EDITORIAL

Clinical Value of Decompressive Craniectomy

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Patients with a variety of intracranial disorders — including traumatic brain injury, stroke, subarachnoid hemorrhage, intracerebral hemorrhage, and brain tumors — often present with a progressive increase in intracranial pressure, leading to clinical deterioration and ultimately to death. Medical therapy[1] can help to mitigate such increases in pressure, but despite the use of the best available measures, intracranial hypertension becomes life-threatening in some patients. More than a century ago, it was suggested that it might be beneficial to "decompress the brain by widely opening the skull to decrease the pressure"[2] in patients with severe traumatic brain injury. This procedure, called decompressive craniectomy, has been shown to decrease intracranial pressure, but since there is no evidence of an association with a better clinical outcome, the procedure is considered optional.[3]

In the past 15 years, the use of decompressive craniectomy has increased substantially. There has also been a tremendous increase in the number of articles that have been published on the subject, mainly retrospective reviews of a limited number of cases. A PubMed search identified 143 articles that were published on this topic for a variety of intracranial disorders in 2009 and 2010.

The list of publications is much shorter, however, when only randomized, controlled trials are considered. In the field of traumatic brain injury, the results of only one small, prospective, randomized trial have been published.[4] This trial involving 27 children showed promising results in favor of decompressive craniectomy. However, the surgical procedure that was used (bitemporal decompression without opening of the dura) is not the standard approach.

In this issue of the *Journal*, Cooper et al. report the results of the Decompressive Craniectomy (DECRA) trial,[5] which investigated the role of early decompressive craniectomy in adults with severe head injury (Glasgow Coma Scale score of 3 to 8). Patients with refractory intracranial hypertension (defined as an intracranial pressure higher than 20 mm Hg for more than 15 minutes despite medical therapy) were randomly assigned either to receive standard care or to undergo standard care plus bifrontotemporoparietal decompression craniectomy. The study showed a significant decrease in intracranial pressure in patients in the surgical group, as was expected. However, clinical outcomes, as assessed by scores on the Extended Glasgow Outcome Scale, were worse in the surgical group than in the standard-care group, a finding that went against expectations.

There are a couple of important concerns regarding this otherwise valuable study. First, most neurosurgeons and intensivists dealing with traumatic brain injury will not consider decompressive craniectomy in patients who have an intracranial pressure of around 20 mm Hg for such a short time. This aggressive approach may be justified in order to decompress the brain as soon as possible, but in patients with diffuse injury without mass lesions, physicians in many centers would use medical therapy for a longer period, leaving decompressive craniectomy as a last resort.

Second, the screening of 3478 patients over a 7-year period to enroll only 155 study patients indicates that the results of this study are limited to a restricted subpopulation of patients with traumatic brain injury. Most of the patients who

were excluded from this trial either had mass lesions (for which a different surgical approach might be appropriate) or had successful control of intracranial hypertension with medical management (thus not requiring surgical intervention at all).

An important question arising from the DECRA study is whether it is now appropriate to continue an ongoing trial of craniectomy, called the Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure (RESCUEicp; Current Controlled Trials number, ISRCTN66202560).[6] As of March 16, 2011, a total of 294 patients had been enrolled in this trial, with an enrollment goal of 400 patients. However, the design of RESCUEicp differs from that of the DECRA study in some important ways. In RESCUEicp, patients are randomly assigned either to undergo craniectomy or to receive standard care (including the use of barbiturates) when maximal medical therapy cannot control intracranial pressure, with a threshold of 25 mm Hg (rather than 20 mm Hg) for more than 1 to 12 hours (rather than 15 minutes) at any time after injury. In addition, in RESCUEicp, as compared with the DECRA study, previous evacuation of a hematoma is allowed before randomization, and the permitted surgical techniques include both bifrontal decompression and unilateral wide decompression. The primary end point is the assessment of outcome at discharge and at 6 months. Thus, because of such differences in trial design, it seems that RESCUEicp should continue.

Another important question is, How do the DECRA and RESCUEicp studies relate to the real practice of decompression in patients with traumatic brain injury? As noted above, the exclusion criteria for the DECRA study were such that the data do not apply to the majority of patients. In a multicenter study involving 729 patients with intradural mass lesions after traumatic injury,[7] we found that about one third of patients undergoing surgery for an intracranial hematoma also required a decompressive procedure. In most of these cases, the decompression was unilateral and associated with hematoma evacuation. Such patients are not considered at all in the DECRA study and are only partially included in the RESCUEicp study. We therefore probably need another study of early decompression associated with hematoma evacuation, as has been suggested previously,[8] since this procedure is a common one.

The main lesson from the DECRA study is that surgical reduction of intracranial pressure by the technique that was used by the investigators does not necessarily result in better outcomes for patients and indeed appears to worsen them in at least some circumstances. However, it is important that the procedure not be simply abandoned on the basis of these data. Rather, we must think more carefully about the risks and benefits of the decompressive craniectomy before performing the procedure and must work to define appropriate clinical settings for this procedure. In the words of Seneca the Younger, *errare humanum est, perseverare autem diabolicum* (to err is human, but to persist [in error] is diabolical).

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

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Decompressive Craniectomy in Diffuse Traumatic Brain Injury

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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.)

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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

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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)	

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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

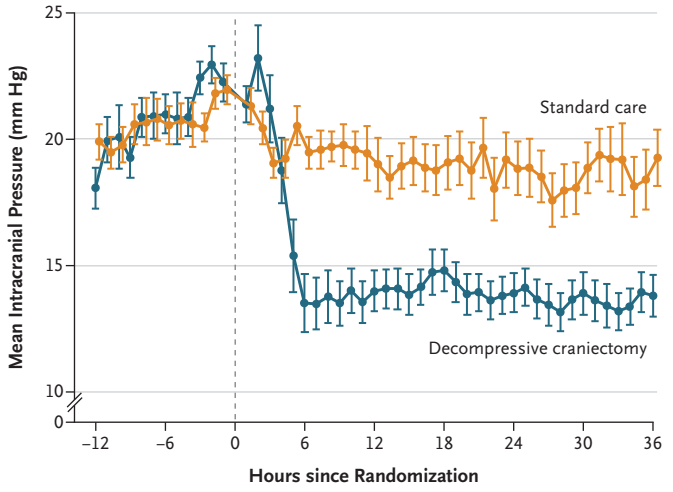

Figure 1. Intracranial Pressure before and after Randomization.

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

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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 Coma 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

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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.

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

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CORRESPONDENCE

Craniectomy in Diffuse Traumatic Brain Injury

TO THE EDITOR: On behalf of the Section on Neurotrauma and Critical Care of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons, we register our concern with the recently published article "Decompressive Craniectomy in Diffuse Traumatic Brain Injury" by Cooper et al. (April 21 issue).[1] We have identified the following problems with the trial design: first, inclusion limited to a small subset of patients with traumatic brain injury (no mass lesions); second, choice of operative technique (bifrontal procedures without division of the sagittal sinus and falx cerebri, limiting the procedural efficacy for lowering intracranial pressure)[2]; third, a long accrual time (over which major differences in treatment may have evolved); fourth, differences in study groups (significantly more patients with bilaterally unreactive pupils included in the surgical group, expected to negatively skew results)[3]; and fifth, minimal mean elevations in intracranial pressure leading up to randomization (median for both groups during the 12 hours before randomization at the upper limit of normal, 20 mm Hg).[4]

It is therefore our view that no conclusions regarding management of the use of decompressive craniectomy in patients with traumatic brain injury should be drawn from this trial, and clinical practice should not be changed on the basis of these results.

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TO THE EDITOR: Cooper et al. found that early bifrontotemporoparietal decompressive craniectomy decreases intracranial pressure and length of stay in the intensive care unit but increases the proportion of patients with an unfavorable outcome. Interestingly, this study focused exclusively on the monitoring of intracranial pressure and focused all its interventions on control of intracranial hypertension. However, there is evidence showing that even when intracranial pressure and cerebral perfusion pressure are normalized, patients with traumatic brain injury may continue to have severe cerebral hypoxia, with reduced oxygen tension in brain tissue, which may explain

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their poor outcome.[1,2] Strategies to improve cerebral oxygenation suggest the benefit of multiple approaches to monitoring for these patients.[3] In this context, the only point the Decompressive Craniectomy (DECRA) trial may demonstrate, in a select group of patients with severe traumatic brain injury, is that early bifrontotemporoparietal decompressive craniectomy may be harmful when its exclusive goal is to reduce intracranial pressure. It would be interesting to know why the investigators did not incorporate any system for the evaluation of cerebral oxygenation.

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TO THE EDITOR: The DECRA trial will probably cause consternation among neurosurgeons and neurointensivists. An important issue inadequately addressed in the trial is the role of medical management in the treatment of elevated intracranial pressure. The trial's quick-trigger criterion for the use of decompressive craniectomy (an increase in intracranial pressure of >20 mm Hg for >15 minutes in any single hour after injury, despite the use of "optimized first-tier interventions") does not give sufficient time to optimize management of intracranial pressure. First-tier protocols, including the use of sedation, maintenance of a normal carbon dioxide level, optimization of blood pressure, use of osmotherapy, and drainage of cerebrospinal fluid,[1] should be implemented in a standardized, escalated manner before proceeding to decompressive craniectomy. Advancements in critical care have led to clinically significant improvements in outcomes in traumatic brain injury.[2] Before exploring a possible niche for decompressive craniectomy in the treatment of traumatic brain injury, we first must ensure that patients receive the best available medical therapies. Moreover, new medical therapies aimed at preventing the early secondary events in patients with traumatic brain injury that cause elevated intracranial pressure (e.g., hemorrhagic transformation or contusion "blossoming")[2] should be given equal attention in future randomized, controlled trials.

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TO THE EDITOR: We read with interest the study by Cooper et al. to assess the use of decompressive craniectomy for adult patients with diffuse traumatic brain injury. However, in addition to supporting the concerns raised in the accompanying editorial,[1] we believe that this study shows that the normalization of intracranial pressure as achieved with decompressive craniectomy is probably not the key issue in managing the care of patients with traumatic brain injury whose injury is diffuse. It is indeed unfortunate that no concomitant measurements of cerebral blood flow were performed while intracranial pressure was increasing. The normalization of intracranial pressure does not mean that brain perfusion has been adequate, as has been shown with the use of severe hyperventilation.[2] Information about cerebral blood flow is readily obtained with the use of transcranial Doppler ultrasonography or a probe to monitor the oxygen tension in brain tissue at the bedside, or possibly with the use of brain perfusion computed tomography. Because brain ischemia is the key factor in determining neurologic outcome after brain injury, measurements of cerebral blood flow should be considered together with measurements of intracranial pressure in order to properly assess the value of aggressive approaches such as decompressive craniectomy in patients with traumatic brain injury.

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TO THE EDITOR: The DECRA study showed that the use of decompressive craniectomy for patients in whom intracranial hypertension develops after traumatic brain injury can ultimately have a negative effect on their functional status. The authors suggest that axonal stretch, caused by shifting brain bulk, could be responsible. Although this suggestion is plausible, it is important to consider the possibility that the release of pressure, in and of itself, may have aggravated the development of brain edema that would otherwise have been self-limiting (as suggested by Fig. 1 of the article and by the fact that mortality remained unaffected). Particularly when the response of the brain to variations in infusion pressure is impaired and the blood–brain barrier is leaky, the sudden increase in transcapillary hydrostatic pressure after decompression can promote the development of vasogenic edema.[1]

Unfortunately, there is still no good evidence that aggressive efforts to reduce intracranial pressure can improve outcome. Previous studies have shown that the use of hypothermia and barbiturates in the treatment of brain injury did not have a positive effect on outcome despite clear evidence that these interventions could effectively reduce the burden of intracranial pressure.[2,3] Craniectomy has become an example of yet another intervention that is effective in reducing intracranial pressure but not in improving outcome.

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TO THE EDITOR: The DECRA trial did not show improved outcome with craniectomy, and in particular showed no reduction in mortality despite lowering intracranial pressure. However, although intracranial pressure was lowered through decompression, intracranial pressure was not excessively high in the medical group.

Recordings of intracranial pressure after head injury show that thresholds of 25 mm Hg determine outcome.[1] Therefore, patients likely to benefit from decompression are those with uncontrollable intracranial pressure above 25 mm Hg.

The protocol for the RESCUEicp (Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure) trial differs from that of the DECRA trial in terms of intracranial pressure threshold, timing of surgery, acceptance of contusions, and duration of follow-up. The cohort profiles and criteria for entry and randomization in the two studies are therefore very different. Hence, the DECRA results should not deter recruitment into other surgical evaluation studies. As of June 30, 309 of the target of 400 patients had been recruited for the RESCUEicp trial.

We believe that other patients should be studied in trials incorporating multicenter randomization, focused imaging, and the monitoring of intensive care to increase our understanding of the pathophysiology of the brain's response to decompressive craniectomy.

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THE AUTHORS REPLY: To respond to the issues raised by Timmons et al.: First, we excluded patients with mass lesions because outcomes for these patients are different from outcomes among patients without lesions, and findings from clinical series with mixed types of traumatic brain injury have been misleading. Further investigation is required to determine the generalizability of findings from the DECRA trial to conditions other than diffuse traumatic brain injury. Second, different surgical approaches to traumatic brain injury are preferred by different neurosurgeons; there is no consensus. The DECRA procedure, a modified version of the Polin procedure,[1] significantly decreased intracranial pressure without evidence of injury caused by leaving the falx intact or by dividing it. Third, we are not aware of any major differences in the treatment of patients with traumatic brain injury that have accrued over the time frame of our study; such differences are not evident in practice guidelines.[2] Furthermore, we stratified randomization according to center and performed randomization in small blocks, such that changes in practice would have applied to both groups. Fourth, there was baseline balance between groups for the two most important prognostic factors: age and motor score on the Glasgow Coma Scale. The treatment effect was still significant after adjustment for four prespecified covariates. In accordance with the protocol, patients with fixed dilated pupils were excluded. IMPACT[3] algorithms make it clear that pupil reactivity is less important than other covariates, and the baseline imbalance was exaggerated due to missing values: after adjustment for pupils alone in all patients, those who had craniectomy had worse outcomes (odds ratio, 2.00; 95% confidence interval, 1.02 to 3.94; P=0.04). Finally, there was a rising trend in intracranial pressure to 23 mm Hg before randomization.[1] Pilot data supported the use of an application of intracranial pressure of 20 mm Hg, as recommended in the practice guidelines.[2,4] We know of no mechanism that would support the suggestion that patients might benefit from a delay in effective intracranial pressure control and acceptance of pressures greater than 20 mm Hg for longer periods before craniectomy.

Six large North American centers agreed to the DECRA protocol before deciding to participate and did not raise concerns about the design. We believe the conclusions derived from the DECRA trial should lead to practice change.

Romero asks about monitoring oxygenation of brain tissue, and Hautefeuille et al. ask about the measurement of cerebral blood flow. Although both procedures are routine in some centers, neither is a standard of care. Patients in the DECRA trial had better functional outcomes when standard care was provided (including inducement of coma with a barbiturate in 77% of patients receiving standard care) than when more effective control of intracranial pressure was provided through craniectomy. It would be interesting to see the result of a randomized trial in which the effect of intracranial-pressure monitoring itself is assessed.

Simard et al. suggest that insufficient time was allowed for the optimization of first-tier therapies. However, a tiered suite of therapies was defined, and after heavy sedation, paralysis was induced in 78% of patients, external ventricular drainage was used in 100%, and barbiturates were used in 77% before randomization. Most (86%) did not require second-tier therapies.

We agree with Cremer and Slooter that vasogenic edema may have contributed to adverse results. In addition, clinicians used fewer intracranial pressure interventions after craniectomy, whereas brain edema may have actually been increasing.

In the RESCUEicp trial, Hutchinson and Kirkpatrick use an intracranial pressure threshold of 25 mm Hg, although this threshold is not recommended in practice guidelines,[2,4] and is not used in routine practice. Their results will complement ours and are eagerly awaited.

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

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