Effect of Continuous Display of Cerebral Perfusion Pressure on Outcomes in Patients With Traumatic Brain Injury
Catherine J. Kirkness, Robert L. Burr, Kevin C. Cain, David W. Newell and Pamela H. Mitchell

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Effect of Continuous Display of Cerebral Perfusion Pressure on Outcomes in Patients With Traumatic Brain Injury

By Catherine J. Kirkness, RN, PhD, Robert L. Burr, MSEE, PhD, Kevin C. Cain, PhD, David W. Newell, MD, and Pamela H. Mitchell, RN, PhD. From Biobehavioral Nursing and Health Systems (CJK, RLB, PHM), Biostatistics and Office for Nursing Research (KCC), University of Washington, Seattle, Wash, and Seattle Neuroscience Institute at Swedish Medical Center, Seattle, Wash (DWN).

- **BACKGROUND** Clinical bedside monitoring systems do not provide prominent displays of data on cerebral perfusion pressure (CPP). Immediate visual feedback would allow more rapid intervention to prevent or minimize suboptimal pressures.

- **OBJECTIVE** To evaluate the effect of a highly visible CPP display on immediate and long-term functional outcome in patients with traumatic brain injury.

- **METHODS** A total of 157 patients with traumatic brain injury at a level 1 trauma center who had invasive arterial blood pressure and intracranial pressure monitoring were randomized to beds with or without an additional, prominent continuous CPP display. Primary end points were scores on the Extended Glasgow Outcome Scale (GOSE) and Functional Status Examination (FSE) 6 months after injury. Secondary end points were GOSE scores at discharge and 3 months after injury and FSE score 3 months after injury.

- **RESULTS** Although GOSE and FSE scores at 6 months were better in the group with the highly visible CPP display, the differences were not significant. Slope of recovery for GOSE and FSE over all follow-up time points did not differ significantly between groups. However, the intervention’s positive effect on odds of survival at hospital discharge was strong and significant. Within a subgroup of more severely injured patients, the intervention group was much less likely than the control group to have CPP deviations.

- **CONCLUSION** The presence of a highly visible display of CPP was associated with significantly better odds of survival and overall condition at discharge. (American Journal of Critical Care. 2006;15:600-610)

Cerebral ischemia after traumatic brain injury (TBI) is associated with adverse outcomes and death. Thus, maintaining adequate cerebral perfusion to prevent secondary ischemic brain injury is a critical goal in the management of acute brain injury.1-15 Cerebral perfusion pressure (CPP), the difference between mean arterial blood pressure (ABP) and mean intracranial pressure (ICP), is commonly

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**CE Article**

Notice to CE enrollees: A closed-book, multiple-choice examination following this article tests your understanding of the following objectives:

1. Identify the relevance of knowledge of CPP level to nursing care.
2. Identify the most critical CPP threshold level supported by findings of this study.
3. Discuss findings of the research related to continuous display of CPP on the outcomes of patients with traumatic brain injury.

To read this article and take the CE test online, visit www.ajcconline.org and click “CE Articles in This Issue.”
monitored as an estimate of global adequacy of cerebral blood delivery in patients with moderate to severe TBI. Decreases in CPP can occur during nursing care activities such as positioning or suctioning. Such decreases, though transient, may contribute to secondary brain injury, particularly in patients with impaired autoregulation who cannot adequately compensate for changes in systemic blood pressure. In addition, monitoring of CPP by nurses is a prerequisite for adjustment of medical management of CPP, such as administration of fluids, vasopressors, or mannitol.

Although nurses are aware of the importance of keeping CPP above a critical threshold, this awareness is generally in the context of 30-minute or hourly recordings of CPP. Current clinical bedside monitoring systems can display digital or analog “snapshots” of the immediate CPP, but the monitors are usually placed out of the clinician’s sightline, the snapshots are often small, and the CPP is often separated into an ABP display and an ICP display. Furthermore, current monitoring systems do not continuously display the trend in CPP over the past minutes or hours. Instead, a record of the trend must be printed out, often away from the patient’s bedside. Thus, changes in CPP that occur on a minute-to-minute basis, in relation to care, may not be visible or easily retrievable by critical care nurses to evaluate the effects of ongoing care.

Even transient decreases in CPP may contribute to secondary brain injury.

Trends of declining CPP may not be recognized until CPP decreases below a critical level, thereby precluding nurses from preventing a serious decrease in CPP and requiring rescue rather than prevention. Therefore, we reasoned that highly visible, prominent displays of CPP information might enhance visibility and awareness of transient alterations in CPP related to care or of early trends of declining CPP. Immediate, sustained, and highly visible CPP information feedback would allow more rapid interventions such as elevation of a patient’s head to decrease ICP or adjustment in doses of sedatives or vasopressors to prevent or minimize suboptimal CPP. Therefore, we would expect to see fewer episodes of suboptimal CPP in patients with this highly visible display. To the extent that suboptimal CPP mediates secondary brain injury, we would expect to see improved short- and long-term functional outcomes in patients managed by using this display.

Objective
This study was a randomized controlled trial in the context of traditional ICP-oriented medical management to evaluate the effect of a bedside system of highly visible CPP information on outcomes over time in patients with TBI. Two research questions are addressed in this report:

1. Compared with the presence of a standard monitoring display, is the presence of the active CPP display associated with a better overall outcome, as indicated by the score on the Extended Glasgow Outcome Scale (GOSE) at discharge and better scores on the GOSE and the Functional Status Examination (FSE) at 3 and 6 months after brain injury?

2. Do deviations of CPP to less than threshold values differ by visibility of display?

Methods
Sample
Consecutive patients 16 years or older who were admitted to an intensive care unit at Harborview Medical Center, a level I trauma center in Seattle, Wash, with moderate to severe TBI and who underwent invasive ICP and ABP monitoring were eligible to be enrolled in the study. Patients were enrolled within 24 hours of having the ICP monitoring catheter inserted. Exclusion criteria included bilateral fixed pupils and impending death. Medical management of patients with TBI at the medical center included early surgical management of intracranial mass lesions and a traditional approach to minimizing or preventing potential secondary brain injuries and treating intracranial hypertension.

In addition to ICP management with sedatives and mannitol or furosemide, CPP management included elevation of ABP by administering fluids and pharmacological agents as needed, generally to maintain CPP above a threshold of 60 mm Hg. Patients’ outcomes were assessed at the time of discharge from the hospital and 3 and 6 months after injury by trained interviewers who were unaware what type of CPP monitoring each patient had (group assignment). Approval for the protection of human subjects was received from the University of Washington’s institutional review board; written consent for follow-up was obtained from the patients and/or their surrogates as appropriate.

Intervention and Randomization
Consecutive eligible patients admitted to the intensive care units during the study period were randomized to beds with either a highly visible active CPP display computer (intervention) or a blank CPP display computer (control) placed on a stand at the head of the bed. The active display consisted of a bar graph reflecting

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CPP during a half-hour period, with bars displayed in different colors depending on whether CPP was greater than or less than a threshold of 70 mm Hg (Figure 1). The threshold of 70 mm Hg was selected on the basis of the recommendation from the guidelines for the management of severe TBI that were current when the study began. The active CPP display also included the numeric CPP value. The display was updated every 5 seconds. The control display showed a black screen with the message “Program Running. Please Do Not Adjust” (Figure 1).

The standard hospital clinical monitors remained in place throughout the study but, as described earlier, were not as highly visible from all angles as were the study monitors. Group assignment could not be masked from the care providers or from the patients and the patients’ families. However, the personnel who assessed patients’ outcomes had no knowledge of group assignments. A block randomization procedure was used; the block size varied randomly between 4 and 6. Randomization assignments were put into consecutively numbered envelopes and sealed. Research nurses selected the envelopes consecutively and set up the appropriate monitor as patients entered the study.

**Outcome Assessment**

The primary end points were the scores on the GOSE and the FSE, assessed 6 months after the injury. Secondary end points were the GOSE score at discharge and 3 months after injury and the FSE score 3 months after injury. The GOSE extends the widely used Glasgow Outcome Scale to an 8-point scale by dividing each of the severe-disability, moderate-disability, and good-recovery categories additionally into an upper and a lower category.

Scores on the GOSE range from 1 (dead) to 8 (upper category of good recovery); higher scores reflect better function. The FSE is used to assess changes that occur as a result of acute brain injury in relation to physical, social, and psychological functioning and financial independence. For each of 10 functional status categories, scores range from 0 (no change in functioning from before brain injury) to 3 (complete dependence). These scores are summed for a total score from 0 to 30; higher scores reflect poorer functioning. An FSE score of 31 is assigned to patients who have died. Thus, mortality is included in the scoring of both functional outcome measures.

**Measurement of Other Variables**

Demographic (age, sex), diagnostic (computed tomography, magnetic resonance imaging), and management (medical, pharmacological, or surgical intervention) data were recorded from medical records. Postresuscitation Glasgow Coma Scale (GCS-PR) scores were recorded to reflect the severity of head injury. To account for other trauma-related injuries, scores on the Injury Severity Scale were also obtained. ABP was monitored via an intra-arterial catheter connected to Transpect pressure transducers (Abbott Laboratories, Abbott Park, Ill). ICP was measured via a Camino transducer-tipped catheter (Integra LifeSciences, Plainsboro, NJ) inserted intraparenchymally. The display computer received analog input from the bedside monitoring system (Spacelabs Medical, Redmond, Wash), sampling the signals at a rate of 100 Hz. CPP was calculated as mean ABP minus mean ICP. ICP and ABP data were saved to the display computers in 5-second summaries.
Statistical Methods

All data analyses were conducted by adjusting for age, sex, and severity of injury (GCS-PR and Injury Severity Scale) because of the strong influence on survival previously established for these variables. The Student t test and χ² test were used to compare baseline characteristics. Both GOSE and FSE scores were treated as interval variables for the main statistical analyses. Logistic regression, with adjustments for age, sex, and severity of injury, was used when the GOSE score was analyzed as a categorical, dichotomous outcome (dead versus alive). We analyzed the overall intervention effect over time by using growth curve analysis based on hierarchical linear mixed modeling. This method allowed us to characterize the typical within-subject pattern of the outcome scale scores over time.

Results

A total of 157 patients were enrolled from March 2000 to January 2002. Baseline demographics of patients and clinical variables are presented in Table 1. Most clinical and demographic factors were similar in the control and intervention groups. However, the percentage of patients with GCS-PR motor scores of 4 or less was significantly higher in the intervention group (P = .02), reflecting a greater proportion with the most severe head injury in this group. Scores on the Injury Severity Scale did not differ significantly between groups. Falls were a more frequent mechanism of injury in the intervention group than in the control group.

The primary prespecified end point was functional outcome as represented by GOSE and FSE scores at 6 months after injury. Although the mean GOSE score adjusted for age, sex, and severity of injury was analyzed as a categorical, dichotomous outcome (dead versus alive). We analyzed the overall intervention effect over time by using growth curve analysis based on hierarchical linear mixed modeling. This method allowed us to characterize the typical within-subject pattern of the outcome scale scores over time.

### Table 1: Comparison of baseline demographics and initial clinical characteristics of patients in the control group and the intervention group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 78)</th>
<th>Intervention (n = 79)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>36 (18)</td>
<td>38 (18)</td>
<td>.60</td>
</tr>
<tr>
<td>Sex, % of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>80</td>
<td>79</td>
<td>.88</td>
</tr>
<tr>
<td>Score on Postresuscitation Glasgow Coma Scale, mean (SD)</td>
<td>7.5 (3.0)</td>
<td>7.0 (3.1)</td>
<td>.43</td>
</tr>
<tr>
<td>No. (%) of patients with scores ≤ 6</td>
<td>27 (35)</td>
<td>43 (54)</td>
<td>.01</td>
</tr>
<tr>
<td>No. (%) of patients with motor scores ≤ 4</td>
<td>31 (40)</td>
<td>46 (58)</td>
<td>.02</td>
</tr>
<tr>
<td>Score on Injury Severity Scale, mean (SD)</td>
<td>29 (10)</td>
<td>29 (10)</td>
<td>.84</td>
</tr>
<tr>
<td>Craniectomy, % of patients</td>
<td>28</td>
<td>22</td>
<td>.36</td>
</tr>
<tr>
<td>Computed tomography findings, % of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contusion</td>
<td>71</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Epidural hematoma</td>
<td>27</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Subdural hematoma</td>
<td>49</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Shear injury</td>
<td>35</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>8</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>30</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Mechanism of injury, % of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor vehicle accident</td>
<td>47</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>12</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Motorcycle accident</td>
<td>12</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Pedestrian hit by a motor vehicle</td>
<td>12</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Assault</td>
<td>8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Bicycle accident</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

* Student t test was used for continuous variables, χ² test for categorical variables. P values were not computed for computed tomography findings or mechanism of injury.
GOSE scores for the intervention group were significantly higher than scores for the control group at discharge ($P = .01$), but not at 3 months (Figure 2, Table 2). FSE scores at 3 months after injury were nearly identical in the 2 groups (Figure 3, Table 2).

**Change in Function Over Time**

At discharge from the hospital, the median GOSE score of survivors reflected severe disability (unable to function for 24 hours without at least some assistance). By 6 months, the median GOSE score of survivors reflected functional status at a level of moderate disability, indicating independence in personal care but ongoing disability and inability to return to prior work. The FSE score is obtainable only at 3 and 6 months and shows a similar but more detailed pattern of increasing independence but not full recovery. When these outcomes were tested with hierarchical linear modeling, no significant difference was found in the slope of the recovery trajectory during the 6 months after injury, according to either GOSE or FSE scores ($P = .88$ and $P = .64$, respectively; Figures 2 and 3; Table 3).

**Table 2** Comparison of scores on the Extended Glasgow Outcome Scale (GOSE) and the Functional Status Examination (FSE) over time between the control group and the intervention group*

<table>
<thead>
<tr>
<th>Time</th>
<th>GOSE score, mean (SD)</th>
<th>FSE score, mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (n = 78)</td>
<td>Intervention (n = 79)</td>
</tr>
<tr>
<td>Discharge</td>
<td>2.55 (0.66)</td>
<td>2.82 (0.66)</td>
</tr>
<tr>
<td>3 months after injury</td>
<td>3.50 (1.37)</td>
<td>3.72 (1.32)</td>
</tr>
<tr>
<td>6 months after injury</td>
<td>4.16 (1.64)</td>
<td>4.37 (1.64)</td>
</tr>
</tbody>
</table>

* Values are adjusted for each patient’s age, sex, and severity of initial injury. Effect size is noted as the difference in means, with 95% confidence interval of the difference.

Abbreviation: NA, not applicable.
Table 3  Hierarchical linear growth curve modeling of outcome trajectory for 6 months after injury*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Coefficient</th>
<th>SE</th>
<th>t ratio</th>
<th>Approximate df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>Control</td>
<td>2.58</td>
<td>0.19</td>
<td>13.72</td>
<td>151</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
<td>0.270</td>
<td>0.12</td>
<td>2.32</td>
<td>151</td>
<td>.02</td>
</tr>
<tr>
<td>Slope</td>
<td>Control</td>
<td>0.81</td>
<td>0.17</td>
<td>4.81</td>
<td>151</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
<td>-0.02</td>
<td>0.11</td>
<td>-0.16</td>
<td>151</td>
<td>.88</td>
</tr>
</tbody>
</table>

Functional Status Examination (FSE)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Coefficient</th>
<th>SE</th>
<th>t ratio</th>
<th>Approximate df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>Control</td>
<td>22.26</td>
<td>0.67</td>
<td>33.17</td>
<td>150</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
<td>0.01</td>
<td>0.98</td>
<td>0.02</td>
<td>150</td>
<td>.99</td>
</tr>
<tr>
<td>Slope</td>
<td>Control</td>
<td>-3.11</td>
<td>0.48</td>
<td>-6.54</td>
<td>150</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
<td>-0.30</td>
<td>0.64</td>
<td>-0.48</td>
<td>150</td>
<td>.64</td>
</tr>
</tbody>
</table>

* The model intercept reflects the estimated outcome at discharge for the GOSE and at 3 months for the FSE. The slope reflects the estimated linear change over time up to 6 months. The regression coefficients for the intervention variable reflect the effect of the intervention on estimated outcome at the initial reference time point (discharge [GOSE] or 3 months [FSE]) and on the course of recovery up to 6 months.

Table 4  Comparison of survival during follow-up in control group and intervention group for full sample (n = 157)*

<table>
<thead>
<tr>
<th>Time</th>
<th>No. (%) of patients who died</th>
<th>Adjusted odds ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control group (n = 78)</td>
<td>Intervention group (n = 79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge</td>
<td>13 (17)</td>
<td>8 (10)</td>
<td>3.82</td>
<td>1.13 to 12.92</td>
</tr>
<tr>
<td>3 months after injury</td>
<td>13 (17)</td>
<td>10 (13)</td>
<td>2.14</td>
<td>0.73 to 6.31</td>
</tr>
<tr>
<td>6 months after injury</td>
<td>14 (18)</td>
<td>13 (17)</td>
<td>1.86</td>
<td>0.64 to 5.40</td>
</tr>
</tbody>
</table>

* Odds ratio is expressed as odds of survival in intervention group compared with control group, and it is estimated by using binary logistic regression, with adjustments for each patient’s age, sex, and severity of initial injury.

However, when outcome was dichotomized to dead or alive, binary logistic regression analysis—with each patient’s injury severity age, and sex controlled for—indicated a significant advantage for the intervention group at the time of discharge (odds ratio 3.82, 95% CI 1.13 to 12.92, P = .03), with trends at 3 and 6 months (Table 4). The data on discharge disposition suggest that this finding largely reflects the lower number of in-hospital deaths in the intervention group. A total of 17% of the control group died in the hospital versus 10% of the intervention group; 8% of the control group was discharged to home versus 13% of the intervention group. Similar percentages of each group were discharged to rehabilitation (50% control, 47% intervention) or skilled nursing facilities (23% control, 27% intervention).

Most deaths occurred in a subgroup of patients with more severe brain injury; by chance, the randomization was imbalanced with respect to the number of severely injured subjects in the control versus the intervention group (a greater number in the intervention group). Therefore, the subgroup of patients with more severe brain injury was analyzed separately. For these analyses, we used GCS-PR motor scores of 4 or less to represent the most seriously injured and to avoid the effects of intubation of responsive patients on the total GCS scores. The intervention effect on survival was strongest in this subgroup of patients with more severe initial brain injury. Of the 77 patients with GCS-PR motor scores of 4 or less, the intervention’s effect on the odds of survival, with age controlled for, was an odds ratio of 3.18 (P = .04) at discharge and at 3 months, and an odds ratio of 2.34 (P = .12) at 6 months (Table 5).

CPP Levels and Outcomes

Given the assumption that maintaining adequate levels of CPP would be mediated by the more visible CPP feedback of the intervention, we then examined...
mean ABP, ICP, CPP, and the percentage of time CPP was below thresholds of 70 mm Hg, 60 mm Hg, and 50 mm Hg during the first 4 days of monitoring. We found no significant differences in any of the daily means or 4-day means for these measures between the intervention and control groups considered as a whole (mean CPP 76.8 [SD 10.1] mm Hg for control; mean CPP 78.3 [SD 10.3] mm Hg for intervention).

However, exploratory analyses of the role of CPP thresholds and the percentage of time that CPP was less than the threshold values revealed associations between outcome and visibility of CPP feedback. Analyses of receiver-operating-characteristic curves were used to maximize sensitivity and specificity of specific CPP cutoff points in relation to survival. We used these cutoff points to specify lesser and greater percentages of time that CPP decreased below 70 mm Hg and 60 mm Hg in the first 4 days of monitoring. (See the Appendix for further details about specifying cutoff points.)

When the full sample (N = 157) was considered, patients randomized to the control group were more likely to have deviations to less than 60 mm Hg than were patients in the intervention group (44.2% control vs 30.8% intervention, \( \chi^2 = 2.96, P = .08 \)). The trend was less strong for mean CPP less than 70 mm Hg (39% control vs 31% intervention, \( \chi^2 = 0.81, P = .37 \)). The relationships of deviations to less than the CPP threshold to randomization group were much stronger in the more severely injured subgroup. When the relationship of CPP level at specified cutoff points at values less than the threshold values was explored for the subgroup with GCS-PR motor scores of less than 4, a clear advantage was apparent for those in the intervention group. In the control group, 63% with low GCS-PR motor scores had a mean CPP less than 60 mm Hg for a critical period, compared with 19% in the intervention group (\( \chi^2 = 7.29, P = .007; \) Figure 4). Similarly, 50% of the control group had CPP deviations to less than 70 mm Hg for a critical period, compared with 14.3% in the intervention group (\( \chi^2 = 5.54, P = .02 \)).

In contrast, no significant differences were found in the percentage of time CPP was less than 60 and 70 mm Hg in patients with GCS-PR motor scores of 5 and greater. Although no significant differences were found between the overall intervention and control groups in relation to mean dosages of vasoactive medications, diuretics, analgesics, sedatives, blood products, or 24-hour fluid balance, either by day or during the 4-day monitoring period, the frequency of use of some vasoactive drugs and mannitol was somewhat increased in the intervention group when only the more severely injured subgroup was considered (data not shown). This finding is suggestive of active intervention in response to CPP, but without direct observation of the actions of nurses and physicians we cannot be certain of the reason for these differences.

These data suggest that the difference in the proportion of patients within the more severely injured...
subgroup whose CPP decreased to values less than the threshold values may have been a factor in the greater survival rate of patients in the intervention group. This survival effect does not appear to be due to shifting of the poorest outcomes after discharge, because few survivors were in a vegetative state in the intervention group, either overall or in the most severely injured subset. Further, survivors in the intervention group were represented at 3 and 6 months in the highest functioning levels as well as among the more severely disabled.

Discussion

Although nurses have an integral role in monitoring and managing CPP after TBI, we are unaware of any research that examines how to present real-time CPP information to nurses at the bedside in the most meaningful and useful way. In this study, we examined the association of the presence of a highly visible, real-time display of CPP on the outcomes of patients with TBI. The presence of the display was associated with significantly better condition at the time of discharge from the hospital. The absolute magnitude of the effect of the intervention on mean adjusted GOSE score was sustained throughout the follow-up times. However, the statistical significance was progressively attenuated at the 3- and 6-month time points because of increasing variance in the outcome variables. This effect appears to be concentrated primarily in the more severely injured group, as evidenced by a GCS-PR motor score of 4 or less.

The mechanism by which patients in the intervention group were in better condition at discharge appears to be mediated in part through CPP, at least for the most severely injured subgroup. The influence of physiological parameters on outcome may be most strongly apparent in the early phase after injury, particularly affecting mortality. The influence on long-term outcome of survivors may be less apparent. Strong evidence, both from previous studies\(^28\)\(^{-30}\) and this one, indicates that CPP level as a major predictor of outcome. In the only study\(^31\) in which CPP was actively manipulated through aggressive management of blood pressure, the intervention group had a designed increase in CPP but also had an increase in the incidence of acute respiratory distress syndrome and no benefit in long-term outcome.

In our study, we manipulated the visibility of CPP information, with the assumption that the response of nurses to this CPP information would be reflected by the use of traditional management strategies: reduction of ICP with sedation, diuretics, and body position, and support of blood pressure with vasoactive drugs. Any brief periods of CPP at values less than the threshold value remained visible to nurses and physicians up to one half hour with the active display. This visibility of CPP levels over time may have encouraged greater attention to overall management. By contrast, this information was lost to caregivers unless the electronic record was consulted when only the blank display and the usual bedside display were present.

The primary limitation of this study was the inability to measure clinicians’ behavior in response to changes in CPP displayed on the active monitors. Therefore, we can only speculate about whether nurses, physicians, and respiratory therapists used the information that was visible to them to tailor the care patients received. Kenner\(^32\) conducted a small thesis study of nursing actions in response to changes in CPP while the present study was in progress. She included 5 patients with the active CPP display, 6 with the blank display, and 6 with the unit’s usual bedside display. Because most episodes of sustained decreased CPP occurred when a nurse was absent from a patient’s room, the information about CPP was lost to clinicians whose patients had the usual monitoring display.\(^32\) Kenner did not query nurses about whether or how they were using information visible on the monitor when CPP was within normal ranges.

The use of a real-time display of CPP resulted in better patient condition at the time of hospital discharge.

With the data available, we cannot be certain of the mechanism behind the improved survival in the intervention group. In addition, we were unable to measure the many potential factors beyond the severity of the initial injury and the hospital course, such as social support and access to rehabilitation, that may have played an important role in influencing outcome at 3 and 6 months in TBI survivors in this study.

Overall, mean CPP levels during the study were almost 80 mm Hg; CPP therefore was not less than the display threshold of 70 mm Hg most of the time. Because of the complex pathophysiology of brain injury—perhaps unless excursions to extreme ranges occur—monitoring and management of any single parameter would be insufficient alone to result in a significant independent improvement in outcome, particularly long-term outcome. Further, the increasing use of decompressive craniectomy in neurosurgical practice maintains CPP at or above minimum desired levels in patients so treated, leaving a smaller subset for whom the careful tracking and adjustment of CPP is more crucial. In such cases, the persistence of the
visible display of decreases in CPP for up to a half hour in the active display group may have provided important cues to the nursing and medical staff.

Although the threshold in the active display was set to 70 mm Hg, analysis of the data showed that the most critical cutoff point for CPP was 60 mm Hg, consistent with the level recommended in the 2003 revision of the guidelines. Because the percentage of time at values less than the threshold value that was related to poorer survival was small, setting the display threshold higher than 60 mm Hg to warn that CPP is approaching the critical threshold may be useful. This adjustment would allow time to carry out interventions before CPP actually decreased to less than that threshold.

Conclusions

In patients with TBI, the presence of a visually prominent continuous display of CPP was associated with significantly better condition at the time of discharge, primarily reflecting the lower number of in-hospital deaths in the intervention group. The intervention appeared to have the greatest benefit in patients with more severe initial brain injury. The mean group difference in GOSE and FSE scores was sustained at 3 and 6 months after injury; however, the statistical significance of the intervention effect became progressively attenuated over these time points. Although the optimal minimal threshold for CPP after TBI is still under debate and most likely varies from patient to patient, maintaining adequate CPP is clearly important to patients’ outcomes. Because CPP is amenable to manipulation, improved display of real-time CPP information may allow early intervention to prevent or minimize episodes of low CPP that may cumulatively contribute to poorer outcomes.

Appendix: Details of Statistical Methods

Minimum sample size at 80% power to detect a clinically meaningful effect size of improvement of 1 level on the Extended Glasgow Outcome Scale (GOSE), with entry covariates of injury severity, age, and sex, was calculated as 128 (64 in each treatment group). Over-sampling was done to ensure sufficient power if sizable numbers of participants were lost to follow-up and to allow subgroup analysis.

The statistical package HLM 5 (Scientific Software International, Lincolnwood, Ill) was used to specify a within-subject linear growth model and an across-subject model. The within-subject model had 2 parameters: intercept and slope. GOSE score was assessed at all time points, but the score on the Functional Status Examination (FSE) was assessed only at the 3-month and 6-month time points because of categories such as financial independence. At the across-subject hierarchy, the 2 implied within-subject coefficients (intercept, slope) were considered to be dependent on the randomized assignment to the intervention or control group.

Also incorporated in the across-subject model were the demographic covariates age and sex and variables reflecting severity of the initial injury, including the motor component of the Postresuscitation Glasgow Coma Scale and the score on the Injury Severity Scale. The conclusions about the intervention effect over time are based on interpretation of the regression coefficients associated with randomization group and the intervention effect on the intercept (estimated outcome at discharge) and the slope (estimated linear change over time in 3-month increments). The time index was adjusted to reference the within-subject level-1 intercept to the hospital discharge time point for the GOSE analyses and to 3 months for the FSE analyses.

Although credible partial information about 6-month status (dead/alive or dead/bad/good outcome) was available for nearly all subjects, approximately 9% of the study participants were missing GOSE or FSE outcome information at either the 3-month or the 6-month follow-up time points. Multiple imputation methods were used to generate plausible values of the missing data consistent with the available partial information about each of these patients. Nine representative complete case data sets were created by using the MICE (Multiple Imputation by Chained Equations, van Buuren and Oudshoorn, TNO Prevention and Health Public Health Institute, Leiden, The Netherlands, 2000) software package. All the covariates to be used in the analysis model (age, sex, severity of initial injury), except design contrast factors (randomization group and cerebral perfusion pressure [CPP] level groups), and all available partial information about 6-month status, were incorporated into the imputation model. The Predictive Mean Matching tabular imputation algorithm was used to ensure that the values that were imputed for the strictly integer GOSE and FSE scales remained whole numbers within the appropriate range for each variable. A total of 21 iterations of the imputation method were executed to ensure convergence of the algorithm. The linear mixed model longitudinal growth curve analyses reported in this article were executed for each of the 9 resulting imputed complete case data sets, and the results were pooled by using the HLM 5 software package.

For analyses less tractable to multiple imputation methods, the 9 imputed data sets were aggregated into a single representative complete case data set by computing the median of each cell across the imputations. Taking the median of an odd number of imputations determined by using the Predictive Mean Matching algorithm for a given cell ensures that the replacement value will be a whole number within the appropriate range for the variable.

Coenrollment

A total of 58 subjects (37%) enrolled in this study were also enrolled in the Magnesium Sulfate for Neuroprotection After Brain Trauma study, a randomized, double-blind controlled trial to evaluate the effect of early administration of magnesium following traumatic brain injury on survival, posttraumatic seizures, and functional status and neurobehavioral functioning. Analyses were carried out to assess for any potential confounding related to coenrollment in the 2 studies. Assignment to the experimental or control arm of the magnesium sulfate study was not significantly different between the intervention and control arms of this study. The outcome analysis for this study was run with and without a dummy variable coding the magnesium sulfate study randomization group assignment. Results were almost identical and did not change any conclusions. Therefore, the magnesium sulfate investigators (and we) concluded that there was no confounding by that study. Participants in the magnesium sulfate study were included in all analyses reported here.

Cutoff Points for CPP Level Related to Survival

For the CPP level of 70 mm Hg, the cutoff point was specified at 31% of monitoring time in which CPP was less than 70 mm Hg. For the CPP level of 60 mm Hg, the cutoff point was 6% of...
monitoring time in which CPP was less than 60 mm Hg. Binary logistic regression was performed by using the dichotomous dependent variable survival (dead or alive) by the categorical lower or higher percentage of time that CPP was less than threshold values, again with each patient’s age, sex, and severity of the initial injury controlled for.

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REFERENCES
1. Why is monitoring of cerebral perfusion pressure (CPP) level thought to be important following traumatic brain injury?
   a. CPP does not influence global blood delivery to the brain.
   b. Inadequate CPP is not associated with cerebral ischemia.
   c. There are no interventions to increase inadequate CPP.
   d. Inadequate CPP may contribute to secondary brain injury.

2. Which of the following statements is not correct regarding CPP?
   a. CPP can change on a minute-to-minute basis.
   b. CPP can be influenced by nursing care activities such as the patient’s positioning.
   c. CPP is not influenced by arterial blood pressure.
   d. Current guidelines for the management of severe traumatic brain injury recommend maintaining CPP at a minimum of 60 mm Hg.

3. Which one of the following is not a purpose of this research study?
   a. To determine whether the presence of a highly visible display of CPP is associated with fewer episodes of lower CPP
   b. To examine the association between CPP and pupillary dilatation
   c. To assess the effect of the presence of a highly visible display of CPP on hospital discharge in individuals with traumatic brain injury
   d. To assess the effect of the presence of a highly visible display of CPP on outcome at 3 and 6 months after injury

4. Which of the following is not correct in relation to the study design and methods?
   a. The mean scores on the Injury Severity Scale were the same for the intervention and control groups.
   b. The mean CPP level over 4 days was significantly different between the intervention and control groups.
   c. The mean CPP level over 4 days was significantly different between the intervention and control groups.
   d. Those with more severe brain injury (GCS < 4) in the control group had a significantly lower proportion of subjects with severe brain injury.

5. Which one of the following is not an inclusion criterion for this research study?
   a. Bilateral fixed pupils
   b. Moderate to severe head injury
   c. Intracranial pressure and arterial blood pressure monitoring
   d. Enrolled within 24 hours after intracranial pressure monitor placed

6. Which of the following statements related to group differences is incorrect?
   a. There was a significantly higher proportion of subjects with more severe brain injury (GCS < 4) in the randomized group than in the control group.
   b. There was no improvement in outcome of survivors between discharge and 6 months after injury.
   c. Inadequate CPP may contribute to secondary brain injury.
   d. There are no interventions to increase inadequate CPP.

7. What were the secondary end points of this study?
   a. The mean GOS score at 6 months after injury, adjusted for age, sex, and injury severity, was not significantly higher in the intervention group than in the control group.
   b. The mean GOSE score at hospital discharge, adjusted for age, sex, and injury severity, was significantly higher in the intervention group than in the control group.
   c. Scores on the GOS and FSE assessed at discharge and 3 months.
   d. Scores on the FSE assessed at discharge and 3 months.

8. Which of the following were not controlled for in the statistical analysis?
   a. Sex
   b. Weight
   c. Age
   d. Injury severity

9. Which of the following statements regarding outcome findings of the study is not correct?
   a. CPP can change on a minute-to-minute basis.
   b. CPP can be influenced by nursing care activities such as the patient’s positioning.
   c. CPP is not influenced by arterial blood pressure.
   d. Inadequate CPP may contribute to secondary brain injury.

10. Which of the following does not reflect the primary prespecified end point of this study?
    a. Range of brain injury severity of subjects enrolled
    b. Sample size less than 100
    c. Inability to measure clinician’s behavior in response to changes in CPP
    d. Lack of use of standardized measures of outcome

11. What was the primary limitation of this study?
    a. Range of brain injury severity of subjects enrolled
    b. Sample size less than 100
    c. Inability to measure clinician’s behavior in response to changes in CPP
    d. Lack of use of standardized measures of outcome

12. What was the most critical CPP cutoff point identified in this study?
    a. 77 mm Hg
    b. 70 mm Hg
    c. 60 mm Hg
    d. 50 mm Hg

Test Answers: Mark only one box for your answer to each question. You may photocopy this form.

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