Effect of intracranial pressure monitoring and targeted intensive care on functional outcome after severe head injury*

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Objective: Intracranial hypertension after severe head injury is associated with case fatality, but there is no sound evidence that monitoring of intracranial pressure (ICP) and targeted management of cerebral perfusion pressure (CPP) improve outcome, despite widespread recommendation by experts in the field. The purpose was to determine the effect of ICP/CPP-targeted intensive care on functional outcome and therapy intensity levels after severe head injury.

Design: Retrospective cohort study with prospective assessment of outcome.

Setting: Two level I trauma centers in The Netherlands from 1996 to 2001.

Patients: Three hundred thirty-three patients who had survived and remained comatose for >24 hrs, from a total of 685 consecutive severely head-injured adults.

Interventions: In center A (supportive intensive care), mean arterial pressure was maintained at approximately 90 mm Hg, and therapeutic interventions were based on clinical observations and computed tomography findings. In center B (ICP/CPP-targeted intensive care), management was aimed at maintaining ICP <20 mm Hg and CPP >70 mm Hg. Allocation to either trauma center was solely based on the site of the accident.

Measurements and Main Results: We measured extended Glasgow Outcome Scale after ≥12 months. Patient characteristics were well balanced between the centers. ICP monitoring was used in zero of 122 (0%) and 142 of 211 (67%) patients in centers A and B, respectively. In-hospital mortality rate was 41 (34%) vs. 69 (33%; $p = .87$). The odds ratio for a more favorable functional outcome following ICP/CPP-targeted therapy was 0.95 (95% confidence interval, 0.62–1.44). This result remained after adjustment for potential confounders. Sedatives, vasopressors, mannitol, and barbiturates were much more frequently used in center B (all $p < .01$). The median number of days on ventilator support in survivors was 5 (25th–75th percentile, 2–9) in center A vs. 12 (7–19) in center B ($p < .001$).

Conclusions: ICP/CPP-targeted intensive care results in prolonged mechanical ventilation and increased levels of therapy intensity, without evidence for improved outcome in patients who survive beyond 24 hrs following severe head injury. (Crit Care Med 2005; 33:2207–2213)

KEY WORDS: head injuries, closed; extended Glasgow Outcome Scale; intracranial pressure monitoring; cerebral perfusion pressure management; goal-directed treatment; therapy intensity level

Monitoring and targeted management of intracranial pressure (ICP) and cerebral perfusion pressure (CPP) are widely advocated for patients with severe head injuries (1, 2). This recommendation is based on physiologic principles and on the association of poor outcome with systemic and cerebral derangements, most importantly arterial hypotension, hypoxia, pyrexia, intracranial hypertension, and low CPP (3). However, the impact of such therapy on outcome is unclear. In particular, the use of ICP monitoring to guide therapy in the intensive care unit (ICU) has never been subjected to a randomized controlled trial. As a consequence, there is considerable variation in the use of monitoring and treatment modalities between trauma centers (4–6).

Surveys of critical care management in Europe and North America indicate that ICP is monitored routinely in approximately 75% of centers that provide care for severely head-injured patients (7, 8). Nonetheless, a randomized trial addressing the efficacy of ICP-guided therapy is still in demand, although—at the same time—many clinicians are reluc-

tant to randomize their patients because they believe that monitoring has become central to appropriate management (8). Infections and bleeding complications resulting from the use of ICP monitoring devices are rare (6, 9). However, there are cardiorespiratory complications that may be associated with a CPP-targeted approach (10, 11). It is conceivable that an ICP/CPP-driven protocol might result in a more frequent use of sedatives, muscle relaxants, osmotic diuretics, vasopressors, fluid loading, and hyperventilation, which all have recognized neurologic and systemic side effects. Furthermore, the impact of such therapy on costs and length of stay in the ICU is unknown.

To determine the effect of ICP/CPP-targeted intensive care on functional outcome, therapy intensity levels, and length of stay after severe head injury, we performed a retrospective cohort study with prospective assessment of functional out-

come in two level I trauma centers in different regions in The Netherlands, with contrasting approaches to intensive care management of head-injured patients. Center A provided supportive intensive care without ICP monitoring, whereas center B provided protocol-driven intensive care targeted to maintain ICP <20 mm Hg and CPP >70 mm Hg.

MATERIALS AND METHODS

Patients. This study was approved by the institutional ethics committee of both hospitals. Inclusion criteria were a) age >16 yrs; b) history of acute blunt traumatic brain injury; c) injury date from January 1996 through June 2001; d) admission to index hospital within 24 hrs of injury; e) intracranial abnormalities on the initial computed tomography (CT) scan consistent with head trauma; and f) initial Glasgow Coma Scale (GCS) score ≤8 or GCS score deteriorating to ≤8 within 24 hrs following injury. If the GCS could not be reliably assessed or was not recorded, a maximum Abbreviated Injury Scale (AIS) score ≥4 in the head region was used as an alternative inclusion criterion (this includes intracranial hemorrhage, large contusions with mass effect, brain swelling with compressed ventricles and cisterns, complex [open] skull fractures, or any brain stem injury) (12). Patients who were unlikely to benefit from ICP/CPP-targeted therapy (i.e., patients who died within 24 hrs of injury, patients who obeyed commands 24 hrs after injury, and patients who were transferred out of the index hospital within 24 hrs of injury) were excluded.

Treatment Allocation. The Dutch trauma care system is organized within 26 regions, in which transfer agreements are operational with one of ten nationally designated level I trauma centers (13). Thus, allocation of patients to hospitals was solely based on the site of the accident. Center A, St. Elisabeth Hospital, Tilburg, serves an area in the southwest with a population of 1,000,000. Center B, University Medical Center, Utrecht, serves a central part of the country with a population of 2,600,000. In both study centers, seriously injured patients were resuscitated according to Advanced Trauma Life Support standards (14). In comatose patients, resuscitation was followed by a head CT scan and prompt evacuation of intracranial mass lesions, if indicated. Subsequently, patients were transferred to the ICU, which in both centers was staffed by intensivists.

In center A, severely head-injured patients were intubated and ventilated to maintain adequate oxygenation and normocarbia. Midazolam or propofol, plus morphine, was used for sedation. Pupillary size, shape, and reactivity to light, as well as spontaneous and evoked motor responses, were assessed and recorded hourly by the ICU nurses. Invasive mean arterial pressure was measured and maintained at approximately 90 mm Hg. ICP and CPP were not monitored, and the use of medical therapies to reduce brain swelling was thus solely based on clinical and radiologic findings. Approximately 24 hrs after injury, the head CT scan was repeated. If the basal cisterns were not compressed, sedation was discontinued (or interrupted) to allow full clinical evaluation by a neurologist. If a risk of cerebral herniation was suspected, or if sedation could not be discontinued for other pertinent reasons, patients were followed up by repeated CT scanning at regular intervals. Antipyretic drugs were used routinely, but physical cooling was initiated only occasionally when fever exceeded 39.0°C.

In center B, severely head-injured patients were managed according to an algorithm, which was in effect since 1996 and in compliance with the guidelines of the European Brain Injury Consortium and the American Brain Trauma Foundation (2, 15). According to this algorithm, all patients were intubated and ventilated to normocapnia. Propofol was used for sedation, with morphine as an analgesic adjunct. Pupillary and motor responses were assessed hourly. In addition to mean arterial pressure, ICP was routinely monitored (using an intraparenchymal pressure transducer) in patients with a GCS score ≤8. The continuous ICP, mean arterial pressure, and CPP recordings were logged into an ICU database (System Critical Care v1.3, Eclipsys Corporation, Delray Beach, FL) on an hourly basis. When intracranial hypertension (ICP >20 mm Hg for >10 mins) developed, a new CT scan was obtained and appropriate surgical measures were taken, if indicated. Patients who had a CPP <70 mm Hg were routinely given a continuous infusion of norepinephrine to maintain their CPP above this threshold. Reasons not to monitor ICP were generally related to the presence of coagulopathy, the judgment of the neurosurgeon after craniotomy, or, occasionally, a limit to the availability of monitoring devices. Second range therapy for intracranial hypertension included mannitol, muscle relaxants, and moderate hyperventilation, guided by jugular venous oximetry. Third range therapy included the use of high-dose barbiturates. When pyrexia evolved, cooling measures were taken to maintain temperature <38.0°C. Sedation and mechanical ventilation were continued until intracranial hypertension resolved.

Data Collection. From the trauma registry in each hospital, we identified all patients who had been admitted for a head injury resulting in loss of consciousness with CT scan abnormalities and assessed them for study eligibility by a review of the medical records. Data included information on neurologic and physiologic status at the accident scene and during in-hospital resuscitation, the presence and severity of associated injuries, laboratory variables, ICU management, surgical interventions, and complications. For patients meeting the inclusion criteria, CT scans were reviewed by one of the authors (GWD) and classified according to the Traumatic Coma Data Bank (16). For patients who were excluded, *a priori* survival probabilities were calculated with the Trauma and Injury Severity Score methodology (17). All clinical data were collected before the outcome was assessed.

Outcome Assessment. The primary study outcome was the extended Glasgow Outcome Scale (GOSe) after ≥12 months (18). Outcome was assessed between July 2002 and November 2003 by a trained research nurse using a structured telephone interview (19). This method allows for a reliable assessment of the GOSe (20). In 68% of survivors, interviews were conducted with both the patient and a family member, in 13% with the patient alone, and in 19% with a caretaker alone. For analysis, the GOSe was collapsed into three ordinal levels: a) dead, vegetative state, and lower severe disability; b) upper severe and moderate disability; and c) good recovery. A secondary measure of outcome was in-hospital mortality. Length of stay in the ICU and days on ventilator support were considered process indicators, reflecting the intensity of treatment and use of hospital resources.

Statistical Analysis. Missing values were present for 1% on injury cause, 4% on admission GCS, 1% on best GCS motor score, 5% on pupil reactivity, 9% on CT classification, 8% on base-deficit on admission, 1% on Revised Trauma Scores, and none on other variables. The distribution was similar across both centers. Since missing information can result in bias and loss of statistical power, we imputed variables with missing values using estimates that were generated by multiple linear regression and adjusted by a random residual value (MVA procedure, SPSS for Windows 10, SPPS, Chicago, IL). Characteristics and treatment-related variables of patients admitted to center A or B were compared by means of Pearson chi-square tests for categorical variables and Mann-Whitney tests for numerical variables. A proportional odds ordinal logistic regression model (S-Plus 2000, Insightful Corp, Seattle, WA) was used to estimate the effect of ICP/CPP-targeted treatment on the primary outcome (trichotomized GOSe) (21). The crude treatment effect was assessed by means of a summary odds ratio with 95% confidence interval (CI). Subsequently, this crude odds ratio was adjusted for potential confounding variables. Briefly, the confounding effect of single variables was first assessed in separate bivariate models. These variables included age, GCS motor score, pupil reactivity, CT classification, intracranial surgery, Injury Severity Score, AIS for the head region, Revised Trauma Score, injury cause, transfer status, hypotension, hypoxia, anemia, and base-deficit on admission. Subsequently, confounding variables were included in a multivariate analysis in a forward stepwise manner. The choice of variables to include in the final adjusted analysis was made by evaluating the change in the
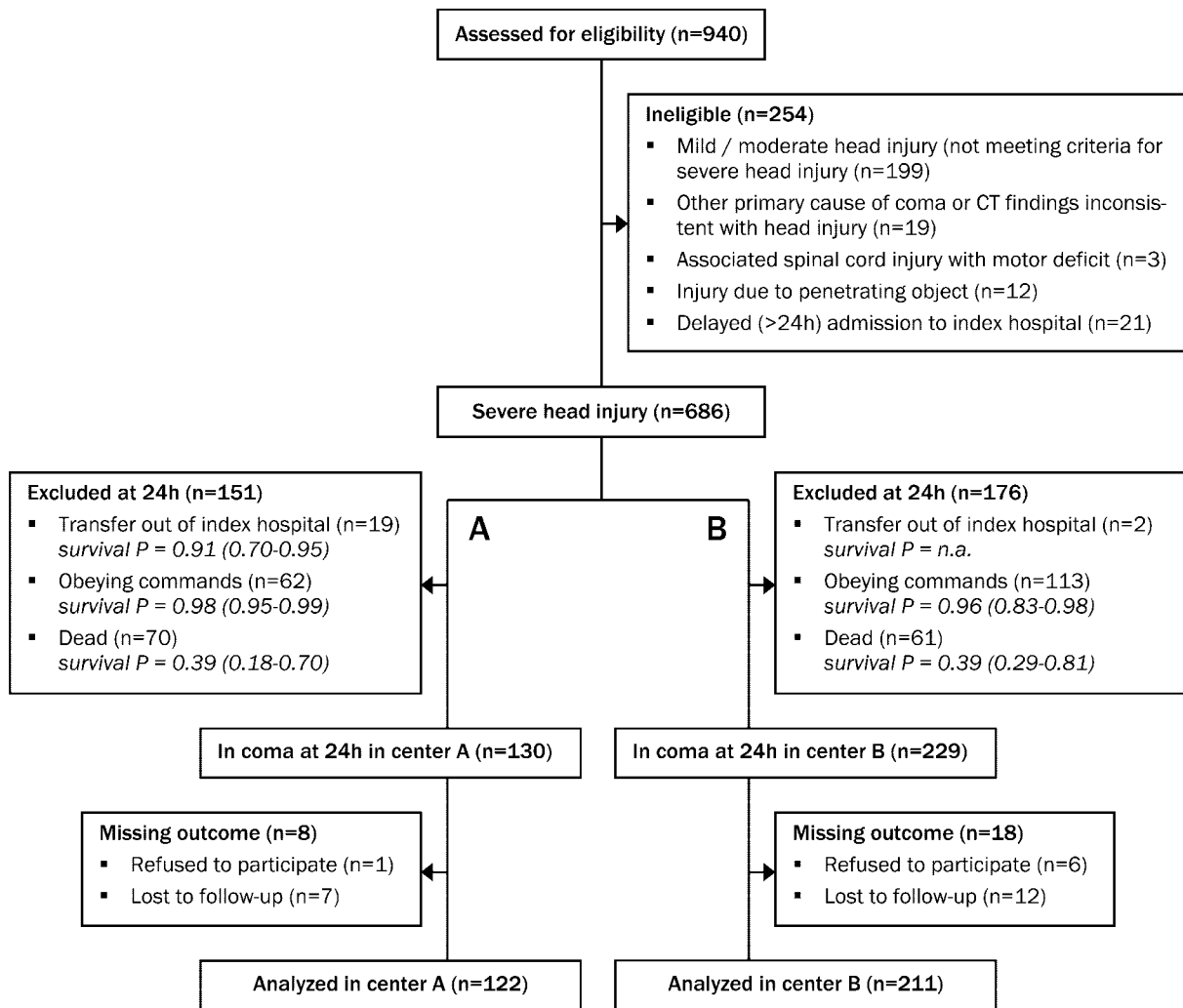
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                    Assessed for eligibility (n=940)
                                │
                                ├──────────────────────────────────────┐
                                │                     Ineligible (n=254)
                                │                     ▪ Mild / moderate head injury (not meeting criteria for
                                │                       severe head injury (n=199)
                                │                     ▪ Other primary cause of coma or CT findings inconsis-
                                │                       tent with head injury (n=19)
                                │                     ▪ Associated spinal cord injury with motor deficit (n=3)
                                │                     ▪ Injury due to penetrating object (n=12)
                                │                     ▪ Delayed (>24h) admission to index hospital (n=21)
                                │
                    Severe head injury (n=686)
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Excluded at 24h (n=151)
▪ Transfer out of index hospital (n=19)
  survival P = 0.91 (0.70-0.95)
▪ Obeying commands (n=62)
  survival P = 0.98 (0.95-0.99)
▪ Dead (n=70)
  survival P = 0.39 (0.18-0.70)

A **B**

Excluded at 24h (n=176)
▪ Transfer out of index hospital (n=2)
  survival P = n.a.
▪ Obeying commands (n=113)
  survival P = 0.96 (0.83-0.98)
▪ Dead (n=61)
  survival P = 0.39 (0.29-0.81)

In coma at 24h in center A (n=130)   In coma at 24h in center B (n=229)

Missing outcome (n=8)
▪ Refused to participate (n=1)
▪ Lost to follow-up (n=7)

Missing outcome (n=18)
▪ Refused to participate (n=6)
▪ Lost to follow-up (n=12)

Analyzed in center A (n=122)   Analyzed in center B (n=211)

Figure 1. Flow diagram of patient screening and study inclusion. *Survival P,* expected survival probability, calculated using the Trauma and Injury Severity Score methodology (17); *CT,* computed tomography.

effect estimate after each step (22). The ordinality and proportional odds assumptions for using the regression model were satisfied for both the determinant and confounding variables.

RESULTS

Figure 1 shows the study inclusion progress of the 940 patients who were initially identified from the trauma registries. The *a priori* predicted survival of patients who eventually died within 24 hrs of trauma was similar in centers A and B (median 0.39 and 0.39, respectively). Likewise, the survival probability of patients who obeyed commands within 24 hrs was also similar (median 0.98 and 0.96, respectively). For the 359 patients who met the inclusion criteria, outcome assessment was obtained in 122 of 130 (94%) and 211 of 229 (92%) of subjects,

in centers A and B respectively. The median duration of follow-up was 47 (25th–75th percentile, 36–67) months (both centers).

Table 1 shows characteristics and clinical features of the included patients. Gender, age, GCS on admission, the number of nonreactive pupils, and CT findings did not differ between the two centers. There were more injuries due to falls around the house in center A, compared with more injuries due to road traffic accidents and combined other causes in center B. Median admission delay differed by only 6 mins, but in center A there was a greater proportion of patients who were admitted with a delay of several hours after initial resuscitation at a local hospital. Also, in center A there were slightly more patients who had maintained spontaneous ventilation initially,

had been obeying commands, and had suffered from neurologic deterioration due to epidural hematoma. There were four (3%) patients in center A and 12 (6%) patients in center B in whom a reliable GCS (motor) score had not been recorded by the end of day 1 (these patients were included based on an AIS score ≥4 in the head region). The median Revised Trauma Score was similar in both centers, but hypoxia was more common in center A, whereas hypotension and anemia were more common in center B. Also, the Injury Severity Scores were very similar. In particular, there was no difference in the extent of associated chest injuries, injuries of other body regions, or rates of emergency laparotomy or thoracotomy.

Table 2 shows variables related to the therapeutic management of patients in

Table 1. Patient characteristics and clinical features on admission to hospital

	Center A (n = 122) No. (%) or Median (25th–75th Percentile)	Center B (n = 211) No. (%) or Median (25th–75th Percentile)	p Value
Female sex	40 (33)	67 (32)	.85
Age, yrs	39 (24–61)	38 (25–54)	.58
Injury cause			.002
Motor vehicle accident	32 (26)	73 (35)	
Pedestrian or cyclist in road traffic accident	46 (38)	80 (38)	
Domestic accident/fall	31 (25)	22 (10)	
Other[a]	13 (11)	36 (17)	
Admission delay to trauma center, hrs	1.1 (0.8–3.0)	1.0 (0.8–1.6)	.03
Secondary transfer to trauma center	34 (28)	39 (19)	.05
GCS on admission to first hospital			.23
3–5	29 (24)	49 (23)	
6–8	37 (30)	52 (25)	
9–12	23 (19)	33 (16)	
13–15	7 (6)	8 (4)	
Intubated/sedated/paralyzed	26 (21)	69 (33)	
Best GCS motor score on day 1			.06
1–3	41 (34)	96 (46)	
4–5	67 (55)	101 (48)	
6	14 (12)	14 (7)	
Number of nonreactive pupils			.86
0	80 (66)	136 (65)	
1	20 (16)	32 (15)	
2	22 (18)	43 (20)	
Admission CT scan classification[b]			.55
Diffuse injury	32 (26)	68 (32)	
Diffuse injury with swelling	49 (40)	84 (40)	
Diffuse injury with shift	7 (6)	13 (6)	
Mass lesions	34 (28)	46 (22)	
Emergency intracranial surgery			.15
None	92 (75)	160 (76)	
Evacuation of EDH	14 (12)	13 (6)	
Evacuation of SDH/ICH/contusion	16 (13)	38 (18)	
Arterial hypotension (systolic BP <90 mm Hg)	6 (5)	25 (12)	.04
Hypoxia (arterial oxygen saturation ≤85%)	24 (20)	26 (12)	.07
Pulmonary aspiration (suspected or definite)	17 (14)	20 (10)	.21
Hypothermia (core temperature <35°C)	44 (36)	64 (30)	.28
Anemia (hemoglobin <5.0 mmol/L)	6 (5)	22 (10)	.08
Base-deficit on admission (mmol/L)	2.8 (1.3–5.3)	3.2 (1.6–5.5)	.29
RTS (possible range 0–7.84; higher is better)	5.97 (4.74–6.17)	5.23 (4.74–5.97)	.17
ISS (possible range 0–75; higher is worse)	25 (17–29)	24 (17–29)	.85

GCS, Glasgow Coma Scale; CT, computed tomography; EDH, extradural hematoma; SDH, subdural hematoma; ICH, intracerebral hematoma; BP, blood pressure; RTS, Revised Trauma Score; ISS, Injury Severity Score.

[a]Other combines the categories work, assault, sport/recreation, fall under influence of alcohol, and suicide attempt; [b]CT scan category according to Traumatic Coma Data Bank classification (16).

the ICU. In center B, ICP monitoring was used in approximately two thirds and jugular venous oximetry in approximately half of the patients. Simultaneously, there was an increased use of therapeutic measures aimed at controlling intracranial hypertension and maintaining CPP above the specified threshold in center B. Although there was an increased use of blood pressure supportive agents, the incidence of low mean arterial pressure was similar in both centers. Fever occurred less frequently and/or was much more aggressively treated in center B.

In-hospital mortality rate was 41 (34%) and 69 (33%) in centers A and B,

respectively (p = .87). At the time of death, the median duration of hospitalization had been 3 (2–8) days in center A vs. 5 (3–9) days in center B (p = .11). In patients who were discharged alive, the duration of mechanical ventilation was 5 (2–9) days in center A vs. 12 (7–19) days in center B (p < .001). Likewise, the period of stay in the ICU was 8 (4–14) and 14 (8–23) days, respectively (p < .001).

Table 3 shows the GOSe at follow-up. There were no significant differences in functional outcome between the supportive and ICP/CPP-targeted centers. The absolute risk difference for attaining good recovery following ICP/CPP-targeted treat-

ment was −1% (90% CI, −8% to + 6%) compared with supportive intensive care. For the poorest outcome level, the risk difference was +1% (90% CI, −8% to +11%). Within this group, case fatality at the time of follow-up had increased to 55 (45%) in center A and 83 (39%) in center B (p = .31). From the survivors, five patients (8%) from center A and 15 patients (12%) from center B resided in a nursing home or comparable facility at the time of follow-up (p = .35), whereas the remainder lived at home.

The crude odds ratio (Table 4) for a more favorable outcome following ICP/CPP-targeted therapy was 0.95 (95% CI, 0.62–1.44). After adjustment for age, best motor score ≥4, presence of two nonreactive pupils, CT scan category, injury cause category, and evacuation of an extradural hematoma, the association remained unchanged. Adjustment for other variables (e.g., hypotension and hypoxia) did not change this result. In addition to the primary analysis that included all patients on an intention to treat basis, we also performed an on-treatment analysis, including all patients in center A and only the 142 patients in center B who actually had an ICP monitor. Compared with the 69 patients who were not monitored, these 142 patients were younger (p < .001), had worse motor scores (p = .05), were more frequently intubated on admission (p = .02), had more diffuse injuries with swelling and less mass lesions on the initial CT scan (p = .04), and required less often emergency intracranial surgery (p = .04). Nonetheless, the on-treatment analysis yielded similar results, with a nonsignificant trend toward improved outcome in center A after multivariate adjustment (Table 4).

DISCUSSION

We performed an observational study in two trauma centers in different regions of The Netherlands with contrasting approaches to intensive care management of severely head-injured patients. Compared with supportive intensive care without ICP monitoring, the use of an ICP/CPP-targeted treatment protocol resulted in a much longer period of mechanical ventilation and a more extensive use of medical therapies to control intracranial hypertension and maintain CPP. However, there was no evidence that such management improved functional status or survival.

Table 2. Characteristics and process variables related to management in the intensive care unit

	Center A (n = 122) No. (%)	Center B (n = 211) No. (%)	p Value
Monitoring			
ICP monitoring	0 (0)	142 (67)	<.001
Jugular venous oxygen saturation monitoring	1 (1)	102 (48)	<.001
Brain tissue oximetry	0 (0)	5 (2)	.09
Therapeutic measures[a]			
Sedatives ± muscle relaxants	100 (82)	195 (92)	.004
Blood pressure supportive agents	15 (12)	148 (70)	<.001
Mannitol	30 (25)	122 (58)	<.001
Hyperventilation ($Paco_2$ ≤30 torr [4.0 kPa])	27 (22)	62 (29)	.15
Barbiturates	0 (0)	33 (16)	<.001
Ventricular drainage	2 (2)	9 (4)	.20
Secondary events			
Mean arterial pressure <90 mm Hg[b]	37/109 (34)	59/163 (36)	.70
Intracranial pressure >20 mm Hg[b]	N/A	30/113 (27)	—
Cerebral perfusion pressure <70 mm Hg[b]	N/A	20/108 (19)	—
Temperature >38.0°C[b]	29/105 (28)	9/128 (7)	<.001
Delayed hematoma requiring evacuation	6 (5)	10 (5)	.94
Central nervous system infection[c]	4 (3)	7 (3)	.99
Sepsis[c]	6 (5)	18 (9)	.22
Adult respiratory distress syndrome[c]	9 (7)	11 (5)	.42

ICP, intracranial pressure; N/A, nonavailable.

[a]Therapeutic measures apply when used >24 hrs consecutively; [b]events apply when present for >50% of the monitored time during the first week of intensive care (only patients who had >24 hrs of continuous monitoring record available were analyzed); [c]diagnosis as recorded in the intensive care unit discharge letter.

Table 3. Extended Glasgow Outcome Scale at follow-up

Category	Center A (n = 122) No. (%)		Center B (n = 211) No. (%)	
Dead	55 (45)		83 (39)	
Vegetative state	1 (1)	58 (48)	1 (1)	103 (49)
Lower severe disability	2 (2)		19 (9)	
Upper severe disability	3 (3)		10 (5)	
Lower moderate disability	16 (13)	42 (34)	35 (17)	72 (34)
Upper moderate disability	23 (19)		27 (13)	
Lower good recovery	10 (8)	22 (18)	23 (11)	36 (17)
Upper good recovery	12 (10)		13 (6)	

Table 4. Summary odds ratios for a more favorable outcome on the extended Glasgow Outcome Scale

Analysis	No.	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Intention to treat	333	0.95 (0.62–1.44)	1.06 (0.63–1.77)
On treatment	264	0.92 (0.58–1.46)	0.83 (0.48–1.43)

OR, odds ratio; CI, confidence interval. A summary OR >1 favors better outcome for intracranial pressure/cerebral perfusion pressure-targeted intensive care (center B); a summary OR <1 favors better outcome for supportive intensive care (center A).

[a]Adjusted for age, best motor score ≥4, presence of 2 nonreactive pupils, computed tomography scan category, injury cause category, and evacuation of extradural hematoma.

The use of ICP monitoring and protocol-driven neurointensive care for severely head-injured patients remains controversial because no randomized controlled trials have been conducted. In the 1980s, several authors argued in favor of ICP/CPP-targeted therapies for traumatic brain injury by comparing mortality rates of 28–36% observed since the introduction of routine ICP monitoring (15), with an often quoted 50% mortality rate observed in 1977 in three centers by Jenett et al. (23). More recently, outcomes were compared between individuals who—during routine clinical practice—either did or did not receive an ICP monitor (4, 6). Obviously, confounding by indication is a major problem in this type of comparison. After adjustment for some markers of injury severity, the effect estimate in these studies varied from improved to worsened outcome when ICP/CPP monitoring was used.

We are aware of only few studies that compared cohorts of head-injured patients who were exposed to different approaches to ICP/CPP management. Gelpke et al. (24) found higher survival rates in centers with a more conservative management regimen compared with more "aggressive" treatment. Patel et al. (25) compared functional outcome between patients managed according to a contemporary ICP/CPP-guided protocol and historical controls from the same center. They found an improved functional status, but not a reduced mortality rate, in a *post hoc* subgroup of the severest cases only. In two other studies, outcome was compared between many trauma centers that were characterized by a more or less aggressive approach to ICP/CPP-targeted therapy (5, 26). Center aggressiveness was estimated from the observed frequency of ICP monitoring. Although in the study by Bulger and colleagues (5), center classification was based on an average of less than six contributing patients per study hospital and the potential for misclassification of the determinant was thus considerable, both studies found evidence of an association between more aggressive ICP/CPP-targeted management and improved clinical outcome. However, there is some inconsistency in the fact that a reduced mortality rate without a difference in functional status in survivors was reported, as well as an improved functional survival without a decrease in the rate of death. These studies relied on medical records to retrieve the GOS, and this may have caused significant misclassification of functional survival status.

In the present study we prospectively assessed long-term functional outcome after severe head injury in two Dutch hospitals and were unable to confirm even a trend toward improved functional survival in patients who were treated at the center that provided strict ICP/CPP-targeted care. Our study was pragmatically designed, implying that we analyzed different approaches to treatment of traumatic brain injury as observed in clinical practice, rather than a single intervention such as ICP monitor placement. As a consequence, our findings must be interpreted knowing that there were most likely differences in various other, unob-

served practices. Although Table 2 suggests that management in center B was much more aggressive, one third of the patients in this center had not actually received an ICP monitor, and this finding may have diluted a potential treatment effect. Reasons not to monitor ICP were most often related to the discretionary judgment of the attending neurosurgeon following decompressive surgery or anticoagulant use. Nonetheless, the 67% monitoring rate achieved in center B is high compared with other trauma centers that routinely use ICP monitors (4–6, 26). Moreover, we performed an on-treatment analysis, which yielded similar results as the intention to treat analysis, although the trend was more in favor of supportive intensive care (Table 4).

We did not investigate the potential benefit of ICP monitoring in the first 24 hrs after injury, for example, for the detection of rapidly expanding mass lesions needing surgical evacuation. We excluded patients who died on day 1, because we made the assumption that early death would be attributable to causes that were not amenable by ICP/CPP-targeted therapy in the ICU. Compared with center A, a smaller proportion of patients were excluded because of early death in center B. This finding could suggest a difference in case-mix and the presence of selection bias in the study. However, it is unlikely that this was the case, because the survival prognosis of excluded patients appeared to be similar on admission to either center (Fig. 1). Moreover, the apparently low number of exclusions for early death in center B could be explained by the fact that patients who had died on arrival in the emergency department were not represented in the original 940 patients who were assessed for study eligibility, because they were not marked as a hospital admission in the trauma registry in this center. In contrast with some of the earlier reports, confounding by indication was not a major problem in our study, because for patients referred to center A, ICP monitoring was simply not available, and for patients referred to center B, the primary analysis was done on an intention to treat basis. Furthermore, markers of injury severity were well balanced between the centers. As a consequence, multivariate statistical adjustment did not alter the interpretation of our crude findings. The possibility of residual confounding cannot be excluded

entirely, however, because this was a retrospective, observational study.

There are several reasons why ICP/CPP-targeted therapy need not necessarily result in improved outcome. First, aggressive goal-directed therapy fails to consistently control ICP below 20 mm Hg in approximately one fourth of patients (Table 2). Second, investigations show that even the successful response of systemic variables to therapy does not always result in a similar improvement of microcirculatory and mitochondrial function. For instance, it has been shown that CPP augmentation is relatively ineffective in reversing hypoperfusion in pericontusional ischemic areas (27) and only variably effective in improving ICP, cerebral autoregulation, and brain tissue oxygenation (28). Third, concerns have been raised that deliberate arterial hypertension to maintain CPP >50 mm Hg may aggravate intracranial hypertension when cerebral autoregulation is disturbed and the blood-brain barrier is disrupted (29). Fourth, there is an increasing awareness that an aggressive ICP/CPP-targeted critical care approach may result in cardiorespiratory complications. The Baylor group reported an increased incidence of adult respiratory distress syndrome with a treatment protocol targeted at maintaining CPP >70 mm Hg (10). In response to this finding, the Brain Trauma Foundation (30) in 2003 issued an update of their guidelines for CPP management, lowering the treatment threshold to 60 mm Hg. We recently reported on the risk of cardiac failure following long-term high-dose infusions of propofol and vasopressors in the setting of ICP/CPP-targeted management of severely head-injured patients (11). In the present study, we observed similar distributions of mean arterial pressure in both centers during the first week of stay in the ICU, despite the fact that more patients in center B received a continuous infusion of dopamine or norepinephrine for ≥24 hrs (Table 2). This finding could be related to the overall increased length of stay and the higher incidence of hypotension on admission in center B, but it is also possible that catecholamines were used more frequently in center B merely to compensate the hemodynamic effects of infusing mannitol and sedatives, including high-dose barbiturates. Together, these observations suggest that ICP/CPP-targeted management does not consistently improve systemic and cerebral physiologic

homeostasis and that its potential benefits may be offset by an increased risk of cardiac and pulmonary complications.

Even though in our study the trend was in favor of supportive intensive care, statistical uncertainty still allowed for a limited potential benefit in favor of ICP/CPP-targeted intensive care. If we consider only the upper limit of the 90% CI for the absolute risk difference for good recovery, however, we can be 95% certain that this potential benefit is <6%. In other words, if we were still to assume that ICP/CPP-targeted treatment is helpful, from this study we can be 95% certain that the number needed to treat would be ≥16 patients to benefit one individual (31). However, there is considerable heterogeneity in the pathophysiology of head injury, and it is conceivable that a possible treatment effect would be more pronounced in specific subgroups of patients. The logical approach to resolving these uncertainties is to conduct a properly designed, adequately powered, randomized controlled trial. Such a trial should be targeted on patients who are most likely to profit from ICP/CPP-targeted therapy (excluding patients with a high likelihood of an extreme outcome) and should use an ordinal outcome measure that is sensitive to changes in the order of magnitude of a potential treatment effect (32). Practically, this means it would require a sample size of approximately 400–600 patients (depending on the observed distribution of outcomes) to detect a 15% absolute increase in the proportion of patients having one of the two better outcomes on the trichotomized GOSe with a power of 90% (33).

CONCLUSIONS

The clinical studies that have estimated the impact of ICP monitoring and aggressive target-driven treatment on outcome after head injury suffer from various methodological limitations. Furthermore, the data indicate that the perceived benefits may be small or nonexistent. Therefore, these studies do not support the use of such therapy as a standard of care. In the present study we were unable to demonstrate even a trend toward a more favorable functional outcome with the use of an ICP/CPP-targeted critical care protocol, but there was a large increase in therapy intensity levels and use of hospital resources. Therefore, a randomized-controlled comparison of ICP/CPP-targeted manage-

Intracranial pressure/ cerebral perfusion pressure-targeted intensive care results in prolonged mechanical ventilation and increased levels of therapy intensity, without evidence for improved outcome in patients who survive beyond 24 hrs following severe head injury.

ment vs. supportive critical care, without ICP monitoring, is warranted and ethically acceptable in patients with severe head injury.

ACKNOWLEDGMENTS

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