CPP/ICP Clinical Trial

Claudia S. Robertson, M.D.[1] *Alex B. Valadka, M.D.*[1] *H. Julia Hannay, Ph.D.*[2]
Charles F. Contant, Ph.D.[1] *Shankar P. Gopinath, M.D.*[1] *Manuela Cormio, M.D.*[1]
Masahiko Uzura, M.D.[1] *Robert G. Grossman, M.D.*[1]
[1] Department of Neurosurgery. Baylor College of Medicine
[2] Department of Psychology. University of Houston

ABSTRACT

The purpose of this study was to compare the effects of two acute-care management strategies on the incidence of jugular venous desaturation, refractory intracranial hypertension, and on long-term neurological outcome in patients with severe head injury. Patients were assigned to either cerebral blood flow (CBF)-targeted or intracranial pressure (ICP)-targeted management protocols during randomly assigned time blocks. In the CBF-targeted protocol, cerebral perfusion pressure was kept > 70 mm Hg, and pC02 was kept approximately 35 mm Hg. In the ICP-targeted protocol, cerebral perfusion pressure was kept > 50 mm Hg, and hyperventilation to a pCO* of 25-30 mm Hg was used to treat intracranial hypertension. The CBF-targeted protocol reduced the incidence of jugular desaturation from 50.6% to 30% (p = .006). Even when the incidence of jugular desaturation was adjusted for al1 confounding factors that were significant, the risk of cerebral ischemia was 2.4-fold greater with the ICP-targeted protocol. Despite the reduction in secondary ischemic insults, there was no difference in neurological outcome. Failure to alter long-term neurological outcome was probably due to two major factors. A low jugular venous oxygen saturation was treated in both groups, minimizing the injury that occurred in the ICP-targeted group. The beneficial effects of the CBF-targeted protocol may have been offset by a 5-fold increase in the incidence of adult respiratory distress syndrome.
Secondary ischemic insults due to systemic factors after severe head injury can be prevented with a targeted management protocol. However, potential adverse effects of this management strategy may offset these beneficial effects.

INTRODUCTION

A number of clinical studies have suggested that a normal cerebral perfusion pressure (CPP) is often inadequate in patients with severe head injury, and that an elevated CPP is necessary to assure adequate cerebral perfusion [1;4]. Clinical series advocating this type of management strategy al1 indicate a reduction in mortality rate of nearly 50% with a corresponding increase in the number of patients with a favorable outcome 2-4. Since these clinical series are not randomized trials, it is difficult to be certain that the patients are comparable, and that there are not other improvements in care, such as in transport, early resuscitation, and other aspects of critica1 care management, that may account for the improved outcome.
The purpose of this study was to compare two management protocols: (1). Intracranial pressure (ICP)-targeted management, where therapies are directed at reducing ICP regardless of the resulting effect on CBF adequacy, and (2). CBF-targeted management, where therapies are

directed at trying to maintain an adequate CBF and to prevent secondary ischemic insults. The adequacy of CBF was judged by monitoring jugular venous oxygen saturation (Sjv02).

METHODS

The following three hypotheses were tested in a randomized clinical trial: (1) The CBF-targeted management will reduce the incidence of jugular venous desaturation, (2) the CBF-targeted management will decrease the incidence of refractory intracranial hypertension, and (3) the CBF-targeted management will result in better long-term outcome.

Eligibility criteria for the trial included: (1) coma (motor Glasgow Coma Score [GCS] $\leq$ 5 due to head injury, (2) age $\geq$ 15 years, (3) admission within 12 hours of injury. Exclusion criteria included the following: (1) GCS 3 with fixed and dilated pupils after resuscitation, (2) contraindication to placement of jugular bulb catheter, (3) severe associated systemic injury.

The major differences between the ICP-targeted protocol and the CBF-targeted protocol were the treatment goals for mean arterial pressure (MAP), CPP, and arterial pCO2 ($paCO_2$). In the ICP-targeted protocol, MAP was kept at least 70 mm Hg, and systolic blood pressures greater than 160 mm Hg were treated with anti-hypertensive agents. CPP was kept at least 50 mm Hg. Although hyperventilation was not used as a routine in either protocol, hyperventilation to a paC02 of 25-30 mm Hg was used as a treatment of increased ICP in the ICP-targeted protocol. In the CBF-targeted protocol, MAP was kept at least 90 mm Hg and CPP was kept at least 70 mm Hg. Hyperventilation was not used to treat intracranial hypertension.

Randomization was performed by time period rather than patient since it would have been difficult to have patients in the ICU on both protocols simultaneously. For this purpose, the year was divided into three four-month periods, corresponding to the rotations of the Neurosurgery residents through the ICU. Each four-month period was divided into two treatment blocks so that both treatment protocols were given in each four-month interval. All patients entering the ICU during each two-month time period received the same treatment. The order in which the treatment protocols were given was randomly selected for each four-month period. Therefore, if the patients were arriving at the hospital as the result of random process, the treatment provided to each patient would also be random.

The primary outcome variable was the incidence of jugular venous desaturation, defined as an SjvOZ < 50% for more than 10 minutes (excluding jugular desaturation occurring as a terminal event). Secondary outcome variables were the incidence of refractory intracranial hypertension and the 3 and 6 month Glasgow Outcome Score (GOS) and Disability Rating Scale (DRS).

Three potential complications of the CBF-targeted protocol were examined in the trial. The first possible problem might be that maintaining the blood pressure at a higher-than-normal level in a patient with severe head injury would result in an increased incidence of intracranial hemorrhage. The remaining two potential complications, adult respiratory distress syndrome (ARDS) and acute renal failure could result from the additional tluid and/or pressor agents required to maintain the blood pressure at the higher than normal level.

Categorical data are presented as proportions. Comparisons of categorical and nominal data were performed using the chi-square test for contingency tables or, when the expected cell sizes were low, Fisher's exact test. Continuous data are presented showing the mean, standard deviation and median. Comparisons of continuous data were performed using the Mann-Whitney or Kruskal-Wallis tests for comparing medians. To evaluate the effect of more than one predictor on a dichotomous variable, a logistic regression model was constructed.

A logistic regression model was fit for the primary and secondary outcome measures to determine if adjustment for potential confounders was required. Each model consisted of an indicator for the treatment group, variables that were a priori considered important, and a group of variables that may contribute to the model. The treatment group variable and the *a priori* selected variables were kept in all models. Other variables were removed using a backward selection procedure. A model was fit using only demographic and injury description variables. Using only the significant predictors from this model, a second model was fit using physiologic variables.

RESULTS

Demographic Characteristics of Patients

One hundred and eighty-nine patients were entered into the study, 100 into the CBF-targeted group and 89 into the ICP-targeted group. The small difference in the total number of patients between the two treatment groups did not reflect an obvious bias in the enrollment of patients. The proportion of patients randomized during the ICP blocks and the CBF blocks were not significantly different ($p = .707$), and the two groups were well-balanced for demographic characteristics and for injury severity parameters.

Primarv Outcome: Incidence of jugular venous desaturation

The primary hypothesis tested by the study was that the CBF-targeted protocol would reduce the incidence of jugular venous desaturation. Seventy-five (39.7%) of the patients had at least one episode of jugular venous desaturation, 45 (50.6%) of the patients in the ICP-targeted group and 30 (30%) of the patients in the CBF-targeted group ($X^2 = 7.81$, $p = .006$). Thirty-eight (20.0%) of the total group of patients had only one episode of jugular venous desaturation, 22 (24.7%) of the patients in the ICP-targeted group, compared to 16 (16%) of the patients in the CBF-targeted group. Thirty (15.9%) of the patients had 2 or more episodes of jugular venous desaturation, 20 (22.5%) of the patients in the ICP-targeted group, and 10 (10%) of the patients in the CBF-targeted group.

Logistic regression analysis was used to adjust the primary outcome variable for demographic characteristics and injury severity parameters. Patients in the ICP-targeted group had a 2.367-fold higher risk of having an episode of jugular venous desaturation than the patients in the CBF-targeted group, when adjusted for the duration of monitoring, day one motor score, presence of a mass lesion on the admission CT scan, and pupillary reactivity on day one.

Differences in Secondarv Outcome Measures

Incidence of Refractory Intracranial Hypertension

The second hypothesis tested by this study was that if the CBF-targeted protocol reduced the incidence of secondary ischemic insults, then the patients would have less severe intracranial hypertension.

The median duration of ICP monitoring was 96 hrs for the ICP-targeted group and 80 hrs for the CBF-targeted group ($p = .890$). The average ICP during the entire monitoring period was similar in the two treatment groups. The number of patients that developed intracranial hypertension severe enough to require treatment with barbiturate coma or that resulted in death was similar in the 2 treatment groups, 22 (24.7%) of the patients in the ICP-targeted group compared to 26 (26%) of the patients in the CBF-targeted group. Thirteen (14.6%) of the patients in the ICP-targeted group died of intracranial hypertension, while 12 (12%) of the patients in the CBF-targeted group died of refractory intracranial hypertension.

Neurological Outcome

Neurological recovery was assessed at 3 and 6 months after injury using GOS and DRS. The proportion of patients having a favorable recovery (good recovery or moderate disability) at 3 months was 37.0% in the ICP-targeted group and 3 1.9% in the CBF-targeted group (p = .554). The median DRS was 6 (4,23) in the ICP-targeted group and 12 (5,28.3) in the CBF-targeted group. At 6 months after injury, 49.3% of the ICP-targeted group and 39.8% of the CBF-targeted group had a favorable outcome (p = .491). The DRS was 5 (2,30) in the ICP-targeted group and 8 (3,30) in the CBF-targeted group.

Potential Complications of the Treatment Protocols

Delayed/Recurrent Intracranial Hematomas

One potential concern about keeping blood pressure at a higher than normal level in a head injured patient is the risk of increasing hemorrhage into the injured brain. The incidence of delayed traumatic intracerebral hematomas, however, was not significantly different in the two treatment groups, 25 (28.1%) and 24 (24%) in the ICP- and CBF-targeted groups, respectively (p = .991). A delayed or recurrent extracerebral hematoma developed in 7 (7.9%1) of the patients in the ICP-targeted group and 14 (14%) of the patients in the CBF-targeted group (p = .469).

Adult Respiratory Distress Syndrome

A second potential concern about maintaining blood pressure at a higher than normal level in a head injured patient is the risk of adult respiratory distress syndrome (ARDS). Overall 18 (10%) of the 189 patients enrolled in the trial developed ARDS. In 5 (3%) of the 189 patients, ARDS either directly caused or contributed to the patient's death.

The incidence of developing ARDS was nearly 5 times more common in the CBF-targeted group, 15% compared to 3.3% (p = .007). In addition, severa1 treatment and physiological parameters were significantly different in the patients that developed ARDS. Fluid intake was greater (p = .004) and the I/O balance was more positive (p = .014) in the patients who developed ARDS. The PWP (p = .0483) and the CVP (p = .0004) were higher in the patients with ARDS. Pressor agents were not used in higher doses, but dopamine (p = .0007) and epinephrine (p = .00l) were both used for a longer period of time in the patients who developed ARDS.

Acute Renal Failure

A third potential concern about maintaining blood pressure higher than normal in a head-injured patient is renal complications caused by pressor agents. Only one of the 189 patients developed acute renal failure. This patient was in the CBF-targeted group, and developed renal failure as one manifestation of multiple organ failure due to sepsis.

DISCUSSION

The CBF-targeted management protocol was successful in the goal of reducing secondary ischemic insults. The incidence of jugular venous desaturation, the number of episodes of desaturation for the group, and the total duration of time that the $SjvO_2$ was less than the critica1 threshold of 50% were al1 significantly less in the CBF-targeted group. However, this reduction in the incidence of secondary insults did not translate into an improvement in long-term neurological outcome. An important factor in the failure of the CBF-targeted treatment protocol to improve outcome was that jugular venous

desaturation, when discovered, was treated in both groups. This treatment tended to minimize the duration of time that $SjvO_2$ was low in both groups and probably minimized any injury that might have otherwise occurred.

Another contributing factor to the lack of treatment effect on long-term outcome may be that any benefits afforded by the reduction in ischemic insults were offset by other adverse effects of the protocol. The first adverse effect observed with the CBF-targeted protocol was that there was a higher incidence of ARDS. The second potential adverse consequence of the CBF-targeted protocol suggested by the present study is the effect on refractory intracranial hypertension.

Another consideration is the small size of the study that was designed primarily to compare the effect of the treatment protocols on the incidence of jugular venous desaturation rather than on the long term neurological outcome. The power calculations suggested that an improvement in the number of favorable outcomes from 35% to 54% could be detected with the numbers of patients included in the study. The contribution of secondary ischemic insults to outcome may be smaller than this.

The approach of treating all patients by artificially maintaining CPP at an elevated leve1 to compensate for the injured brain's inability to autoregulate at more normal CPP levels may be too simplistic. If used in all patients, potential adverse effects of this management strategy may offset beneficial effects. Future research should concentrate on understanding the underlying mechanism for impaired autoregulation after trauma and on identifying individual patients in whom CBF-targeted management might be specifically indicated.

REFERENCES

1. Changaris DG, McGraw CP, Richardson JD, et al: Correlation of cerebral perfusion pressure and Glasgow Coma Scale to outcome. J Trauma 27: 1007- 10 13, 1987

2. Marion DW, Carlier PM, Obrist WD, et al: Treatment of cerebral ischemia improves outcome following severe traumatic brain injury. J Neurotrauma I0(supp1 I):SI02,1993(Abstract)

3. Rosner MJ, Daughton S: Cerebral perfusion pressure management in head injury. J Trauma 30 :933-941,1990

4. Rosner MJ, Rosner SD, Johnson AH: Cerebral perfusion pressure: management protocol and clinical results. J Neurosurg 83:949-962, 1995

Address for correspondence:
Dr. Claudia Robertson
Dep. of Neurosurgery.
Baylor College of Medicine 1 B Plaza
Houston Texas
77030 USA