department, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia (Y.M.A.). Address reprint requests to Dr. Cooper at the Department of Intensive Care, Alfred Hospital, Commercial Road, Melbourne, VIC 3004, Australia, or at jamie.cooper@monash.edu.

*Investigators in the Decompressive Craniectomy (DECRA) trial are listed in the Supplementary Appendix, available at NEJM.org.

This article (10.1056/NEJMoa1102077) was published on March 25, 2011, and updated on November 23, 2011, at NEJM.org.

N Engl J Med 2011;364:1493-502.

Among patients who are hospitalized with severe traumatic brain injury, 60% either die or survive with severe disability.[1-3] Of Australia's population of 22 million,[4] approximately 1000 patients annually sustain a severe traumatic brain injury, with associated lifetime costs estimated at $1 billion.[5] In the United States, the annual burden of traumatic brain injury is more than $60 billion.[6]

After severe traumatic brain injury, medical and surgical therapies are performed to minimize secondary brain injury.[7-9] Increased intracranial pressure, which is typically caused by cerebral edema, is an important secondary insult.[7,9,10] Although few data regarding the monitoring of intracranial pressure are available from randomized, controlled trials, such monitoring is recommended by international clinical practice guidelines, and first-tier therapies are used to control intracranial pressure.[11] However, many patients with severe traumatic brain injury have raised intracranial pressure that is refractory to first-tier therapies.[11,12] In such cases, surgical decompressive craniectomy is performed with increasing frequency to control intracranial pressure.[10] We designed the multicenter, randomized, controlled Decompressive Craniectomy (DECRA) trial[13,14] to test the efficacy of bifrontotemporoparietal decompressive craniectomy in adults under the age of 60 years with traumatic brain injury in whom first-tier intensive care and neurosurgical therapies had not maintained intracranial pressure below accepted targets.

METHODS

TRIAL DESIGN

From December 2002 through April 2010, we recruited adults with severe traumatic brain injury in the intensive care units (ICUs) of 15 tertiary care hospitals in Australia, New Zealand, and Saudi Arabia. The trial protocol (available with the full text of this article at NEJM.org) was designed by the study's executive committee and approved by the ethics committee at each study center.

PATIENTS

Patients were eligible for participation in the trial if they were between the ages of 15 and 59 years and had a severe, nonpenetrating traumatic brain injury. Among patients who were evaluated either after resuscitation or before intubation, this injury was defined as a score of 3 to 8 on the Glasgow Coma Scale (on which scores range from 3 to 15, with lower scores indicating reduced levels of consciousness) or Marshall class III (moderate diffuse injury on computed tomography [CT]).[15] Patients were excluded if they were not deemed suitable for full active treatment by the clinical staff caring for the patient or if they had dilated, unreactive pupils, mass lesions (unless too small to require surgery), spinal cord injury, or cardiac arrest at the scene of the injury. In all cases, the patients' next of kin provided written informed consent.

STUDY PROCEDURES

All patients in the study were treated in ICUs with advanced neurosurgical management capabilities and equipment, including the availability of intracranial-pressure monitoring with the use of either an external ventricular drain or a parenchymal catheter. Patients received treatment for intracranial hypertension whenever the intracranial pressure was greater than 20 mm Hg.[8,9,11,12,16] We defined an early refractory elevation in intracranial pressure as a spontaneous (not stimulated) increase in intracranial pressure for more than 15 minutes (continuously or intermittently) within a 1-hour period, despite optimized first-tier interventions. Such interventions included optimized sedation, the normalization of arterial carbon dioxide pressure, and the use of mannitol, hypertonic saline, neuromuscular blockade, and external ventricular drainage.

Within the first 72 hours after injury, we randomly assigned patients either to undergo decompressive craniectomy plus standard care or to receive standard care alone, using an automated telephone system. Randomization was stratified according to center and the technique that was used to measure intracranial pressure (external ventricular drain or parenchymal catheter) in blocks of two or four patients. A standardized surgical approach, modeled on the Polin technique,[17] was used. This approach included a large bifrontotemporoparietal craniectomy with bilateral dural opening to maximize the reduction in intracranial pressure[13,14] (for details, see the Supplementary Appendix, available at NEJM.org). The sagittal sinus and falx cerebri were not divided. After craniectomy, the excised bone was stored at −70°C or in a subcutaneous abdominal pouch, according to the standard practice of the operating surgeon. After all swelling and infection

had resolved, 2 to 3 months after craniectomy, the bone was replaced.

Standard care from the time of enrollment followed clinical practice guidelines[13] that were based on those recommended by the Brain Trauma Foundation.[8] In the two study groups, second-tier options for refractory elevation of intracranial pressure included mild hypothermia (to 35°C), the optimized use of barbiturates, or both. For patients receiving standard care, the trial protocol permitted the use of lifesaving decompressive craniectomy after a period of 72 hours had elapsed since admission.

ASSESSMENTS AND DATA COLLECTION

Research coordinators at each institution collected the trial data. All source data were verified in every patient by monitors. At baseline, demographic and clinical characteristics were recorded from medical files. These data included the initial CT findings, which were scored with the use of the Marshall criteria, and the Injury Severity Score (on a scale ranging from 0 to 75, with higher scores indicating greater injury severity). The Trauma Score–Injury Severity Score[18] (on a scale ranging from 0 to 1, with lower scores representing a lower probability of survival) was also calculated.

Hourly intracranial pressure and mean arterial pressure measurements were recorded for 12 hours before randomization and 36 hours after randomization. Also recorded were first- and second-tier therapeutic interventions and surgical complications of craniectomy and of subsequent cranioplasty (surgical reversal of the craniectomy).

OUTCOME MEASURES

Outcome measures were evaluated by telephone by three trained assessors who were unaware of study-group assignments. The original primary outcome was the proportion of patients with an unfavorable outcome, a composite of death, a vegetative state, or severe disability (a score of 1 to 4 on the Extended Glasgow Outcome Scale), as assessed with the use of a structured, validated telephone questionnaire[19-22] at 6 months after injury.[21] (The Extended Glasgow Outcome Scale ranges from 1 to 8, with lower scores indicating a poorer functional outcome.) After the interim analysis in January 2007, the primary outcome was revised to be the functional outcome at 6 months after injury on the basis of proportional odds analysis of the Extended Glasgow Outcome Scale.[19] Secondary outcomes were intracranial pressure measured hourly, the intracranial hypertension index[23] (defined as the number of end-hourly measures of intracranial pressure of more than 20 mm Hg divided by the total number of measurements, multiplied by 100), the proportion of survivors with a score of 2 to 4 on the Extended Glasgow Outcome Scale (defined as severe disability and requiring assistance in daily living activities), the numbers of days in the ICU and in the hospital, and mortality in the hospital and at 6 months.

STUDY OVERSIGHT

Funding was provided by the National Health and Medical Research Council of Australia; the Transport Accident Commission of Victoria, Australia; the Intensive Care Foundation of the Australian and New Zealand Intensive Care Society; and the Western Australian Institute for Medical Research. The funders had no role in the design of the trial protocol; in the collection, analysis, or interpretation of the trial data; or in the writing of the manuscript. The members of the executive committee attest that the trial was performed in accordance with the protocol, including revision of the primary outcome measure as described above, and vouch for the accuracy and completeness of the reported data.

STATISTICAL ANALYSIS

The trial was originally designed to identify an increase in the proportion of favorable outcomes (defined as a score of 5 to 8 on the Extended Glasgow Outcome Scale) from 30% among patients receiving standard care to 50% among patients undergoing craniectomy, with a two-sided type I error of 0.05 and a power of 80%[14] with a sample size of 210 patients. (This design is equivalent to the identification of a reduction in the rate of unfavorable outcomes from 70% to 50%.) At the interim analysis (with the study-group assignments concealed), it was determined that if the score on the 8-grade Extended Glasgow Outcome Score were analyzed by ordinal logistic regression, 150 patients would be required to detect a between-group difference of 1.5 in the median score with a power of 80% and a two-sided type I error of 0.05. An ordinal logistic-regression analysis of the score on the Extended Glasgow Outcome Scale was then defined as the main pri-

mary outcome. To allow the trial to be completed within a reasonable time frame, the sample size was decreased to 150, with an additional enrollment of 15 patients permitted if necessary to replace patients lost to follow-up.[14] Both the original primary and final primary outcomes are reported. At the point at which enrollment reached 150 patients, no patients had been lost to follow-up, and recruitment ceased at 155 patients.

All analyses were performed according to the intention-to-treat principle. We used ordinal logistic regression for univariate between-group comparisons of scores on the Extended Glasgow Outcome Scale and logistic regression for comparisons of unfavorable outcomes. These analyses were followed by adjusted comparisons with inclusion in the regression models of the prespecified covariates[17]: age, the last Glasgow Coma Scale

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Decompressive Craniectomy (N=73)	Standard Care (N=82)	P Value†
Age — yr			0.89
Median	23.7	24.6	
Interquartile range	19.4–29.6	18.5–34.9	
Male sex — no. (%)	59 (81)	61 (74)	0.44
Systolic blood pressure — mm Hg	135.4±32.0	135.7±27.6	0.95
Glasgow Coma Scale			
Overall score‡			0.31
Median	5	6	
Interquartile range	3–7	4–7	
Motor score§			0.49
Median	3	3	
Interquartile range	1–4	1–5	
Maximum score for head injury on Abbreviated Injury Scale — no. (%)¶			0.52
3 or 4	35 (48)	44 (54)	
5	38 (52)	38 (46)	
Injury Severity Score‖			0.88
Median	33	32	
Interquartile range	25–38	24–41	
Trauma Score–Injury Severity Score **			0.46
Median	0.74	0.72	
Interquartile range	0.42–0.88	0.51–0.90	
Reactivity of pupils — no./total no. (%)			0.04
Neither pupil	19/71 (27)	10/80 (12)	
One or both pupils	52/71 (73)	70/80 (88)	
Hypotension — no. (%)	24 (33)	25 (30)	0.93
Hypoxemia — no. (%)	18 (25)	24 (29)	0.55
Traumatic subarachnoid hemorrhage — no. (%)	42 (58)	48 (59)	0.90
Cause of injury — no./total no. (%)			0.72
Motor-vehicle or motorcycle accident	45/70 (64)	55/81 (68)	
Bicycle accident	4/70 (6)	2/81 (2)	
Pedestrian accident	5/70 (7)	4/81 (5)	
Other	16/70 (23)	20/81 (25)	

Table 1. (Continued.)

Characteristic	Decompressive Craniectomy (N=73)	Standard Care (N=82)	P Value†
Time from injury to hospital — hr			0.90
Median	1.0	1.2	
Interquartile range	0.8–1.8	0.7–1.9	
Time from injury to randomization — hr			0.60
Median	35.2	34.8	
Interquartile range	23.3–52.8	25.8–45.4	
Marshall class — no. (%)††			0.39
Diffuse injury II	17 (23)	27 (33)	
Diffuse injury III or IV	53 (73)	53 (65)	
Nonevacuated mass lesion (VI)	3 (4)	2 (2)	

* Plus–minus values are means ±SD.
† All P values were calculated with the use of the chi-square test to compare proportions and the Wilcoxon rank-sum test to compare distributions.
‡ The overall score on the Glasgow Coma Scale ranges from 3 to 15, with lower scores indicating reduced levels of consciousness.
§ The motor score on the Glasgow Coma Scale ranges from 1 to 6, with lower scores indicating more limited motor response.
¶ The score for head injury on the Abbreviated Injury Scale ranges from 1 to 6, with higher scores indicating more severe injury.
‖ The Injury Severity Score ranges from 0 to 75, with higher scores indicating greater injury severity.
** The Trauma Score–Injury Severity Score ranges from 0 to 1, with lower scores indicating a lower probability of survival.
†† The Marshall classification is based on findings on computed tomography as follows: class I, diffuse injury with no visible signs; class II, diffuse injury with basal cisterns intact, a midline shift of 0 to 5 mm, and a high- or mixed-density lesion of 25 ml or less with the possibility of bone fragments or foreign bodies; class III, diffuse injury with swelling, including compressed or absent cisterns with a midline shift of 0 to 5 mm and a high- or mixed-density lesion of 25 ml or less; class IV, diffuse injury with shift, including a midline shift of more than 5 mm and a high- or mixed-density lesion of 25 ml or less; class V, surgical evacuation of a mass lesion; and class VI, a high- or mixed-density lesion of more than 25 ml that has not been surgically evacuated.

score before intubation, the Glasgow Coma Scale motor score after resuscitation, and the Marshall class.[15] A post hoc adjusted comparison included one variable (pupil reactivity) that differed significantly between groups at baseline. Cox proportional-hazards regression was used for the comparison of the numbers of days in the ICU and in the hospital. A P value of less than 0.05 was considered to indicate statistical significance. All analyses were performed with the use of Stata statistical software.

RESULTS

PATIENTS

Of 3478 patients who were assessed for trial eligibility, 155 were enrolled (Fig. 1 in the Supplementary Appendix). The first 5 patients who were enrolled in the trial participated in a pilot study,[13] and data from these patients were included in all the analyses. The most common reasons for exclusion from the trial were the presence of a cerebral mass lesion and successful control of intracranial pressure with the use of first-tier therapies. A total of 136 patients (88%) were from either Australia or New Zealand.

The patients were randomly assigned to one of the two treatment groups: 73 to undergo early decompressive craniectomy and 82 to receive standard care. Baseline characteristics of the two study groups were similar in most respects, except that fewer patients in the craniectomy group had reactive pupils (Table 1). The median age was 23.7 years in the craniectomy group and 24.6 in the standard-care group. The median intracranial pressure during the 12 hours before randomization was 20 mm Hg (interquartile range, 18 to 22) in the two groups (Fig. 1). The median

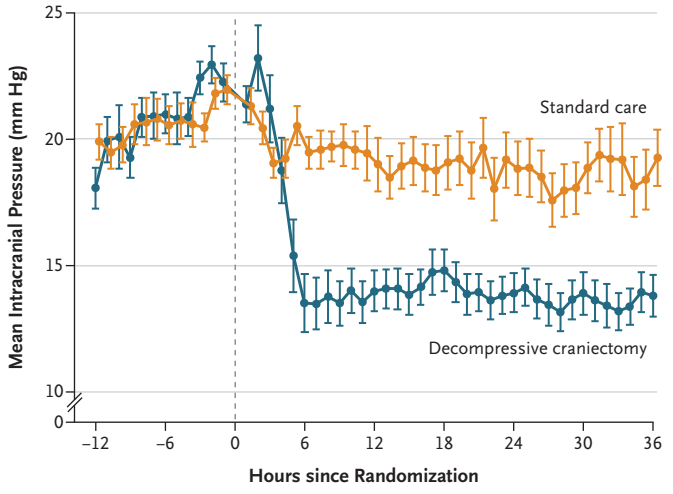

Figure 1. Intracranial Pressure before and after Randomization.

Shown are the mean measurements of intracranial pressure in the two study groups during the 12 hours before and the 36 hours after randomization. The I bars indicate standard errors.

times from injury to hospitalization and from injury to randomization were similar in the two groups (Table 1, and Table 1 in the Supplementary Appendix). Before randomization, 93% of patients in the two study groups received similar volumes of hypertonic saline, mannitol, or both for intracranial hypertension (Table 2 in the Supplementary Appendix).

The assigned trial treatment (craniectomy or standard care) was administered to 96% of all patients (Fig. 1 in the Supplementary Appendix). The median time from randomization to surgery in the craniectomy group was 2.3 hours (interquartile range, 1.4 to 3.8) (Table 1 in the Supplementary Appendix). Fifteen patients (18%) in the standard-care group underwent delayed decompressive craniectomy as a lifesaving intervention, according to the protocol. In four patients (5%) in the standard-care group, craniectomy was performed less than 72 hours after admission, contrary to the protocol.

OUTCOMES

After randomization, fewer interventions were required to decrease intracranial pressure in patients undergoing craniectomy (Table 2 in the Supplementary Appendix). Such interventions included the use of mannitol, hypertonic saline, neuromuscular blockade, venting of cerebrospinal fluid through the ventricular drain, and barbiturates. After randomization, the mean intracranial pressure was lower in the craniectomy group than in the standard-care group (14.4 mm Hg vs. 19.1 mm Hg, P<0.001) (Table 2 and Fig. 1). The median intracranial hypertension index[23] (the number of end-hourly measures of intracranial pressure of more than 20 mm Hg divided by the total number of measurements, multiplied by 100) was also lower in the craniectomy group than in the standard-care group (11.5 vs. 19.9, P<0.001) (Table 2).

Patients in the craniectomy group had a shorter duration of mechanical ventilation and a shorter stay in the ICU than patients in the standard-care group, although there was no significant between-group difference in the total time in the hospital (Table 2). A total of 37% of patients in the craniectomy group and 17% of those in the standard-care group had one or more medical or surgical complications (Table 3). Hydrocephalus was more common in the craniectomy group (10%) than in the standard-care group (1%). Cranioplasty also led to complications (Table 3 in the Supplementary Appendix).

Six months after injury, the primary outcome (functional assessment on the Extended Glasgow Outcome Scale) was worse in the craniectomy group than in the standard-care group (median score, 3 vs. 4; odds ratio for a worse functional outcome in the craniectomy group, 1.84; 95% confidence interval [CI], 1.05 to 3.24; P=0.03) (Table 2 and Fig. 2). Unfavorable outcomes occurred in 51 patients (70%) in the craniectomy group and in 42 patients (51%) in the standard-care group (odds ratio, 2.21; 95% CI, 1.14 to 4.26; P=0.02) (Table 2, and Fig. 2 in the Supplementary Appendix). After adjustment for prespecified covariates, the results were similar for the score on the Extended Glasgow Outcome Scale (adjusted odds ratio for a lower score in the craniectomy group, 1.66; 95% CI, 0.94 to 2.94; P=0.08) and for the risk of an unfavorable outcome (adjusted odds ratio, 2.31; 95% CI, 1.10 to 4.83; P=0.03). After post hoc adjustment for pupil reactivity at baseline (Table 1), the between-group differences were no longer significant for the score on the Extended Glasgow Outcome Scale (adjusted odds ratio, 1.53; 95% CI, 0.86 to 2.73; P=0.15) and for the risk of an unfavorable

Table 2. Primary and Secondary Outcomes.*

Outcome	Decompressive Craniectomy (N=73)	Standard Care (N=82)	P Value†
Intracranial pressure and cerebral perfusion pressure			
Intracranial pressure after randomization — mm Hg	14.4±6.8	19.1±8.9	<0.001
No. of hr of intracranial pressure >20 mm Hg — median (IQR)	9.2 (4.4–27.0)	30.0 (14.9–60.0)	<0.001
Intracranial hypertension index — median (IQR)‡	11.5 (5.9–20.3)	19.9 (12.5–37.8)	<0.001
Cerebral hypoperfusion index — median (IQR)§	5.7 (2.5–10.2)	8.6 (4.0–13.8)	0.03
Duration of hospital intervention			
Days of mechanical ventilation — median (IQR)	11 (8–15)	15 (12–20)	<0.001
Days of ICU stay — median (IQR)	13 (10–18)	18 (13–24)	<0.001
Days of hospitalization — median (IQR)	28 (21–62)	37 (24–44)	0.82
Extended Glasgow Outcome Scale			
Score — no. (%)			
1 (dead)	14 (19)	15 (18)	
2 (vegetative state)	9 (12)	2 (2)	
3 (lower severe disability)	18 (25)	17 (21)	
4 (upper severe disability)	10 (14)	8 (10)	
5 (lower moderate disability)	13 (18)	20 (24)	
6 (upper moderate disability)	6 (8)	13 (16)	
7 (lower good recovery)	2 (3)	4 (5)	
8 (upper good recovery)	1 (1)	3 (4)	
Median score (IQR)	3 (2–5)	4 (3–5)	0.03
Unfavorable score of 1 to 4 — no. (%)	51 (70)	42 (51)	0.02

* Plus–minus values are means ±SD. IQR denotes interquartile range.
† All P values were calculated with the use of the chi-square test to compare proportions and the Wilcoxon rank-sum test to compare distributions.
‡ The intracranial hypertension index is the number of end-hourly measures of intracranial pressure of more than 20 mm Hg divided by the total number of measurements, multiplied by 100.
§ The cerebral hypoperfusion index is the number of observations of cerebral perfusion pressure of less than 60 mm Hg divided by the total number of measurements, multiplied by 100. Cerebral perfusion pressure is the mean arterial pressure minus the intracranial pressure.

outcome (adjusted odds ratio, 1.90; 95% CI, 0.95 to 3.79; P=0.07). A total of 14 patients (19%) in the craniectomy group and 15 patients (18%) in the standard-care group died. (Details about the causes of death are provided in Table 4 in the Supplementary Appendix.)

DISCUSSION

Among adults with severe diffuse traumatic brain injury and refractory intracranial hypertension in the ICU, we found that decompressive craniectomy decreased intracranial pressure, the duration of mechanical ventilation, and the time in the ICU, as compared with standard care. In the craniectomy group, the duration of the hospital stay was unchanged, and the rate of surgical complications was low. However, patients in the craniectomy group had a lower median score on the Extended Glasgow Outcome Scale and a higher risk of an unfavorable outcome (as assessed on that scale) than patients receiving standard care.

Our findings differ from those of most nonrandomized studies of decompressive craniectomy[24,25] and are contrary to our hypothesis. We had speculated that in patients with severe traumatic brain injury, decompressive craniectomy would decrease intracranial pressure, improve

Table 3. Medical and Surgical Complications.

Adverse Event	Decompressive Craniectomy (N=73)	Standard Care (N=82)
	number (percent)	
Wound infection or breakdown	5 (7)	7 (9)
Meningitis or ventriculitis	2 (3)	3 (4)
Subgaleal infection	2 (3)	3 (4)
Cerebral abscess	2 (3)	0
Cerebrospinal fluid leak	4 (5)	2 (2)
Hematoma		
Subgaleal	5 (7)	2 (2)
Subdural, extradural, or intracerebral	3 (4)	1 (1)
Cerebral infarction	1 (1)	0
Hydrocephalus	7 (10)	1 (1)
Cranioplasty revision for cosmetic defect	2 (3)	0
Pulmonary embolus	1 (1)	2 (2)
Pneumonia	0	3 (4)
Septic shock	1 (1)	2 (2)
Acute renal failure	1 (1)	1 (1)

Figure 2. Cumulative Proportions of Results on the Extended Glasgow Outcome Scale.

In this study, an unfavorable outcome was defined as a composite of death, vegetative state, or severe disability, corresponding to a score of 1 to 4 on the Extended Glasgow Outcome Scale, as indicated by the vertical line. According to this measure, an unfavorable outcome occurred in 70% of patients in the craniectomy group and 51% of those in the standard-care group (P=0.02). The cumulative proportion is the percentage of all scores that are lower than the given score.

functional outcomes, and decrease the proportion of survivors with severe disability. Despite the positive clinical signs in the ICU, decompressive craniectomy instead increased the likelihood of a poor outcome.

It is unlikely that our findings were due to an increased rate of survival of severely injured patients in a vegetative state (grade 2 on the Extended Glasgow Outcome Scale), because even though the number of such patients increased after craniectomy, the rates of death were similar in the two study groups. Decompressive craniectomy instead shifted survivors from a favorable outcome to an unfavorable outcome (i.e., dependence on assistance to complete activities of daily living). One possible explanation is that craniectomy allowed expansion of the swollen brain outside the skull and caused axonal stretch,[26,27] which in vitro causes neural injury.[28-30] Alterations in cerebral blood flow and metabolism may also be relevant.[31,32]

Another possible explanation for the inferior outcomes with craniectomy concerns the characteristics of the surgical procedure. Some surgeons prefer a unilateral procedure, with studies (in retrospective, nonrandomized series with mixed causes of brain injury) suggesting that the bilateral approach may have more complications.[33] Some surgeons divide the sagittal sinus and falx cerebri, which is a component of the original Polin procedure,[17] but others do not. Complications are possible with both alternatives. The results of this trial can be said to apply only to the specific craniectomy procedure that was performed; they may not necessarily apply to other approaches or in other types of brain injury.

Craniectomy or cranioplasty may also have had other harmful complications, including hydrocephalus. However, complications occurred at rates that were lower than those that have been reported previously,[34,35] and the rates of most complications were similar in the two study groups.

Some limitations of our trial should be noted. First, because we were evaluating a neurosurgical procedure, the medical and surgical teams were obviously aware of study-group assignments, although the assessors were not. Second, one center recruited more than one third of trial participants. Third, there were imbalances in some baseline characteristics of the patients, particularly the proportion of patients without pupil

reactivity at hospital admission. However, even after post hoc adjustment for this variable, the overall effect size did not change, although the harmful effect of craniectomy was no longer significant. A beneficial effect of craniectomy was excluded. Finally, as noted above, we revised the primary outcome measure during the course of the trial, though with preservation of blinded study-group assignments. Such a change in protocol is not optimal from the standpoint of trial design, although ultimately, the same results were observed for both the original primary outcome measure and the final primary outcome measure.

Decompressive craniectomy is increasingly performed in many neurotrauma centers internationally.[10] To our knowledge, there are very few data from randomized, controlled trials comparing a neurosurgical procedure with standard care in adults with traumatic brain injury,[10] and our unexpected findings underscore the critical importance of conducting such trials to test common therapies, particularly in patients with complex critical illnesses.

In conclusion, in patients with severe diffuse traumatic brain injury and increased intracranial pressure that was refractory to first-tier therapies, the use of craniectomy, as compared with standard care, decreased the mean intracranial pressure and the duration of both ventilatory support and the ICU stay but was associated with a significantly worse outcome at 6 months, as measured by the score on the Extended Glasgow Outcome Scale.

Supported by grants from the National Health and Medical Research Council of Australia (NHMRC 314502), the Transport Accident Commission of Victoria (Victorian Trauma Foundation and Victorian Neurotrauma Initiative), the Intensive Care Foundation (Australia), and the Western Australian Institute for Medical Research.

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

REFERENCES

1. Myburgh JA, Cooper DJ, Finfer SR, et al. Epidemiology and 12-month outcomes from traumatic brain injury in Australia and New Zealand. J Trauma 2008;64:854-62.
2. Murray GD, Teasdale GM, Braakman R, et al. The European Brain Injury Consortium survey of head injuries. Acta Neurochir (Wien) 1999;141:223-36.
3. 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.
4. Population clock, 2011. Canberra, ACT: Australian Bureau of Statistics. (http://www.abs.gov.au/ausstats/abs@.nsf/94713ad445ff1425ca25682000192af2/1647509ef7e25faaca2568a900154b63?OpenDocument.)
5. The Victorian Neurotrauma Initiative. The economic cost of spinal cord injury and traumatic brain injury in Australia. Canberra, ACT, Australia: Access Economics, 2009. (http://www.accesseconomics.com.au/publicationsreports/showreport.php?id=209.)
6. Maas AI, Roozenbeek B, Manley GT. Clinical trials in traumatic brain injury: past experience and current developments. Neurotherapeutics 2010;7:115-26.
7. Bullock AR, Chesnut R, Ghajar J, et al. Introduction: surgical management of traumatic brain injury. Neurosurgery 2006;58:Suppl 3:S2-1–S2-3.
8. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. VII. Intracranial pressure thresholds. J Neurotrauma 2007;24:Suppl 1:S55-S58.
9. Chesnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. J Trauma 1993;34:216-22.
10. Sahuquillo J, Arikan F. Decompressive craniectomy for the treatment of refractory high intracranial pressure in traumatic brain injury. Cochrane Database Syst Rev 2006;1:CD003983 (updated May 2008).
11. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. J Neurotrauma 2007;24:Suppl 1:S14-S44.
12. Menon DK. Cerebral protection in severe brain injury: physiological determinants of outcome and their optimisation. Br Med Bull 1999;55:226-58.
13. Cooper DJ, Rosenfeld JV, Murray L, et al. Early decompressive craniectomy for patients with severe traumatic brain injury and refractory intracranial hypertension — a pilot randomized trial. J Crit Care 2008;23:387-93.
14. The DECRA (DECompressive CRAniectomy trial) protocol, 2007. (http://www.decra.org.au/protocol/multi-centre_%20protocol%20v29_Jul07.pdf.)
15. Marshall LF, Marshall MD, Bowers Marshall S, Klauber MR, van Berkum Clark M. A new classification of head injury based on computerized tomography. J Neurosurg 1991;75:Suppl:S14-S19.
16. Maas AI, Steyerberg EW, Marmarou A, et al. IMPACT recommendations for improving the design and analysis of clinical trials in moderate to severe traumatic brain injury. Neurotherapeutics 2010;7:127-34.
17. Polin RS, Shaffrey ME, Bogaev CA, et al. Decompressive bifrontal craniectomy in the treatment of severe refractory posttraumatic cerebral edema. Neurosurgery 1997;41:84-92.
18. Boyd CR, Tolson MA, Copes WS. Evaluating trauma care: the TRISS method: Trauma Score and the Injury Severity Score. J Trauma 1987;27:370-8.
19. Teasdale GM, Pettigrew LEL, Wilson JT, Murray G, Jennett B. Analyzing outcome of treatment of severe head injury: a review and update on advancing the use of the Glasgow Outcome Scale. J Neurotrauma 1998;15:587-97.
20. Pettigrew LE, Wilson JT, Teasdale GM. Assessing disability after head injury: improved use of the Glasgow Outcome Scale. J Neurosurg 1998;89:939-43.
21. *Idem*. Reliability of ratings on the Glasgow Outcome Scale from in-person and telephone structured interviews. J Head Trauma Rehabil 2003;18:252-8.
22. Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. J Neurotrauma 1998;15:573-85.
23. Venkatesh B, Garrett P, Fraenkel DJ, Purdie D. Indices to quantify changes in intracranial and cerebral perfusion pressure by assessing agreement between hourly and semi-continuous recordings. Intensive Care Med 2004;30:510-3.
24. Whitfield PC, Patel H, Hutchinson PJ, et al. Bifrontal decompressive craniectomy in the management of posttraumatic intracranial hypertension. Br J Neurosurg 2001;15:500-7.

25. Aarabi B, Hesdorffer DC, Ahn ES, Aresco C, Scalea TM, Eisenberg HM. Outcome following decompressive craniectomy for malignant swelling due to severe head injury. J Neurosurg 2006;104:469-79.
26. Cooper PR, Hagler H, Clark WK, Barnett P. Enhancement of experimental cerebral edema after decompressive craniectomy: implications for the management of severe head injuries. Neurosurgery 1979; 4:296-300.
27. Stiver SI. Complications of decompressive craniectomy for traumatic brain injury. Neurosurg Focus 2009;26(6):E7.
28. Chung RS, Staal JA, McCormack GH, et al. Mild axonal stretch injury in vitro induces a progressive series of neurofilament alterations ultimately leading to delayed axotomy. J Neurotrauma 2005;22: 1081-91.
29. Staal JA, Dickson TC, Gasperini R, Liu Y, Foa L, Vickers JC. Initial calcium release from intracellular stores followed by calcium dysregulation is linked to secondary axotomy following transient axonal stretch injury. J Neurochem 2010;112: 1147-55.
30. Tang-Schomer MD, Patel AR, Baas PW, Smith DH. Mechanical breaking of microtubules in axons during dynamic stretch injury underlies delayed elasticity, microtubule disassembly, and axon degeneration. FASEB J 2010;24:1401-10.
31. Timofeev I, Czosnyka M, Nortje J, et al. Effect of decompressive craniectomy on intracranial pressure and cerebrospinal compensation following traumatic brain injury. J Neurosurg 2008;108:66-73.
32. Soustiel JF, Sviri GE, Mahamid E, Shik V, Abeshaus S, Zaaroor M. Cerebral blood flow and metabolism following decompressive craniectomy for control of increased intracranial pressure. Neurosurgery 2010;67:65-72.
33. Gooch MR, Gin GE, Kenning TJ, German JW. Complications of cranioplasty following decompressive craniectomy: analysis of 62 cases. Neurosurg Focus 2009;26(6):E9.
34. Yang XF, Wen L, Shen F, et al. Surgical complications secondary to decompressive craniectomy in patients with a head injury: a series of 108 consecutive cases. Acta Neurochir (Wien) 2008;150:1241-7.
35. Honeybul S. Complications of decompressive craniectomy for head injury. J Clin Neurosci 2010;17:430-5.