Decompressive craniectomy or medical management for refractory intracranial hypertension: An AAST-MIT propensity score analysis

Ram Nirula, MD, MPH, D. Millar, MD, Tom Greene, PhD, Molly McFadden, MS, Lubdha Shah, MD, Thomas M. Scalea, MD, Deborah M. Stein, MD MPH, Louis J. Magnotti, MD, Gregory J. Jurkovich, MD, Gary Vercruysse, MD, Demetrios Demetriades, MD PhD, Lynette A. Scherer, MD, Andrew Peitzman, MD, Jason Sperry, MD, MPH, Kathryn Beauchamp, MD, Scott Bell, MD, Iman Feiz-Erfan, MD, Patrick O'Neill, PhD, MD, *and* **Raul Coimbra, MD, PhD,** *Salt Lake City, Utah*

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From the University of Utah (R.N., D.M., T.G., M.M., L.S.), Salt Lake City, Utah; University of Maryland Medical Center (T.M.S., D.M.S.), Baltimore, Maryland; University of Tennessee (L.J.M.), Memphis, Tennessee; University of Washington (G.J.J.), Seattle, Washington; Emory University (G.V.), Atlanta, Georgia; University of Southern California–Los Angles County Medical Center (D.D.), Los Angeles; University of California Davis (L.A.S.), Sacramento; and University of California, San Diego (R.C.), San Diego, California; University of Pittsburgh Medical Center (A.P., J.S.), Pittsburgh, Pennsylvania; University of Colorado (K.B., S.B.), Denver Health, Denver, Colorado; and Maricopa Integrated Health Systems (IF-E, P.O.), Phoenix, Arizona.

Address for reprints: Ram Nirula, MD, University of Utah, Department of Surgery, 50 North Medical Drive, Salt Lake City, UT 84132; email: r.nirula@hsc.utah.edu.

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BACKGROUND: Moderate/severe traumatic brain injury (TBI) management involves minimizing cerebral edema to maintain brain oxygen delivery. While medical therapy (MT) consisting of diuresis, hyperosmolar therapy, ventriculostomy, and barbiturate coma is the standard of care, decompressive craniectomy (DC) for refractory intracranial hypertension (ICH) has gained renewed interest. Since TBI treatment guidelines consider DC a second-tier intervention after MT failure, we sought to determine if early DC (<48 hours) was associated with improved survival in patients with refractory ICH.

METHODS: Eleven Level 1 trauma centers provided clinical data and head computed tomographic scans for patients with a Glasgow Coma Scale (GCS) score of 13 or less and radiographic evidence of TBI excluding deaths within 48 hours. Computed tomographic scans were graded according to the Marshall classification. A propensity score to receive DC (regardless of whether DC was performed) was calculated for each patient based on patient characteristics, physiology, injury severity, GCS, severity of intracranial injury, and treatment center. Patients who actually received a DC were matched to patients with similar propensity scores who received MT for analysis. Outcomes were compared between early (<48 hours of injury) primary or secondary DC and matched controls and then between early primary DC only and matched controls.

RESULTS: There were 2,602 patients who met the inclusion criteria ,of whom 264 (10.1%) received DC (either primary or secondary to another cranial procedure) and 109 (5%) had a DC that was primary. Variables associated with performing a DC included sex, race, intracranial pressure monitor placement, in-house trauma attending, traumatic subarachnoid hemorrhage, midline shift, and basal cistern compression. There was no survival benefit with early primary DC compared with the controls (relative risk, 1.07; 95% confidence interval, 0.67–1.73; $p = 0.77$), and resource use was higher.

CONCLUSION: Early DC does not seem to significantly improve mortality in patients with refractory ICH compared with MT. Neurosurgeons should pause before entertaining this resource-demanding form of therapy. (*J Trauma Acute Care Surg*. 2014;76: 944–955.

LEVEL OF EVIDENCE: Therapeutic care/management, level III.
KEY WORDS: Decompressive craniectomy; mortality; propensity; brain injury.

Traumatic brain injury (TBI) is a serious US public health problem secondary to death and permanent disability. Approximately 1.4 million people sustain a TBI, with 50,000 dying and 235,000 hospitalized yearly.[1] There are currently 5.3 million Americans requiring assistance to perform their activities of daily living as a result of TBI. The direct medical costs and societal costs are an estimated $60 billion in the United States.[2]

Managing patients with severe TBI has traditionally focused on minimizing secondary brain injury from cerebral edema to maintain brain oxygen delivery. Medical therapies consist of diuresis, sedation, hyperosmolar therapy, and barbiturate coma. Placement of ventricular drainage catheters may also assist in relieving elevated intracranial pressures by allowing fluid displacement. These therapeutic modalities increase space within the cranial vault through decreasing cerebrospinal fluid and tissue edema; however, they become less efficacious because the brain continues to swell, eventually leading to medically refractory intracranial hypertension. The relationship between intracranial hypertension and poor neurologic outcome or death is well-known, fueling trials that evaluate methods to reduce intracranial hypertension. Despite these studies, a consistent and effective approach to refractory intracranial hypertension is lacking.

Decompressive craniectomy (DC) has been used for refractory intracranial hypertension (ICH) for more then a century and has recently regained therapeutic interest. However, TBI treatment guidelines from German, European,[3] North-American,[4] and international[5] medical societies consider DC only as a last resort after failure of conservative therapy. Not surprisingly, DC was viewed as a maneuver with little therapeutic benefit since it had traditionally been applied after failure of days of medical therapy when the degree of secondary brain injury had already reached an irreversible point.

More recently, DC has been incorporated into intracranial pressure treatment algorithms at an earlier time point with encouraging results.[6–12] Unfortunately, the majority of these trials are case series lacking appropriate controls for comparison. Furthermore, the time frame during which DC is used in these trials ranges from less then 24 hours after injury to several days, making it difficult to draw conclusions regarding DC's efficacy. In addition, because of head injury variability, it is difficult to obtain large numbers of patients with similar injuries to determine the true efficacy of the procedure. Given the variation of DC use across the country, we proposed a propensity score analysis to measure the survival benefit of early DC compared with medical treatment of ICH.

PATIENTS AND METHODS

This propensity score analysis was performed using retrospective data of TBI patients acquired from 11 Level I US trauma centers. After each site obtained institutional review board approval, hospital characteristics and clinical data for each patient along with their actual head computed tomographic (CT) scans from 2008 to 2009 were uploaded to the American Association for the Surgery of Trauma's multicenter study Web server. Each center was given electronic access to an online, secure research Web portal requesting specific hospital- and patient-related variables. Each patient meeting inclusion criteria during the specified period was entered into the electronic registry. Inclusion criteria were patients 16 years or older with evidence of blunt TBI on their admission head CT and an admission Glasgow Coma Scale (GCS) score of 13 or less.

Polytrauma patients were not excluded. A single physician, blinded to the clinical information of each patient as well as to the radiology read of the head CT, reviewed and graded each admission head CT. A second reviewer read 96 randomly selected head CTs from the entire sample, and the two reads were compared to determine interobserver variability using the weighted κ statistic, which was determined to be 0.5631 (95% confidence interval [CI], 0.4233–0.7030), which indicates a moderate agreement between readers (Fig. 1).

The primary end point was in-hospital death comparing patients with ICH who underwent medical management with those who had primary DC performed within 48 hours of injury. Primary DC was defined as DC performed solely for the purpose of relieving ICH. Secondary DC was defined as a craniotomy performed with the primary intention of evacuating a space-occupying lesion such as an epidural, subdural, or intraparenchymal hematoma where the bone flap is left off at the end of the procedure due to ICH. Outcomes were also assessed for patients who underwent primary or secondary DC within 48 hours. Secondary outcomes included hospital and intensive care unit (ICU) length of stay, hospital charges, ventilator-associated pneumonia, adult respiratory distress syndrome (ARDS), deep venous thrombosis (DVT), catheter-related blood stream infection (CRBSI), intracranial abscess, and meningitis.

Mortality of patients with moderate-to-severe TBI ranges from 20% to 50% with standard medical therapy.[1,2,13] Since DC is not routinely performed at most centers, we conservatively estimated that 5% of moderate-to-severe TBI patients would undergo primary early DC. Assuming a reduction in mortality of 18% with early DC (50% relative risk [RR] reduction) and an average mortality rate of 35% in the medical treatment group, a total sample size of 2,080 would achieve 80% power with a two-sided α level of 0.05 to obtain a sufficient number of DC patients (n = 104).

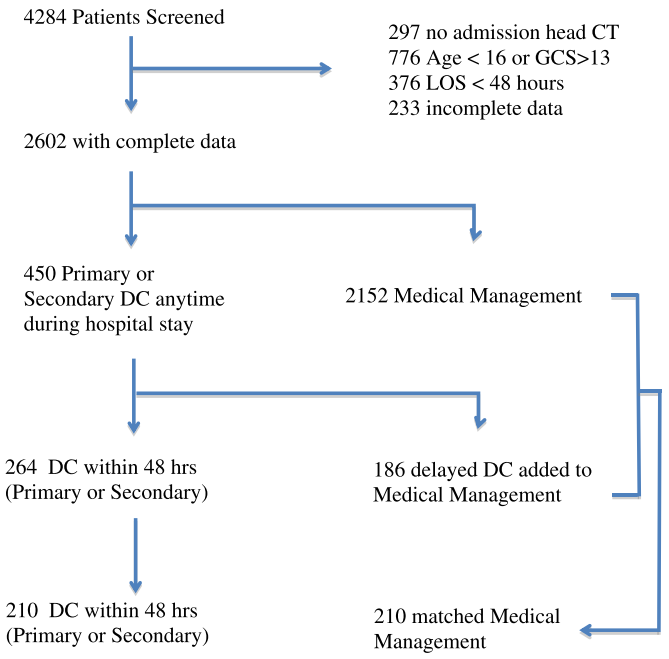

Figure 1. Study population flow diagram. LOS, length of stay.

Development of Propensity Model

Logistic regression was used to determine the propensity to receive primary DC. To avoid immortality time bias, analyses were restricted to patients who survived the first 48 hours. Among this subgroup, patients were classified in the DC group if they had a DC within 48 hours of injury and in the control group if not. Additional propensity models were developed for patients undergoing primary or secondary DC within 48 hours for similar outcome comparisons. Accordingly, the precise statement of the research question addressed by our analyses is, "What is the effect of implementation of DC within 48 hours of injury on survival among those who survive at least 2 days after injury?"

Variables in the Propensity Model

Continuous variables include age, admission heart rate (HR), admission systolic blood pressure (SBP), Injury Severity Score (ISS), GCS score, head Abbreviated Injury Scale (AIS) score, lactate level in the first 24 hours, volume of the largest intracranial mass lesion (CT estimate in milliliter), lowest mean arterial blood pressure (MAP) on Day 1, maximum intracranial pressure (ICP) in the first 24 hours, first ICP measurement, and INR level in the first 24 hours.

For INR, lactate, and ICP readings, a variable was included in the categorical variables later to indicate whether the measurement could be performed. Those who were in less severe condition would not necessarily need the measurement, and this provides information about the patient's status, which would otherwise be counted as missing.

Categorical variables include sex, race, when and if intubated, whether an ICP monitor was placed, whether an INR level was done, presence of an intraventricular hemorrhage (IVH), traumatic subarachnoid hemorrhage (SAH), class of midline shift (Class 0, 0 mm; Class 1, 1–5 mm; Class 2, 6–10 mm; Class 3, >10 mm), presence of multiple lesions, diffuse injury and basal cisterns on CT, insurance status, history of drug or alcohol (ETOH) abuse, smoking status, whether the institution is in ICP compliance (defined as placing an ICP in at least 50% of patients who meet Brain Trauma Foundation guidelines),[4] in-house trauma attending, type of admission unit, and number of trauma admissions per year.

All variables were retained in formulating the propensity score regardless of statistical significance because these were believed to be clinically relevant (Table 1). Patients for whom complete data were available were used in the creation of the propensity score.

Propensity Score Matching and Balance

Propensity scores, the estimated probability of receiving a DC for each subject, were then used to match control subjects with DC cases using a 1-to-1 matching without replacement.[14] Matches had to be within two tenths of the SD of the logit of the propensity score. For our sample, the SD of the logit of the propensity score was 2.24, so the caliper size for an allowable match was ±0.47.

TABLE 1. Predictors of Undergoing Early DC (Propensity Score Variables)

Predictor	*df*	Wald χ^2
Sex	1	0.1638
Race	3	3.1193
Smoker	1	0.4838
Volume of largest mass	3	8.8873
ICP placed	1	10.7595
Lactate level done	1	0.5566
MAP Day 1 done	1	0.0045
INR done	1	3.2242
Self-pay	1	0.4513
Medicaid	1	1.5399
In-house trauma attending	1	27.5511
Trauma admissions per year	1	4.4737
ICP compliance	1	16.4657
Traumatic SAH	1	5.1039
IVH	1	0.6970
Class midline shift	3	48.7825
Basal cisterns	2	1.3098
Lesions present on CT	1	0.0025
Admission unit	3	3.5705
Intubated	2	1.6449
History of drug or alcohol	1	0.0020
Diffuse injury on CT	1	4.2638
GCS	1	1.4435
Head AIS	1	0.0345
ISS	1	0.0748
Lactate level first 24 h	1	0.9275
INR level first 24 h	1	0.1194
Admission SBP	1	1.2620
Admission HR	1	3.5518
Age	1	19.9123
MAP Day 1	1	0.0250
First ICP	1	0.1806
Max ICP Day 1	1	0.2191

To verify that the matching procedure produced a balanced sample, differences in the propensity model variables (univariate analysis) by whether a DC was performed were tested on the unmatched sample as well as on the matched pairs sample. If good balance has been achieved by the matching procedure, any standardized differences in the original sample, which are substantially larger than 0.10, should become reduced to values close to 0.10 or smaller (Tables 2 and 3, before and after matching).

Primary Outcome

The primary outcome was an in-hospital death. RRs of an in-hospital death by DC status (either primary or secondary DC combined or primary DC alone compared with controls) were calculated using a Poisson regression with a logarithmic link function to obtain estimates of RR using Proc Genmod in SAS 9.3. Confidence intervals and *p* values were obtained using robust estimates of SEs for the log RRs.

In sensitivity analyses, the RRs for primary or secondary DC or for primary DC alone compared with controls were estimated in the matched data set using generalized linear mixed-effects models for binary outcomes with a logarithmic link function and with a random effect term for clinical center to account for any clustering of death rates across hospitals.

Secondary Outcomes

Secondary outcomes included hospital and ICU length of stay, hospital charges, ventilator-associated pneumonia (VAP), ARDS, DVT, CRBSI, intracranial abscess, and meningitis. Positive skewness was apparent in hospital and ICU length of stay and hospital charges; hence, they were log transformed before statistical analyses. Analysis of variance using Proc GLM in SAS 9.3 was used to test for the difference in means by DC status within the propensity-matched sample. For clarity, the means of the log-transformed variables are expressed on the original scale as geometric means.

RESULTS

Initially 4,284 patients were entered; however, patients were excluded if they were younger than 16 years old, were not bluntly injured, did not have a CT scan on admission, or did not survive/had a length of stay less than 48 hours after injury. Outcomes were compared with propensity score–matched controls for patients who had primary or secondary DC performed within 48 hours of their injury (DC48PS) and then for only those patients who had a primary DC performed within 48 hours (DC48P). In the final sample of 2,602 patients, 450 underwent a primary or secondary DC at some point during their hospital stay. There were 264 patients who underwent DC within the first 48 hours (DC48PS). After propensity score matching, there were 210 patients in the DC48PS group matched to 210 medically treated patients. When considering only those patients who had a DC performed primarily (DC48P), there were 109 patients (41.3% of those receiving DC in the first 48 hours), thus meeting our projected sample size. Of these 109 DC48P patients, however, only 91 had propensity score–matched controls (data not shown).

The entire population was predominantly middle-aged white men; however, patients undergoing DC were younger, were more frequently intubated in the field, had a higher ISS, had a lower admission GCS score, had a higher head AIS score, had a higher initial ICP, had a larger mass lesion, had greater cistern compression, and had greater midline shift compared with non-DC patients before propensity matching (Tables 2 and 3, before matching). Propensity matching produced two well-balanced groups with no significant differences in any of the covariates examined for both the DC48PS relative to controls (data shown) and the DC48P (data not shown) relative to controls (Tables 2 and 3, after matching).

While all preoperative variables collected were included in the propensity score model, those that were independently associated with an increased likelihood of performing DC included volume of the largest mass, ICP monitor placement, in-house trauma attending, higher volume trauma centers, compliance with ICP placement guidelines, traumatic SAH,

TABLE 2. Comparison of Categorical Variables for DC48PS and Controls Before and After Propensity Score Matching

	Before Matching			After Matching		
	No DC (n = 2,338)	DC (n = 264)		Control (n = 210)	Case (n = 210)	
Characteristics	**n (%)**	**n (%)**	**Std. Diff.**	**n (%)**	**n (%)**	**Std. Diff.**
Female	586 (25.1)	56 (21.2)	0.091	43 (20.5)	47 (22.4)	0.046
Race						
African American	352 (15.1)	35 (13.3)	0.052	23 (11)	27 (12.9)	0.059
Hispanic	359 (15.4)	39 (14.8)	0.016	36 (17.1)	32 (15.2)	0.059
White	1,343 (57.4)	152 (57.6)	0.003	123 (58.6)	123 (58.6)	0
Other	284 (12.1)	38 (14.4)	0.066	28 (13.3)	28 (13.3)	0
Smoker	184 (7.9)	22 (8.3)	0.79	17 (8.1)	16 (7.6)	0.86
ETOH or drugs	640 (27.4)	65 (24.6)	0.063	52 (24.8)	51 (24.3)	0.011
Self Pay	467 (20)	53 (20.1)	0.003	44 (21)	40 (19)	0.048
Medicaid	331 (14.2)	40 (15.2)	0.028	37 (17.6)	33 (15.7)	0.051
GCS category						
8–13	1,207 (51.6)	61 (23.1)	0.647	56 (26.7)	52 (24.8)	0.047
3–8	1,131 (48.4)	203 (76.9)	0.617	154 (73.3)	158 (75.2)	0.044
If and when Intubated						
No	514 (22)	23 (8.7)	0.375	25 (11.9)	22 (10.5)	0.045
In the field	911 (39)	146 (55.3)	0.332	107 (51)	109 (51.9)	0.019
In the ED	913 (39.1)	95 (36)	0.063	78 (37.1)	79 (37.6)	0.01
ICP placed	977 (41.8)	216 (81.8)	0.904	169 (80.5)	162 (77.1)	0.082
Lactate measured in 24 h	1,436 (61.4)	172 (65.2)	0.077	135 (64.3)	137 (65.2)	0.02
MAP measured on Day 1	1,050 (44.9)	211 (79.9)	0.775	166 (79)	157 (74.8)	0.102
IVH	340 (14.5)	32 (12.1)	0.071	18 (8.6)	26 (12.4)	0.125
INR measured in 24 h	2,260 (96.7)	263 (99.6)	0.106	209 (99.5)	209 (99.5)	0.007
Traumatic SAH	1,441 (61.6)	201 (76.1)	0.317	150 (71.4)	151 (71.9)	0.011
Midline shift, mm						
0	1,362 (58.3)	32 (12.1)	1.103	40 (19)	32 (15.2)	0.101
1–5	746 (31.9)	85 (32.2)	0.006	75 (35.7)	78 (37.1)	0.03
6–10	116 (5)	79 (29.9)	0.697	56 (26.7)	54 (25.7)	0.022
>10	114 (4.9)	68 (25.8)	0.606	39 (18.6)	46 (21.9)	0.083
Basal cisterns						
Compressed	534 (22.8)	202 (76.5)	1.272	151 (71.9)	154 (73.3)	0.032
Absent	31 (1.3)	13 (4.9)	0.208	6 (2.9)	8 (3.8)	0.053
Diffuse injury on CT	1,697 (72.6)	39 (14.8)	1.434	40 (19)	39 (18.6)	0.012
Volume of largest mass, mL						
None	1,077 (46.1)	15 (5.7)	1.039	15 (7.1)	14 (6.7)	0.019
0 to 10	742 (31.7)	68 (25.8)	0.132	66 (31.4)	63 (30)	0.031
10+ to 25	221 (9.5)	66 (25)	0.421	44 (21)	46 (21.9)	0.023
25+ to 50	298 (12.7)	115 (43.6)	0.729	85 (40.5)	87 (41.4)	0.019
Mass lesion present	1,334 (57.1)	251 (95.1)	0.995	197 (93.8)	197 (93.8)	0
Admission unit						
Other	471 (20.1)	23 (8.7)	0.33	20 (9.5)	22 (10.5)	0.032
Medical/surgical ICU	426 (18.2)	33 (12.5)	0.159	32 (15.2)	28 (13.3)	0.054
Neuro-ICU	522 (22.3)	124 (47)	0.536	84 (40)	91 (43.3)	0.068
Trauma ICU	919 (39.3)	84 (31.8)	0.157	74 (35.2)	69 (32.9)	0.05
Proportion of subjects from centers with ICP compliance >50%	1,160 (49.6)	155 (58.7)	0.17	122 (58.1)	125 (59.5)	0.041
In-house trauma attending	1,940 (83)	200 (75.8)	0.179	168 (80)	169 (80.5)	0.012
Proportion of subjects by trauma center volume						
1,000–4,000 admissions per year	791 (33.8)	92 (34.8)	0.021	74 (35.2)	68 (32.4)	0.06
>4,000 admissions per year	1,547 (66.2)	172 (65.2)	0.021	136 (64.8)	142 (67.6)	0.06

degree of midline shift, the presence of diffuse injury, and age (Table 1).

After propensity score matching, mortality risk in the DC48PS patients (30%) was the same as that of the controls (28.6%) (RR, 1.05; 95% CI, 0.79–1.40; $p = 0.74$) (Fig. 2*A*). The use of a generalized mixed models with clinical center as a random effect produced an essentially identical result (RR, 1.04; 95% CI, 0.77–1.40; $p = 0.82$). When analyzing DC48P

TABLE 3. Comparison of Continuous Variables for DC48PS and Controls Before and After Propensity Score Matching

	Before Matching			After Matching		
	No DC (n = 2,338)	DC (n = 264)		Controls (n = 210)	Cases (n = 210)	
Characteristic	Mean (SD)	Mean (SD)	Std Diff	Mean (SD)	Mean (SD)	Std Diff
Admission HR	98 (26)	89 (26)	0.358	91 (28)	92 (26)	0.034
Admission SBP	137 (33)	141 (34)	0.126	141 (38)	140 (35)	0.002
Age	43 (20)	39 (17)	0.252	39 (18)	40 (17)	0.032
First ICP (mmHg)	5.7 (9.7)	12.4 (11.9)	0.622	12.3 (13.1)	11.7 (11.8)	0.047
GCS	8.9 (3.8)	6.7 (2.9)	0.647	6.9 (3.3)	6.8 (3.0)	0.047
Head AIS	4.1 (0.8)	4.5 (0.7)	0.594	4.5 (0.8)	4.5 (0.8)	0.051
INR first 24	1.15 (0.6)	1.23 (0.84)	0.106	1.25 (0.87)	1.25 (0.94)	0.007
ISS	27.6 (12.5)	29.8 (12.1)	0.179	29.2 (11.1)	29.6 (12.6)	0.033
Lactate first 24	2.2 (3.6)	2.0 (2.0)	0.066	1.9 (2.0)	2.1 (2.1)	0.079
MAP Day 1	39 (45)	72 (39)	0.768	70 (39)	67 (41)	0.085
Max ICP Day 1	8.3 (12.8)	18.3 (15.1)	0.707	18.8 (16.9)	17.0 (15.7)	0.111

(excluding secondary DC patients) compared with controls, there was again no significant difference in mortality (37.3% in both groups; RR, 1.00; 95% CI, 0.66–1.51; $p = 1.00$) (Fig. 2*B*).

When comparing DC48PS patients to controls, there was no statistical difference in VAP, ARDS, CRBSI, DVT, meningitis, or hospital charges; however, VAP, ARDS, intracranial abscess, and hospital charges tended to be higher in the DC48PS group. ICU and hospital lengths of stay were statistically significantly higher in the DC48PS group (Fig. 3). Among the DC48P patients, VAP, intracranial abscess, meningitis, as well as hospital and ICU lengths of stay were significantly greater compared with controls (data not shown).

Excluding patients with a length of stay less than 48 hours in the analysis was necessary to avoid immortality time bias. To understand the impact of this exclusion, we assessed the proportion of patients who received DC who died in this group relative to those that were treated medically who died. There were 376 patients excluded because of a length of stay of less than 48 hours, of whom 28 had DC, all of whom died, while 348 were treated medically, of whom 286 (82.2%) died. The exclusion of patients with a length of stay of less than 48 hours therefore may result in an underestimation of the benefits of medical therapy relative to DC on mortality.

DISCUSSION

DC has struggled to find its place in the treatment of TBI. While it is clear that DC is associated with a reduction in ICP, it is unclear if this translates to an improvement in survival and neurologic outcome.

Numerous case reports have touted the survival and outcome benefits of DC, while others have failed to identify a survival benefit or at best suggest an increase in the proportion of survivors in vegetative states.[7,9,11,15–31] Most studies suffer from selection bias and lack appropriate controls for outcome comparisons. Furthermore, numerous other factors that may contribute to outcome, such as age, other injuries, ICP management variation, timing of DC, and nature of TBI to name a few, are unaddressed in many of these small series and thus contribute to confounding.[7,32–34] Interpretation of these studies is further complicated by the fact that patients undergoing primary or secondary DC are included within the same analysis as a singular group; however, patients undergoing DC for the primary purpose of relieving medically refractory ICH are very different from those patients who undergo a secondary DC after evacuation of a hematoma/devitalized brain tissue.[35,36]

In a study of 40 patients who underwent DC, 27 had their procedure performed before ICP measurements on the basis of a low GCS score in the setting of CT findings of cerebral swelling/herniation with or without hematoma. In the remaining patients, DC was performed after the development of medically refractory ICH or absence of unilateral or bilateral pupillary reflexes with similar CT findings. The authors reported that 25% of the patients attained social rehabilitation at 1 year, which was felt to be a surprisingly good outcome for this cohort.[9] What is not known is whether this outcome could have been achieved with medical therapy alone, in particular among the patients who underwent surgery before any medical management.

An analysis of 49 patients of whom 63% underwent rapid DC (within several hours of injury) and the remainder receiving their DC several days after injury showed that rapid DC and age less then 50 years were associated with a better outcome. The overall mortality, however, was comparable with reports of non-DC patients from the Traumatic Coma Data Bank, leading the authors to conclude that DC did not improve patients' outcomes.[29]

In a case-control study, patients undergoing DC at the University of Virginia for refractory posttraumatic ICH were matched to non-DC patients from the Traumatic Coma Data Bank on the basis of age, sex, preoperative GCS score, and maximum preoperative ICP. The rate of good recovery/moderate disability was 37%, with a 23% mortality rate in the DC patient group compared with 16.1% and 31%, respectively, in the control group. They reported a significantly increased rate of favorable outcomes (15.4%) in the DC group compared with controls. Patients who had a persistently elevated ICP more then 40 torr and those whose DC was performed more then 48 hours after injury did poorly.[37] While this study adjusted for confounders, it was noted that shock was present in a third of the control patients, but this was not considered in the

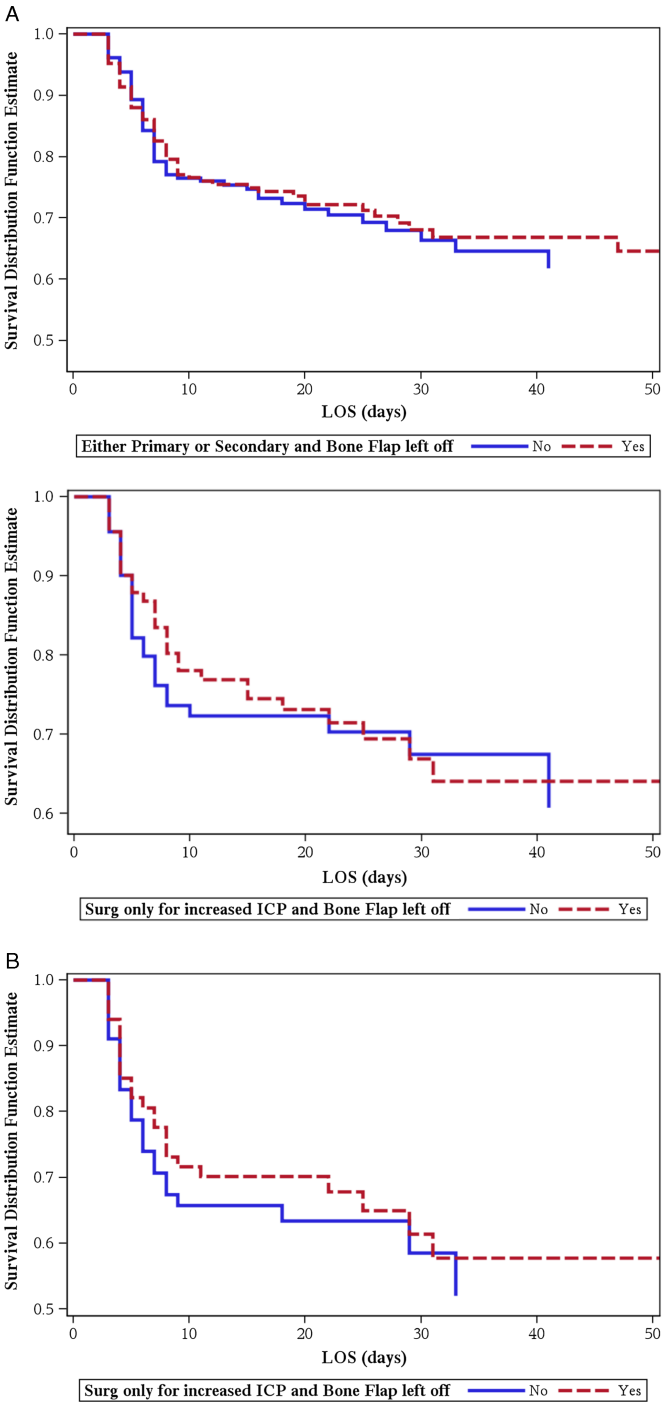

Figure 2. *A, Dotted red line* indicates patients who underwent a primary or secondary DC within 48 hours. *Solid blue line* indicates controls. Kaplan-Meier survival analysis of DC48PS compared with controls in the propensity-matched sample. *B, Dotted red line* indicates patients who underwent a primary DC within 48 hours. *Solid blue line* indicates controls.

matching scheme. In addition, patients in whom mass lesions were evacuated were included in the surgical group but were excluded from the control group. Lastly, the nonoperative approach used in the Traumatic Coma Data Bank control patients calls into question selection/center bias, and without the CT imaging of these patients, it is difficult to know if they had similar brain injury severity to the DC patients.

In 2011 Cooper et al.[38] published the first multicenter randomized trial of DC for blunt TBI. Patients between 15 years and 59 years were randomized (within 72 hours) to DC or continued medical therapy if they had medically refractory ICH in the absence of a surgical mass lesion. The primary outcome measure was the proportion of patients who died or were in a poor neurologic state (vegetative/severely disabled) at 6 months after injury. An unfavorable outcome occurred in 70% of DC patients and in 51% of the medically treated. Mortality was equivalent between the two groups. This study demonstrated that DC did not reduce mortality and was associated with worse neurologic outcome at 6 months compared with medical therapy.

Our study addresses some of the limitations of previous studies in that it defines brain injury through head abbreviated injury severity, GCS, ICP, and CT scan appearance. It further adjusts for patient characteristics, other injuries, admission physiology, center bias, and the indication for DC. Our results indicate no survival benefit for DC compared with medical treatment with an associated increase in hospital resource use and a trend toward increased complications.

This study does have several important limitations including the potential for unmanaged center and selection bias. We have tried to address this by using trauma center volume, presence of an in-house trauma attending, and the use of Brain Trauma Foundation guidelines by centers to minimize the effect of center bias. Selection bias was addressed through the development of a robust propensity score model that included head injury severity based both on clinical presentation and the admission head CT appearance. This study also did not have the power to assess the association between the DC technique used and outcome. As previously mentioned, the study had 91 patients who underwent early primary DC who were able to be matched to controls, which raises the possibility of

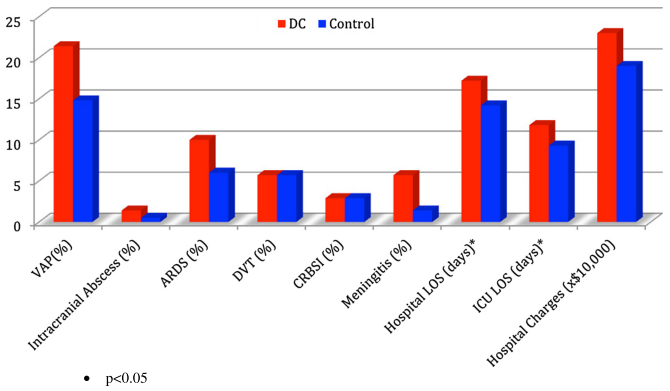

Figure 3. Secondary outcome measures for early primary or secondary DC (*red*) and controls (*blue*). Secondary outcomes of DC48PS patients compared with controls in the propensity matched sample ($p < 0.05$).

a Type II error; however, given that the sample size was not far off the estimated sample size needed to detect an 18% mortality improvement and the fact that the RR of death was at the null, it is unlikely that our estimate is far from the estimate that we would have measured with an additional 12 patients in the study. Another consideration is that each center provided medical management based on their institutional protocols and biases. We tried to adjust for differences in ICU settings that would be associated with treatment by including ICP monitor placement, ICP protocol compliance, admission unit type, and trauma center volume. How ICP was specifically managed with respect to medical therapy was not considered in the analysis for obvious reasons related to the inability to determine the precise medical treatments given in the time course of the patient management that would be extremely cumbersome in a retrospective study such as this and therefore impractical. While this is a limitation of the study, in terms of generalizability of a study, allowing the variability of medical treatment to exist in the study and not adjust for it speaks to the current state of what we would say is standard of care with respect to medical treatment across centers. Therefore, in comparing DC with the current medical therapy, not adjusting for differences across centers with respect to medical therapy provides us a real assessment of the current state. What we can report is that DC, when compared with medical therapy as it is currently used across major Level I trauma centers, does not improve survival. Had a strict medical protocol or adjustment regarding variation of medical management been used in this study, it is quite possible that medical management would be superior to DC but we are unable to know this based on the current analysis. Another limitation of this study is the timing of DC. While we tried to address this by focusing on a time cutoff point of 48 hours for DC, there was an insufficient number of patients to assess whether DC within 24 hours might have provided a survival benefit. Another potential concern is a selection bias through exclusion of patients dying within 48 hours. The restriction of the analysis to subjects who survived at least 2 days, which was necessary to avoid immortality time bias, may have led to some degree of selection bias in the composition of the treated and untreated groups at the 2-day point after surgery, which was taken as the baseline for our analyses. This leaves us with a population of patients whose head injuries are not the worst of the worst. Therefore, there is the potential that by excluding these most severe head injuries in whom DC may have been beneficial, we fail to capture the true effect of DC. Even if DC was performed in these patients and we excluded them, this would only serve to further reduce the efficacy of DC compared with medical therapy, supporting our conclusions that DC was not superior to medical therapy. Therefore, it is unlikely that excluding these patients would have altered our results. While propensity score analysis serves to limit potential bias in the selection of treatment between groups. we acknowledge that it does not control for unmeasured or inadequately measured factors. The greatest limitation, however, is that we did not examine long-term outcomes. Our initial intent was to determine if there was a survival benefit from DC compared with well-matched patients.

A well-balanced randomized trial of early primary DC (within 24 hours of injury) compared with a standard medical management protocol for ICH is needed to definitively state whether DC should be used. Our data will provide support to those wishing to pursue such an investigation as it shows clinical equipoise between the two treatment strategies with respect to survival. The biggest question for such a study will be how the medical management protocol should be structured. Should mannitol or hypertonic saline be used, and if so, what are the cutoffs for initiating treatment? Should treatments be titrated to jugular venous oxygen saturation or parenchymal oxygen levels? The standard medical approach should be that which is currently used, realistically, in the majority of trauma centers across the country so that it truly represents the current state of medical management.

It is plausible that DC may not necessarily improve mortality but might result in an improvement in neurologic outcome among survivors since it reduces ICP, which is the cornerstone of TBI management. DC does have its own detrimental effects; however, including contralateral subdural formation after expansion, brain ischemia along the craniectomy edge, and meningitis may counteract the beneficial effects on ICP.[12,39,40] Cooper's randomized trial clearly shows that neurologic outcome was worse with DC and there was no survival benefit. Our study results confirm the lack of survival benefit demonstrated in Cooper's trial. Taken together with the fact that DC did not lead to an improvement in neurologic outcome in Cooper's study and is associated with increased complications and resource use and now that two studies demonstrate no survival benefit, neurosurgeons should take pause before using DC for refractory ICH.

AUTHORSHIP

R.N., T.G., M.M., G.J.J., and R.C. designed this study. All authors contributed to the data acquisition. R.N., D.M., T.G., and M.M. analyzed and interpreted the data. All authors participated in writing and revising the manuscript.

DISCLOSURE

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DISCUSSION

Dr. Samir M. Fakhry (Charleston, South Carolina): Ram, that was a great study and a very nice presentation. You and your colleagues conducted an excellent study to attempt to address one of the really controversial subjects in the care of patients with severe traumatic brain injury.

You performed a retrospective, multi-center analysis that compared decompressive craniectomy for refractory intracranial hypertension to medical therapy in adult patients with severe and moderate TBI.

You used propensity scoring to reduce bias between these patients and you concluded there was no difference in hospital mortality at the end of the trial.

These findings are consistent, as you mentioned, with the only randomized controlled study of decompressive craniectomy published recently by Cooper et al.

Now, absent a randomized controlled study, propensity scoring provides a means to control confounding in pseudo-experimental design such as this one. According to Stermer et al, propensity scores estimate the predictive probability or propensity of use of a given drug or procedure in a particular subject based on his or her characteristics when the treatment is chosen. In principle the effect of the treatment can then be measured among patients who then have the same predicted propensity of treatment, thus controlling for confounding without randomization.

The reason I am bringing this up is this is not something that rolls off the tip of my tongue very easily.

Use of propensity scores, thus, reduces bias and it's especially appealing because under the assumption that all relevant predictors of treatment have been adequately captured, subjects with the same propensity scores should have the same chance of receiving treatment. Propensity scores are, therefore, often conceptualized as mimicking randomized trials, although they do so only with respect to factors that have been adequately measured.

This is a very important consideration because randomization, in contrast, removes bias from both measured and unmeasured factors and variables. So propensity scoring is appealing when studying treatment effects on patient cohorts.

There is much to like in this study about the authors' methodological implementation of propensity scoring. They did a sample size calculation a priori, considered many variables as they developed their model, matched patients carefully using accepted techniques, including probably something called "greedy matching" if you get into this; and they carefully verified that the two groups were balanced so this was a very robust methodological approach.

I have the following comments and questions for the authors.

1. How did you confirm that all pertinent variables were considered in your model? Or is there really a way to do that?
2. Several cases were excluded because they could not be matched or because of missing data. What effect, if any, would there be from excluding 16.% percent of the DC48P and 20.5% of the DC48APS patients? It would be helpful to know how the excluded groups compared to the included ones.
3. Why include patients with Glascow greater than eight? They are much less likely to need craniectomy and will dilute your sample and effect?
4. Cooper et al. did not include patients over 59 years old but you did. Since older patients probably have worse severe TBI outcomes, do your results change if you exclude that cohort?
5. How were data collected at the individual centers? Was this from trauma registries? chart abstraction? Did you utilize the data dictionary?
6. Who interpreted and rated the brain CT scans? Did you use a standardized scale like the Marshall Scale?
7. How did you define failure of medical management? And was this standardized amongst the study centers?
8. Did you standardize decompressive craniectomy, for example using Poland's technique of bifrontal temporoparietal craniectomy amongst all the centers?
9. As you pointed out in your manuscript, the sample is heavily weighted to middle-aged Caucasian men, raising questions of external validity or generalizability. Would you comment on that, please.
10. Do you have a measure of neurologic status at hospital discharge in your current study?

And finally and perhaps most importantly, as you mentioned, why not wait until you have six months follow up of survival and neuro status to report your results?

In spite of these limitations the authors should be congratulated for taking on this important clinical controversy.

Their application of propensity scoring was very well conducted and methodologically sound, even to my amateur eyes but I did get some help analyzing that.

However, by failing to address long-term mortality and neurologic outcomes they leave open the question of whether decompressive craniectomy allows some patients to survive with better neurologic outcomes.

In my opinion the fundamental question of "if, when, and how" to perform decompressive craniectomy remains the subject of some debate for now and one that will likely require another randomized controlled trial to resolve.

Thank you.

Dr. Norman McSwain, Jr. (New Orleans, Louisiana): Decompression of compartment syndromes works everywhere else: in the leg, in the abdomen, in the heart, the lung. Why does it not work in the brain just as well?

Dr. Eileen M. Bulger (Seattle, Washington): Can you clarify the variability among the centers and the rates of decompressive craniectomy? I suspect there is considerable variability. And, if so, how did you account for that in the model?

Dr. Faran Bokhari (Chicago, Illinois): I had a question about this propensity scoring. Do you give all the various factors an equal weight in this model that you developed? Because that might affect what your results are. Thanks.

Dr. A. Brent Eastman (San Diego, California): Congratulations on a very well-presented topic. You mentioned intracranial abscesses.

When we looked at this we were also struck with the problem of wound infections when the bone plate was replaced. Did you include that with intracranial abscesses or did you see wound infections separate from intracranial abscesses?

Dr. Marc A. deMoya (Boston, Massachusetts): My question, like Dr. McSwain's, that intracranial hypertension is a compartment syndrome and therefore very time-dependent. Given it is a time-dependent problem was there any information about the time to decompression once the diagnosis of refractory intracranial hypertension was obtained? Thank you.

Dr. David Livingston (Newark, New Jersey): My questions are very similar to Marc and Dr. McSwain's. Are we just getting to the party too late? Forty-eight hours with intracranial hypertension is clearly far too long to see any

positive outcomes. Do you have the ability to break the data up into discrete time intervals from injury to decompressive craniectomy?

Dr. Babak Sarani (Washington, D.C.): Did you guys separate out the underlying cause for the elevated intracranial pressure? The reason I ask is because the DECRA trial clearly showed that there is very limited utility to decompressive craniectomy for what essentially is DAI or cerebral edema. And I just wonder if the disease progress is different based on the underlying cause of the elevated ICP.

Dr. John B. Holcomb (Houston, Texas): My comment is about timing as well. It appears you must account for time as a confounding variable, potentially with a Cox proportional hazards analysis in addition to your propensity score.

Dr. Avery Nathens (Toronto, Ontario, Canada): I'd like to know what the mortality was in the two groups, the crude mortality. Doing this in patients that don't necessarily benefit–that is, low survival–won't make a difference. And those doing it in patients who are too sick would make a difference. Thanks.

Dr. Reginald Burton (Lincoln, Nebraska): Was there a difference in infection rates between bone flaps that were freeze dried and those that were "banked" in a subcutaneous pocket in the abdominal wall?

Dr. Raminder Nirula (Salt Lake City, Nevada): Well, I'm glad that this topic created such vigorous discussion. I will try and address as many of these questions as time will permit.

Dr. Fakhry, thanks for your insightful comments. The first question is how do you confirm whether or not all the variables are present within the model you that are required. You have to, obviously, include those variables that are statistically significant but then you have to go through the literature and use some clinical acumen to determine what variables you feel are appropriate to include. In general, the dictum is if there is any chance that a variable might be associated with the decision to perform the treatment, in this case decompressive craniectomy, then you should include that variable and be more encompassing.

Why did we include patients with a GCS more than eight? There were actually three reasons. One is that by including patients with a higher GCS we didn't miss those few patients that might initially come in with a reasonable GCS and then decompensate. Secondly, by including these patients it gives us more strength in terms of our ability to build the model because it will identify those patients that have characteristics that are not associated with the use of DC which is equally as important as finding those characteristics which are associated with DC. Thirdly, because this was a multi-institutional trial supported by the AAST I felt that this cohort could be useful for subsequent studies. In fact there is a second study that's being presented at this meeting that will utilize these data. So rather than duplicating the efforts we decided to throw a broad net initially.

Regarding your question about age, in the Cooper trial they limited their study to those under the age of 60. When we looked at our data and we excluded those patients under the age of 60, which was about 18% of patients, and we still did not find a survival benefit. Further, even though we included older patients they are being matched to patients that are of the same age so, in two ways, we did adjust for age in our analysis.

How was the data collected? At each center the registries were screened using the inclusion criteria and thereafter data was extracted from the charts, including the radiographic data.

Who interpreted the CT scans? There was a combination of a research resident under the guidance of a neurological radiologist. And we randomly selected patients and assessed interobserver reliability which was good. And we did use the Marshall Scoring System as you implied.

In terms of defining the failure of medical management and the standardization of craniectomy, this was not done as this was a retrospective study so we did not impose upon the treatment centers any kind of standardization. Having said that, we did control for the degree of intracranial hypertension in the analysis as well as head AIS and GCS, of course. However, we did not control for the way the craniectomy was done. However, about 70 percent of patients underwent a bifrontal temporo-craniectomy.

In terms of external validity, Dr. Fakhry is absolutely right. The majority of the patients were Caucasian, middle-aged males. Whether or not this is a reflection of the inability to generalize, I'm not exactly sure because this is a representation of 11 Level I trauma centers. This is the group of patients that presented to a large number of centers across the US so the idea that this may be not generalizable is, I think, debatable.

We did make a measurement of GCS at discharge. The results I did not show but, on average the decompressive craniectomy group had a one point lower GCS score at discharge, for what that's worth.

Why not wait and do follow up? We thought–we actually decided that we were, in order to do the follow up and get long-term data we would need to do the propensity analysis first in order to figure out who the sample was that we were going to compare to. Otherwise, we would have to get a long-term follow up on some 2,600 patients.

Now that we have the propensity-matched sample, we have a much smaller sample. We can now go ahead and focus in on those patients and get their follow up. And we hope to present that data in the near future.

But the fact that there was no survival benefit found, and that was the primary intent of this study, we felt compelled that we needed to report those results.

So why doesn't decompressive craniectomy work when decompression everywhere else seems to work? People brought up the issue of timing. And I think that we're very good at recognizing the need to decompress other compartments in a timely fashion but not in the same way with the brain.

And the fact of the matter is that while other areas can tolerate ischemia, the brain cannot. And when you get irreversible ischemia in the brain, you are subject to, obviously, irreversible damage.

The other problem is that decompressing the other elements does not leave you with a confined skull that can cause damage to the surrounding brain tissue when it does herniate through that craniotomy site. And that's different

for when you are decompressing the abdomen or the leg where the soft tissue is much more forgiving and yielding.

In terms of the variability in DC across the country, we did not adjust specifically for the variability of the use of DC across the country.

We did adjust for other center variables which, hopefully, will act as surrogates for the variability in DC. But we did not specifically look at that.

The last question related to the raw scores of the mortality. In the match samples mortality rate was 30% in the DC group and 28% for the medical therapy group. Prior to matching, the mortality in the DC group was 40% and 21% in the medical therapy group.

I think that's it for me in terms of my time so I'd like to again thank the AAST for the privilege of the floor.