ORIGINAL ARTICLE

Trial of Decompressive Craniectomy for Traumatic Intracranial Hypertension

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ABSTRACT

BACKGROUND

The effect of decompressive craniectomy on clinical outcomes in patients with refractory traumatic intracranial hypertension remains unclear.

METHODS

From 2004 through 2014, we randomly assigned 408 patients, 10 to 65 years of age, with traumatic brain injury and refractory elevated intracranial pressure (>25 mm Hg) to undergo decompressive craniectomy or receive ongoing medical care. The primary outcome was the rating on the Extended Glasgow Outcome Scale (GOS-E) (an 8-point scale, ranging from death to "upper good recovery" [no injury-related problems]) at 6 months. The primary-outcome measure was analyzed with an ordinal method based on the proportional-odds model. If the model was rejected, that would indicate a significant difference in the GOS-E distribution, and results would be reported descriptively.

RESULTS

The GOS-E distribution differed between the two groups (P<0.001). The proportional-odds assumption was rejected, and therefore results are reported descriptively. At 6 months, the GOS-E distributions were as follows: death, 26.9% among 201 patients in the surgical group versus 48.9% among 188 patients in the medical group; vegetative state, 8.5% versus 2.1%; lower severe disability (dependent on others for care), 21.9% versus 14.4%; upper severe disability (independent at home), 15.4% versus 8.0%; moderate disability, 23.4% versus 19.7%; and good recovery, 4.0% versus 6.9%. At 12 months, the GOS-E distributions were as follows: death, 30.4% among 194 surgical patients versus 52.0% among 179 medical patients; vegetative state, 6.2% versus 1.7%; lower severe disability, 18.0% versus 14.0%; upper severe disability, 13.4% versus 3.9%; moderate disability, 22.2% versus 20.1%; and good recovery, 9.8% versus 8.4%. Surgical patients had fewer hours than medical patients with intracranial pressure above 25 mm Hg after randomization (median, 5.0 vs. 17.0 hours; P<0.001) but had a higher rate of adverse events (16.3% vs. 9.2%, P=0.03).

CONCLUSIONS

At 6 months, decompressive craniectomy in patients with traumatic brain injury and refractory intracranial hypertension resulted in lower mortality and higher rates of vegetative state, lower severe disability, and upper severe disability than medical care. The rates of moderate disability and good recovery were similar in the two groups. (Funded by the Medical Research Council and others; RESCUEicp Current Controlled Trials number, ISRCTN66202560.)

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A Quick Take is available at NEJM.org

After traumatic brain injury (TBI), intracranial pressure can be elevated owing to a mass effect from intracranial hematomas, contusions, diffuse brain swelling, or hydrocephalus.[1] Intracranial hypertension can lead to brain ischemia by reducing the cerebral perfusion pressure.[2] Intracranial hypertension after TBI is associated with an increased risk of death in most studies.[3,4] The monitoring of intracranial pressure and the administration of interventions to lower intracranial pressure are routinely used in patients with TBI, despite the lack of level 1 evidence.[5]

Decompressive craniectomy is a surgical procedure in which a large section of the skull is removed and the underlying dura mater is opened.[6] Primary decompressive craniectomy refers to leaving a large bone flap out after the evacuation of an intracranial hematoma in the early phase after a TBI.[7,8] Cranial reconstruction is undertaken a few weeks to months later with autologous bone (the removed bone flap is stored in the patient's abdominal wall or a freezer) or an implant (titanium or other synthetic material). A secondary decompressive craniectomy is used as part of tiered therapeutic protocols that are frequently used in intensive care units (ICUs) in order to control raised intracranial pressure and to ensure adequate cerebral perfusion pressure after TBI.[7,8] For example, in the Decompressive Craniectomy (DECRA) trial,[9] patients who had an intracranial pressure of more than 20 mm Hg for more than 15 minutes (continuously or intermittently) within a 1-hour period, despite optimized first-tier interventions, were randomly assigned to early bifrontal decompressive craniectomy and standard care or to standard care alone. The authors found that decompressive craniectomy was associated with more unfavorable outcomes than standard care alone. Alternatively, craniectomy can be performed as a last-tier intervention when the intracranial pressure remains elevated despite all other measures.[10,11] We conducted the Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure (RESCUEicp) trial to assess the effectiveness of craniectomy as a last-tier intervention in patients with TBI and refractory intracranial hypertension.

METHODS

TRIAL DESIGN AND OVERSIGHT

In this international, multicenter, parallel-group, superiority, randomized trial, we compared last-tier secondary decompressive craniectomy with continued medical management for refractory intracranial hypertension after TBI. Ethics approval in the United Kingdom was obtained in 2003 from the Cambridgeshire 4 research ethics committee (formerly known as the Eastern multicenter research ethics committee); ethics committees at all other participating institutions also approved the trial.

Because the trial enrolled patients with severe TBI, written informed consent was obtained from the nearest relative or a person who had been designated to give consent on admission of the patient. An independent steering committee and an independent data monitoring and ethics committee reviewed the trial regularly to assess conduct, progress, and safety.

The trial protocol, available with the full text of this article at NEJM.org, was designed in a collaborative fashion by the Divisions of Neurosurgery and Anaesthesia at the University of Cambridge, collaborating clinicians, and the European Brain Injury Consortium. Full details of the protocol have been published previously.[11] The investigators vouch for the completeness and accuracy of the data and the analyses and for the fidelity of this report to the trial protocol and the statistical analysis plan.

PARTICIPANTS AND TRIAL SITES

To undergo randomization in the trial, patients had to be between 10 and 65 years of age, have a TBI with an abnormal computed tomographic (CT) scan of the brain, have an intracranial-pressure monitor already in place, and have raised intracranial pressure (>25 mm Hg for 1 to 12 hours, despite stage 1 and 2 measures, as defined below and in Fig. 1). Patients who had undergone an immediate operation for evacuation of an intracranial hematoma could be included as long as the operation was not a craniectomy (i.e., the bone flap was replaced at the end of procedure). Patients with bilateral fixed and dilated pupils, bleeding diathesis, or an injury that was deemed to be unsurvivable were excluded. Trial sites were hospitals that provide acute neurosciences care for patients with severe TBI and that have 24-hour neurosurgical services (see the Supplementary Appendix, available at NEJM.org).

INTERVENTIONS AND RANDOMIZATION

Patients were treated in ICUs according to a protocol that was aimed at maintaining an intracra-

nial pressure of 25 mm Hg or less by applying treatments in a stepwise manner (Fig. 1). The initial stage (stage 1) included sedation, analgesia, and head elevation; neuromuscular paralysis was optional. Other targets included a cerebral perfusion pressure (the difference between the mean blood pressure and intracranial pressure) of more than 60 mm Hg, normothermia, normoglycemia, mild hypocapnia (partial pressure of arterial carbon dioxide [$PaCO_2$], 4.5 to 5.0 kPa [34 to 38 mm Hg]), and adequate oxygenation (oxygen saturation, >97%). If the intracranial pressure was not controlled, stage 2 options included ventriculostomy (if an external ventricular drain had not already been inserted for intracranial-pressure monitoring), pharmacologic blood-pressure augmentation, osmotherapy, moderate hypocapnia ($PaCO_2$, 4.0 to 4.5 kPa [30 to 34 mm Hg]), and therapeutic hypothermia (not <34°C).

If the intracranial pressure remained above 25 mm Hg for 1 to 12 hours despite these measures, then at stage 3 of the protocol, patients were randomly assigned to undergo decompressive craniectomy with medical therapy or to receive continued medical therapy with the option of adding barbiturates to reduce the intracranial pressure. Patients underwent randomization, in a 1:1 ratio, with the use of permuted blocks of random sizes and with stratification according to trial site. To ensure concealment, the block sizes were not disclosed. Participants underwent randomization with the use of a central telephone randomization service. Concealment of the trial-group assignments was ensured, because the service did not release the randomization code until the patient had reached stage 3 of the protocol.

The surgical treatment was either large unilateral frontotemporoparietal craniectomy (hemicraniectomy), which was recommended for patients with unilateral hemispheric swelling, or bifrontal craniectomy, which was recommended for patients with diffuse brain swelling that affected both hemispheres on imaging studies. The exact type of craniectomy was left to the discretion of the surgeons. Details of the recommended surgical technique are provided in the protocol. In addition, it was recommended that surgery should be performed no later than 4 to 6 hours after randomization.

Patients who were assigned to receive medical treatment alone could undergo a decompressive craniectomy later in case their condition deteriorated further, at the discretion of treating clinicians. Similarly, patients who were assigned to undergo decompressive craniectomy could have barbiturate infusion in case of further deterioration of their condition.

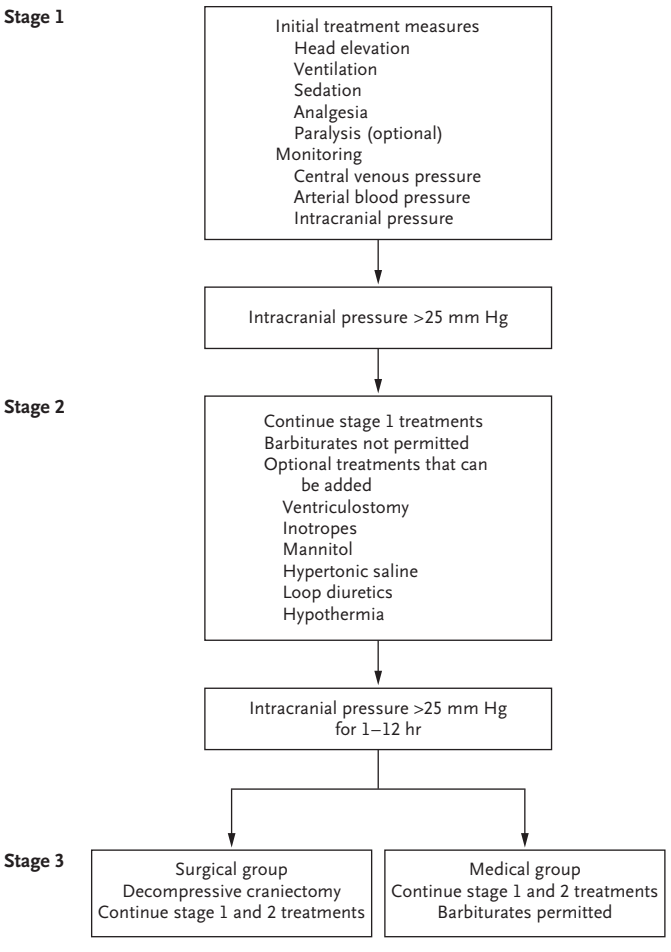

Figure 1. Stages of Therapeutic Management.
Agreement for participation was obtained from the nearest relative or a person who had been designated to give consent preemptively on admission of the patient in order to avoid delays in treatment. Randomization was performed after stage 2 if the intracranial pressure was more than 25 mm Hg for 1 to 12 hours. The protocol stages 1 and 2 reflected the therapeutic protocols that were followed in the participating units.

OUTCOMES

The primary-outcome measure was assessed with the use of the Extended Glasgow Outcome Scale (GOS-E) at 6 months after randomization.[12] The GOS-E is a global outcome scale assessing functional independence, work, social and leisure activities, and personal relationships. Its eight outcome categories are as follows: death, vegetative state (unable to obey commands), lower se-

vere disability (dependent on others for care), upper severe disability (independent at home), lower moderate disability (independent at home and outside the home but with some physical or mental disability), upper moderate disability (independent at home and outside the home but with some physical or mental disability, with less disruption than lower moderate disability), lower good recovery (able to resume normal activities with some injury-related problems), and upper good recovery (no problems). Details are provided in the Supplementary Appendix.

In the United Kingdom, the trial office in Cambridge mailed the GOS-E questionnaires to surviving participants. If no response was received, a trial team member contacted the patient or a caregiver by telephone to complete the questionnaire. At international sites, local staff were responsible for the above processes. Two trial team investigators, who were unaware of the trial-group assignments, centrally adjudicated outcomes on the basis of the GOS-E questionnaires independently of each other according to a standardized approach.[13] Disagreements were resolved by consensus between them or with the consultation of a third trial team investigator who was also unaware of the trial-group assignments.

The secondary outcomes were the following: GOS-E results at 12 and 24 months after randomization; mortality at 6, 12, and 24 months after randomization; quality of life at 6, 12, and 24 months after randomization; Glasgow Coma Scale (GCS) score at discharge from the neurosciences hospital; assessment of intracranial-pressure control; time in the ICU; time to discharge from the neurosciences hospital; and economic evaluation. Quality of life was assessed with the 36-item Short-Form Health Survey in adults and the 10-item Short-Form Health Survey in children. Assessment of intracranial-pressure control included the mean intracranial pressure in the period after randomization, the number of hours with the intracranial pressure above 25 mm Hg in the period after randomization, the intracranial hypertension index 20 (the number of end-hourly measures of intracranial pressure of >20 mm Hg divided by the total number of measurements, multiplied by 100), the intracranial hypertension index 25 (the number of end-hourly measures of intracranial pressure of >25 mm Hg divided by the total number of measurements, multiplied by 100), and the cerebral hypoperfusion index (the number of end-hourly measures of cerebral perfusion pressure of <60 mm Hg divided by the total number of measurements, multiplied by 100). Data on complications and serious adverse events were also collected.

STATISTICAL ANALYSIS

We calculated that a target sample of 400 patients would allow us to detect a treatment effect of 15 percentage points between the two groups (difference in favorable-outcome rate of 45% vs. 60%; see the definition of favorable outcome later in this section) with 80% power at the 5% significance level (two-sided), allowing for a loss to follow-up of up to 15%.[11] The analysis was performed according to a statistical analysis plan, which was agreed on without reference to the unblinded data (see the protocol).[14]

Outcomes were reported in the intention-to-treat population, which was modified to exclude patients who were lost to follow-up or who withdrew consent. Missing outcome data were not imputed. As prespecified in the statistical analysis plan, a sensitivity analysis was performed for the primary-outcome measure in the per-protocol population. The per-protocol population was defined as the patients in the intention-to-treat population who did not have a severe breach of protocol.

The primary-outcome measure was analyzed with an ordinal analysis method that was based on the proportional-odds model.[15] The goodness of fit of the unadjusted proportional-odds models was tested with the use of a likelihood-ratio test. The rejection of the proportional-odds model at the 5% significance level indicated a difference in the GOS-E distribution between the two randomized groups. In this situation, the presentation of the results was prespecified to describe the difference in outcomes between the groups, and the groups were compared formally with the use of an unordered chi-square test. For the primary analysis, the GOS-E categories of upper good recovery and lower good recovery were pooled, since a blinded review of the distribution of GOS-E ratings revealed that there were too few patients in these categories for them to be analyzed separately.

In a prespecified sensitivity analysis, we compared the proportion of patients who had an outcome of upper severe disability or better on the GOS-E scale ("favorable outcome") between the

randomized groups, using a chi-square test. Conventionally, the GOS-E scale is dichotomized so that upper severe disability is categorized as being an unfavorable outcome, together with vegetative state and lower severe disability. Patients who are in the category of upper severe disability are largely independent around their homes but need assistance with traveling or shopping, whereas patients who are in the category of lower severe disability live in a supervised facility (care facility) or, if at home, need assistance most of the time. In view of the anticipated high proportion of poor outcomes in this trial population, it was agreed a priori by the trial team and the steering committee that the upper-severe-disability category would be included in the definition of favorable outcome. A similar approach has been followed in some trials of craniectomy for middle-cerebral-artery infarction, in which moderately severe disability (modified Rankin scale score, 4 [unable to walk without assistance and unable to attend to own bodily needs without assistance]) was categorized as a favorable outcome, although most stroke trials conventionally categorize it as unfavorable.[16,17]

Prespecified exploratory analyses examined the effect of covariate adjustment (age, GCS motor score, pupillary reactivity, and the Marshall grade of the last available prerandomization CT of the brain) on the analyses described above. The duration of ICU stay was analyzed with the use of Kaplan–Meier estimates and log-rank tests. The time to discharge from the neurosciences hospital and the GCS score at discharge from the neurosciences hospital were not analyzed because the data were not collected. Instead, the GCS score at the time of discharge from the ICU was available and was analyzed with the use of the same ordinal method as described above for the GOS-E. All other analyses of categorical data were based on chi-square tests, and analyses of continuous variables were based on Mann–Whitney U tests. The GOS-E ratings at 24 months, quality-of-life data, and the planned economic evaluation have not yet been analyzed.

RESULTS

RECRUITMENT AND CHARACTERISTICS OF THE PATIENTS

The first patient was enrolled in January 2004, and the trial was closed to recruitment in March 2014, when the intended sample size was reached. A total of 2008 patients were assessed for trial eligibility, and 409 patients at 52 centers in 20 countries underwent randomization; of these patients, 291 (71.1%) were recruited in the United Kingdom. One patient underwent randomization twice in error, therefore leaving 408 patients. Of these patients, 206 were assigned to the surgical group and 202 to the medical group (see the Supplementary Appendix). Five patients were excluded from the analysis owing to withdrawal of consent, and 5 were excluded owing to a lack of valid informed consent, leaving 202 patients in the surgical group and 196 in the medical group. Of the 398 remaining patients, 389 were evaluated for the primary outcome (201 patients in the surgical group and 188 in the medical group), and 373 were evaluated at 12 months (194 in the surgical group, and 179 in the medical group). The characteristics of the two groups were similar at baseline, except that fewer patients in the surgery group than in the medical group had a history of drug or alcohol abuse (Table 1).

INTERVENTIONS

Similar numbers of patients in the two groups received stage 1 and stage 2 treatments that had been designated as optional (Table 2). No significant between-group differences were observed in the rate of craniotomies performed before randomization or in the type of evacuated hematomas.

In the surgical group, 92.6% of the patients underwent decompressive craniectomy (Table 2). The median time from randomization to craniectomy was 2.2 hours.

In the medical group, 87.2% of the patients received a barbiturate infusion (Table 2). The median time from randomization to barbiturate infusion was 1.5 hours. The median duration of barbiturate therapy was 53 hours. Decompressive craniectomy was performed in 37.2% of the patients in the medical group. (See Tables S3 and S8 in the Supplementary Appendix.)

OUTCOMES

Primary Outcome

In a modified intention-to-treat analysis, the prespecified ordinal regression showed evidence of a difference in the 6-month GOS-E distribution between the two groups ($\chi^2 = 7.72$, 1 df, $P = 0.005$). However, the goodness-of-fit test rejected the proportional-odds assumption that underlies the

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Surgical Group (N = 202)	Medical Group (N = 196)
Age — yr	32.3±13.2	34.8±13.7
Male sex — no./total no. (%)	165/202 (81.7)	156/195 (80.0)
GCS motor score at first hospital — no./total no. (%)†		
1 or 2	96/181 (53.0)	85/170 (50.0)
3–6	85/181 (47.0)	85/170 (50.0)
Pupillary abnormality — no. (%)‡	59 (29.2)	57 (29.1)
Hypotension — no. (%)§	40 (19.8)	42 (21.4)
Hypoxemia — no. (%)¶	49 (24.3)	52 (26.5)
History of drug or alcohol abuse — no. (%)	50 (24.8)	69 (35.2)
Extracranial injury — no. (%)	75 (37.1)	83 (42.3)
Injury classification on basis of CT imaging — no./total no. (%)‖		
Diffuse injury	161/198 (81.3)	141/186 (75.8)
Mass lesion	37/198 (18.7)	45/186 (24.2)

* Plus–minus values are means ±SD. There were no significant between-group differences in these baseline characteristics except for history of drug or alcohol abuse (P = 0.02). Additional baseline data are provided in Tables S1, S2, and S4 through S7 in the Supplementary Appendix.
† A Glasgow Coma Scale (GCS) motor score of 1 indicates that the patient makes no movements to painful stimuli, 2 has extension, 3 has abnormal flexion, 4 has normal flexion, 5 localizes to painful stimuli, and 6 obeys commands.
‡ Pupil abnormality was defined as the presence of unreactive pupils or anisocoria.
§ Hypotension was defined as a systolic blood pressure of less than 90 mm Hg.
¶ Hypoxemia was defined as a partial pressure of arterial oxygen of less than 8 kPa (60 mm Hg).
‖ Injury classification was determined on the basis of the Marshall classification of the prerandomization CT image of the head (Table S5 in the Supplementary Appendix). If the prerandomization CT image of the head was not available, the classification was done on the basis of the Marshall classification of the initial CT of the head, taking into account whether a craniotomy for evacuation of a mass lesion had occurred before randomization.

ordinal regression analysis (χ^2=22.86, 5 df, P<0.001). Therefore, the common odds ratio could not be used to describe the direction and magnitude of the treatment effect that was observed with the ordinal regression. Hence, as prespecified, the remaining analyses aimed to describe the way in which the distribution of GOS-E ratings differed between the two randomized groups. The unordered test comparing the distribution of the GOS-E ratings over the two groups yielded a χ^2 of 30.69 (7 df, P<0.001).

At 6 months after randomization, the GOS-E distributions were as follows: death, 26.9% among 201 patients in the surgical group and 48.9% among 188 patients in the medical group; vegetative state, 8.5% versus 2.1%; lower severe disability (dependent on others for care), 21.9% versus 14.4%; upper severe disability (independent at home), 15.4% versus 8.0%; moderate disability, 23.4% versus 19.7%; and good recovery, 4.0% versus 6.9% (Table 3 and Fig. 2). In a prespecified sensitivity analysis, favorable outcomes (prespecified as upper severe disability or better on the GOS-E) occurred in 42.8% of the patients in the surgical group and in 34.6% of those in the medical group (P=0.12) (Fig. S1 in the Supplementary Appendix). Using the absolute differences presented in Table 3, we estimated that for every 100 patients treated with surgical rather than medical intent, there were 22 more survivors; of these 22 patients, 6 were in a vegetative state (27%), 8 were categorized as having lower severe disability (36%), and 8 were categorized as having upper severe disability or better (36%).

Secondary Outcomes

At 12 months after randomization, the GOS-E distributions were as follows: death, 30.4% among 194 patients in the surgical group versus 52.0% among 179 patients in the medical group; vegetative state, 6.2% versus 1.7%; lower severe disability, 18.0% versus 14.0%; upper severe disability, 13.4% versus 3.9%; moderate disability, 22.2% versus 20.1%; and good recovery, 9.8% versus 8.4%

Table 2. Treatments and Interventions.*

Treatment or Intervention	Surgical Group (N = 202)	Medical Group (N = 196)
Craniotomy for evacuation of hematoma — no. (%)	26 (12.9)	30 (15.3)
Ventriculostomy — no. (%)	34 (16.8)	43 (21.9)
Neuromuscular paralysis — no. (%)	101 (50.0)	103 (52.6)
Pharmacologic blood-pressure augmentation — no. (%)	112 (55.4)	116 (59.2)
Osmotherapy — no. (%)	146 (72.3)	144 (73.5)
Therapeutic hypothermia — no. (%)	47 (23.3)	53 (27.0)
Decompressive craniectomy — no. (%)†	187 (92.6)	73 (37.2)
Bifrontal — no./total no. (%)	109/173 (63.0)	NA
Unilateral — no./total no. (%)	64/173 (37.0)	NA
Barbiturates — no. (%)‡	19 (9.4)	171 (87.2)

* There were no significant between-group differences with respect to therapeutic interventions administered before randomization. Decompressive craniectomy and barbiturates were administered only in the period after randomization. NA denotes not applicable.

† The reasons for not performing decompressive craniectomy were further deterioration of the patient, control of intracranial pressure while waiting for surgery, uncorrected coagulopathy, and massive epistaxis on positioning of the patient. The type of decompressive craniectomy was unknown in 14 patients in the surgical group. Information on decompressive craniectomy was only collected in the surgical group.

‡ The median duration of barbiturate therapy in the medical group was 53 hours (interquartile range, 24.5 to 115). Data on the duration of therapy were available for 122 patients.

(Table 3 and Fig. 2). In a prespecified sensitivity analysis, favorable outcomes (upper severe disability or better) occurred in 45.4% of the patients in the surgical group, as compared with 32.4% of those in the medical group (P=0.01). Using the absolute differences presented in Table 3, we estimated that for every 100 patients treated with surgical rather than medical intent, there were 22 more survivors; of these 22 patients, 5 were in a vegetative state (23%), 4 were categorized as having lower severe disability (18%), and 13 were categorized as having upper severe disability or better (59%). Adjustment of the GOS-E ratings at 6 months and at 12 months for the prespecified covariates did not alter the results. (Details are provided in Fig. S2 and Tables S12 and S16 in the Supplementary Appendix.)

Similar to the GOS-E results at 6 months, the goodness-of-fit test rejected the proportional-odds assumption in analyses of the GCS scores (χ^2=10.79, 3 df, P=0.01); descriptive results are shown in Table 3. Control of intracranial pressure was better in the surgical group than in the medical group, as shown by the significant differences in the five relevant prespecified measures (Table 3). There was no between-group difference in the median values of time to discharge (including death) in the ICU. A time-to-event analysis of length of stay, with follow-up data censored at death for patients who died in the ICU, showed that the median time to discharge among survivors was 15.0 days in the surgical group, as compared with 20.8 days in the medical group (P=0.01). Adverse events were reported in 16.3% of the patients in the surgical group, as compared with 9.2% of those in the medical group (P=0.03). (Details are provided in Tables S9, S10, S17, and S18 in the Supplementary Appendix.)

Four patients had a severe breach of protocol (intracranial pressure not monitored before randomization in one patient in the surgical group, age outside the upper cutoff in two [one patient in each group], and uncorrected bleeding diathesis in one in the surgical group) and were not included in the per-protocol population. The per-protocol analysis of the GOS-E results at 6 months did not alter the findings that were observed in the modified intention-to-treat analysis. A post hoc sensitivity analysis of the worst-case scenario for mortality at 6 months did not alter the results. In a further sensitivity analysis, results were explored for six a priori subgroups. (See Tables S13, S14, and S15 in the Supplementary Appendix.)

Table 3. Analysis of Primary and Secondary Outcomes.*

Variable	Surgical Group (N = 202)	Medical Group (N = 196)	Absolute Difference (95% CI)†	P Value
			percentage points	
GOS-E result — no./total no. (%)‡				<0.001
At 6 mo				
Death	54/201 (26.9)	92/188 (48.9)	−22.1 (−31.5 to −12.7)	
Vegetative state	17/201 (8.5)	4/188 (2.1)	6.3 (2.0 to 10.7)	
Lower severe disability	44/201 (21.9)	27/188 (14.4)	7.5 (−0.1 to 15.1)	
Upper severe disability	31/201 (15.4)	15/188 (8.0)	7.4 (1.1 to 13.8)	
Lower moderate disability	20/201 (10.0)	19/188 (10.1)	−0.1 (−6.1 to 5.8)	
Upper moderate disability	27/201 (13.4)	18/188 (9.6)	3.9 (−2.5 to 10.2)	
Lower good recovery	5/201 (2.5)	6/188 (3.2)	−0.7 (−4.0 to 2.6)	
Upper good recovery	3/201 (1.5)	7/188 (3.7)	−2.2 (−5.4 to 1.0)	
At 12 mo				<0.001
Death	59/194 (30.4)	93/179 (52.0)	−21.5 (−31.3 to −11.8)	
Vegetative state	12/194 (6.2)	3/179 (1.7)	4.5 (0.6 to 8.4)	
Lower severe disability	35/194 (18.0)	25/179 (14.0)	4.1 (−3.3 to 11.5)	
Upper severe disability	26/194 (13.4)	7/179 (3.9)	9.5 (3.9 to 15.1)	
Lower moderate disability	20/194 (10.3)	14/179 (7.8)	2.5 (−3.3 to 8.3)	
Upper moderate disability	23/194 (11.9)	22/179 (12.3)	−0.4 (−7.1 to 6.2)	
Lower good recovery	14/194 (7.2)	7/179 (3.9)	3.3 (−1.3 to 7.9)	
Upper good recovery	5/194 (2.6)	8/179 (4.5)	−1.9 (−5.7 to 1.9)	
GCS score or death at discharge from ICU — no./total no. (%)§				<0.001
Death	42/185 (22.7)	83/171 (48.5)	−25.8 (−35.5 to −16.2)	
GCS score				
3–5	13/185 (7.0)	11/171 (6.4)	0.6 (−4.6 to 5.8)	
6–8	22/185 (11.9)	10/171 (5.8)	6.0 (0.2 to 11.9)	
9–12	67/185 (36.2)	37/171 (21.6)	14.6 (5.3 to 23.9)	
13–15	41/185 (22.2)	30/171 (17.5)	4.6 (−3.6 to 12.9)	
Intracranial-pressure control¶				
Median mean intracranial pressure after randomization (IQR) — mm Hg	14.5 (1.7–18.0)	17.1 (4.2–21.8)	−3.0 (−4.1 to −1.8)	<0.001
Median duration of intracranial pressure >25 mm Hg after randomization (IQR) — hr	5.0 (0.0–17.0)	17.0 (5.0–35.0)	−8.0 (−12.0 to −5.0)	<0.001
Median intracranial hypertension index 20 (IQR)	18.1 (9.9–36.7)	31.4 (18.2–54.2)	−10.4 (−14.5 to −6.7)	<0.001
Median intracranial hypertension index 25 (IQR)	6.6 (3.1–13.6)	11.8 (5.6–27.8)	−4.2 (−6.2 to −2.5)	<0.001
Median cerebral hypoperfusion index 60 (IQR)	6.8 (3.1–16.6)	11.1 (4.4–24.8)	−2.8 (−4.9 to −1.0)	0.002

* ICU denotes intensive care unit, and IQR interquartile range.

† Absolute differences between percent values are percentage points and may not sum exactly owing to rounding. For median values, the treatment groups were compared with the use of the Mann–Whitney U test and the corresponding confidence interval. The estimated difference between the median values is not simply the observed difference between the median values.

‡ P values for the comparisons of the Extended Glasgow Outcome Scale (GOS-E) results were calculated by means of unordered chi-square tests. The eight outcome categories on the GOS-E are death, vegetative state (unable to obey commands), lower severe disability (dependent on others for care), upper severe disability (independent at home), lower moderate disability (independent at home and outside the home but with some physical or mental disability), upper moderate disability (independent at home and outside the home but with some physical or mental disability, with less disruption than lower moderate disability), lower good recovery (able to resume normal activities with some injury-related problems), and upper good recovery (no problems). See the Supplementary Appendix for additional descriptions of the outcome categories.

§ The GCS was used for assessing impairment of the level of consciousness. Scores range from 3 to 15, with lower scores indicating greater impairment. The P value was calculated by means of an unordered chi-square test.

¶ The mean intracranial pressure after randomization and the duration of intracranial pressure of more than 25 mm Hg after randomization could be calculated for 165 patients in the surgical group and for 160 in the medical group. The three indexes could be calculated for 192 patients in the surgical group and for 183 in the medical group. The intracranial hypertension index 20 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 intracranial hypertension index 25 is the number of end-hourly measures of intracranial pressure of more than 25 mm Hg divided by the total number of measurements, multiplied by 100. The cerebral hypoperfusion index 60 is the number of end-hourly measures of cerebral perfusion pressure of less than 60 mm Hg divided by the total number of measurements, multiplied by 100.

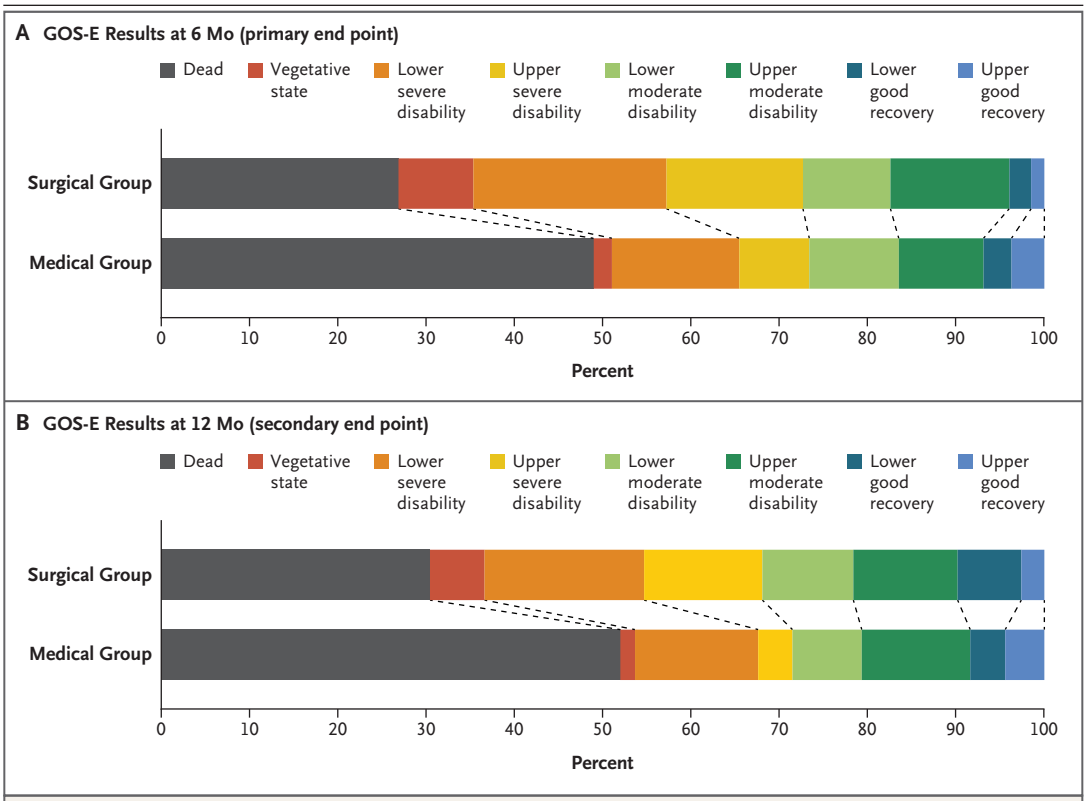

Figure 2. Stacked Bar Chart of Extended Glasgow Outcome Scale (GOS-E) Results at 6 Months and 12 Months.

The primary-outcome measure was assessed with the use of the GOS-E, a global outcome scale assessing functional independence, work, social and leisure activities, and personal relationships.[12] The eight outcome categories are death, vegetative state (unable to obey commands), lower severe disability (dependent on others for care), upper severe disability (independent at home), lower moderate disability (independent at home and outside the home but with some physical or mental disability), upper moderate disability (independent at home and outside the home but with some physical or mental disability, with less disruption than lower moderate disability), lower good recovery (able to resume normal activities with some injury-related problems), and upper good recovery (no problems). See the Supplementary Appendix for additional descriptions of the outcome categories.

DISCUSSION

In this trial involving patients with sustained and refractory intracranial hypertension after TBI, the GOS-E distributions at 6 months were as follows: death, 26.9% in the surgical group and 48.9% in the medical group; vegetative state, 8.5% versus 2.1%; lower severe disability (dependent on others for care), 21.9% versus 14.4%; upper severe disability (independent at home), 15.4% versus 8.0%; moderate disability, 23.4% versus 19.7%; and good recovery 4.0% versus 6.9%. The rate of an outcome of upper severe disability or better was 42.8% in the surgical group versus 34.6% in the medical group.

The treatment protocol of the trial was organized in three hierarchical stages, with treatment intensity increasing at every stage. All stage 2 interventions, neuromuscular paralysis (stage 1), and barbiturate infusion after randomization in the medical group were designated as optional in view of the lack of level 1 evidence regarding their efficacy at the time of trial initiation and during the conduct of the trial. This decision was in keeping with the pragmatic nature of the trial. The treatment protocol in this trial was also similar to the treatment protocol that was used in a trial of hypothermia for intracranial hypertension after TBI.[18] The numbers of patients who received the optional stage 1 and stage 2 interventions were similar in the two groups, a finding that suggests that concomitant interventions were not responsible for the observed result.

In contrast to the present trial, the DECRA

trial[9] showed that patients undergoing craniectomy had worse ratings on the GOS-E at 6 months than those receiving standard care (P=0.03), although the rates of death were similar at 6 months (19% and 18%, respectively). The DECRA trial aimed to assess the effectiveness of early craniectomy — offered as a stage 2 treatment within 72 hours after injury — for moderate intracranial hypertension (intracranial pressure, >20 mm Hg for 15 minutes within a 1-hour period [continuous or cumulative]) in patients with diffuse TBI.[9] The RESCUEicp trial aimed to assess the effectiveness of decompressive craniectomy offered as a last-tier treatment.[11] In addition, patients with intracranial hematoma (evacuated or nonevacuated) were excluded from the DECRA trial, whereas they represented almost 20% of the patients in the RESCUEicp trial. Moreover, unilateral decompressive craniectomy (hemicraniectomy) was not allowed by the protocol of the DECRA trial, whereas it was an option in the protocol of the RESCUEicp trial.

Our trial provides quantitative evidence to inform the debate around historical concerns that decompressive craniectomy simply increases the number of patients who survive in a vegetative state.[8] The survival advantage of decompressive craniectomy in this trial was translated to both dependent and independent living. Clinicians and family members will need to be aware of this issue when making decisions regarding treatment options. Improved control of intracranial pressure with surgery may have accounted for mortality that was lower than that observed with medical management, but our trial did not test this hypothesis.[4]

Some limitations of the present trial should be noted. First, the clinical teams who cared for the patients were aware of trial-group assignments. However, outcome adjudication on the basis of the GOS-E questionnaires was done at the coordinating center by personnel who were unaware of the group assignments. Second, a relatively large proportion of patients in the medical group underwent decompressive craniectomy; this situation may have diluted the observed treatment effect. Third, 10 patients were excluded from all analyses owing to withdrawal of consent or to a lack of valid consent, and 7 more patients in the medical group were lost to primary follow-up. Fourth, long-term data on cranial reconstruction — a procedure that is usually necessary a few weeks to months after decompressive craniectomy — were not systematically obtained owing to the pragmatic nature of the trial. This important aspect of treatment needs to be explored in future studies. Finally, the present trial did not examine the effectiveness of primary decompressive craniectomy, which is undertaken more frequently than secondary decompressive craniectomy.[19,20]

In conclusion, at 6 months, decompressive craniectomy for severe and refractory intracranial hypertension after TBI resulted in mortality that was 22 percentage points lower than that with medical management. Surgery also was associated with higher rates of vegetative state, lower severe disability, and upper severe disability than medical management. The rates of moderate disability and good recovery with surgery were similar to those with medical management.

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APPENDIX

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