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# Evaluation of optimal cerebral perfusion pressure in severe traumatic brain injury

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## Summary

Traumatic brain injury (TBI) is a major cause of death and disability. In the 2000 guidelines, one of the suggestions for TBI treatment was to maintain cerebral perfusion pressure (CPP) $\leq 70$ mmHg. But in the 2003 guidelines, the suggestion was changed to $\leq 60$ mmHg. There have been some discrepancies of opinions about this recommendation in recent publications.

In this study, we retrospectively reviewed 305 severe TBI (STBI) patients with Glasgow Coma Scales (GCS) $\leq 8$ between January 1, 2002 and March 31, 2003. The study group was stratified according to use or nonuse of intracranial pressure (ICP) monitoring, ICP levels, ages, and GCS levels in order to test the correlation between CCP and the prognosis.

The patients <50-year-old, with higher GCS level, with ICP monitoring, and with ICP levels <20 mmHg had lower mortality rates and better prognosis (GOS) ($p < 0.05$ or 0.001). The patients in the GCS 3–5 subgroup had a significantly lower mortality and better prognosis if the CPP value was maintained higher than 70 mmHg ($p < 0.05$)

The optimal CPP maintained $\leq 60$ mmHg did not fit in all STBI patients. Our study concludes that it is critical to maintain CPP substantially higher in lower GCS level patients.

*Keywords:* Traumatic brain injury (TBI); cerebral perfusion pressure (CPP); intracranial pressure (ICP); Glasgow coma scale (GCS); Glasgow outcome scale (GOS).

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## Introduction

Traumatic brain injury (TBI) is a major cause of death and disability. In the United States, 1.5 million people have head trauma every year and 1.1 million people are treated in emergency [14]. Among them, 235,000 persons are hospitalized for TBI, 50,000 patients die, and 90,000 patients are disabled [5, 11, 12]. The Brain Trauma Foundation Neurological Surgeons and American Association, according to Evidence-Based Medicine, developed guidelines for managing patients with severe TBI (STBI) in 1995 [10]. Treating patients with guidelines can indeed reduce mortality. The 2000 guidelines of cerebral perfusion pressure-oriented treatment for TBI suggested that the adequate cerebral perfusion pressure (CPP) must be higher than 70 mmHg [7]. But in 2003, the concept was changed: It was also suggested that that the maintenance of CPP at more than 60 mmHg was now considered adequate to prevent brain ischemic damage [15]. It was also suggested that the changes would reduce complications (such as acute respiratory distress syndrome (ARDS) [4]) related to the excessive use of fluid and inotropic drugs for maintaining cerebral perfusion pressure. In recent articles, there was still some argument against this drastic change, especially in how to achieve an

optimal cerebral perfusion pressure to prevent brain ischemia and how to avoid complications [4, 6, 12]. The main purpose of this study was to seek the optimal CPP for STBI patients with special characteristics and prognosis.

## Materials and methods

In this study, we retrospectively reviewed 305 patients from eight medical centers in Taiwan between January 1, 2002 and March 31, 2003. Eligible candidates were those in-patients with STBI (initial Glasgow Coma Scale (GCS) $\leq 8$). Medical records were collected and analyzed. The exclusion criteria included (1) death on arrival, (2) complete recovery within 24 h of admission without neurological deficits, (3) drunkenness, and (4) coma due to severe traumatic injury but without any definite lesion found in brain CT scans.

The patients were divided into two groups. Based on STBI guidelines, the study group patients were treated with the application of intracranial pressure (ICP) monitoring for adjusting ICP and CPP. The control group patients were treated mainly by conventional lowering of ICP (such as hyperventilation, head-up position, and empirical use of the osmotic diuretics) without ICP monitoring. We stratified the study group by (1) ICP, (2) age, and (3) GCS 6 h within admission to correlate the relationships between CPP and prognosis among these subgroups. We recorded age, diagnosis, GCS, use of ICP monitoring, ICP level, CPP, partial pressure of carbon dioxide in arterial blood ($PaCO_2$), use of vasopressors, and use of sedations during the intensive care period for further analysis.

For the outcome, we evaluated the prognosis at the time of discharge and on the third month after trauma. All the outcomes were scored with the Glasgow Outcome Scale (GOS). The score were then stratified into two major categories, namely, death (GOS 1) vs. survival (GOS 2–5) and poor outcome (GOS 1–3) vs. good outcome (GOS 4–5). The prognosis between the study group and control group were analyzed with variables of ICP, ages, CPP, and GCS.

The whole statistical analysis was performed with SPSS 11.0. We analyzed the basic information on patients with descriptive statistics and compared the variables and GOS between both groups with the Chi-square test. The differences between the groups were considered significant if $p$-values were less than 0.05.

## Results

Among these 305 patients, 283 patients had complete data available for analysis. The male-to-female sex ratio was 3:1. Some factors were correlated with mortality before the discharge of patients and at 3 months follow-up (Table 1). The analyzed factors included age, GCS level, ICP monitoring or not, ICP level, and the CPP value during the period of intensive care. All the $p$-values were $<0.05$ or 0.001. The patients younger than 50 Y/O appeared to have a better chance to survive ($p<0.05$). The more severe the GCS, the higher the mortality rate was. Incorporation of the ICP monitoring effectively reduced the mortality ($p<0.001$). If the ICP level was ever raised up over 20 mmHg during the intensive care, the patients had

Table 1. *Factors influencing the patient mortality rate*

| | Mortality before discharge | | | Mortality in 3 months F/U | | |
|---|---|---|---|---|---|---|
| | Death | Survive | $p$-value | Death | Survive | $p$-value |
| Age | | | | | | |
| <50 Y/O | 70 (43.5%) | 91 (56.5%) | 0.040 | 70 (44.6%) | 87 (55.4%) | 0.025 |
| ≥50 Y/O | 66 (55.9%) | 52 (44.1%) | | 66 (58.4%) | 47 (41.6%) | |
| GCS | | | | | | |
| 3 | 69 (81.2%) | 16 (18.8%) | <0.001 | 69 (84.1%) | 13 (15.9%) | <0.001 |
| 4 | 26 (70.3%) | 11 (29.7%) | | 26 (72.2%) | 10 (27.8%) | |
| 5 | 9 (45.0%) | 11 (55.0%) | | 9 (45.0%) | 11 (55.0%) | |
| 6 | 17 (34.7%) | 32 (65.3%) | | 17 (37.0%) | 29 (63.0%) | |
| 7 | 10 (23.8%) | 32 (76.2%) | | 10 (24.4%) | 31 (75.6%) | |
| 8 | 3 (9.7%) | 28 (90.3%) | | 3 (9.7%) | 28 (90.3%) | |
| ICP monitoring | | | | | | |
| Yes | 38 (33.9%) | 74 (66.1%) | <0.001 | 38 (34.5%) | 72 (65.5%) | <0.001 |
| No | 102 (59.3%) | 70 (40.7%) | | 102 (61.8%) | 63 (38.2%) | |
| ICP | | | | | | |
| <20 mmHg | 14 (19.2%) | 59 (80.8%) | <0.001 | 14 (20.0%) | 56 (80.0%) | <0.001 |
| ≥20 mmHg | 23 (53.5%) | 20 (46.5%) | | 23 (53.5%) | 20 (46.5%) | |
| CPP | | | | | | |
| <60 mmHg | 13 (76.5%) | 4 (23.5%) | <0.001 | 13 (76.5%) | 4 (23.5%) | <0.001 |
| ≥60 mmHg | 12 (14.5%) | 71 (85.5%) | | 12 (14.5%) | 71 (85.5%) | |
| <70 mmHg | 17 (43.6%) | 22 (56.4%) | <0.001 | 17 (43.6%) | 22 (56.4%) | <0.001 |
| ≥70 mmHg | 8 (13.1%) | 53 (86.9%) | | 8 (13.1%) | 53 (86.9%) | |

High lighted data were the $p$-values without significant difference.
Mortality: GOS 1.
Survival: GOS 2–5.

Table 2. *Factors influencing the patient outcome and prognosis*

| | Outcome before discharge | | | 3 months F/U outcome | | |
|---|---|---|---|---|---|---|
| | Poor | Good | *p*-value | Poor | Good | *p*-value |
| Age | | | | | | |
| <50 Y/O | 115 (71.4%) | 46 (28.6%) | 0.035 | 104 (66.2%) | 53 (33.8%) | 0.014 |
| ≥50 Y/O | 97 (82.2%) | 21 (17.8%) | | 90 (79.6%) | 23 (20.4%) | |
| GCS | | | | | | |
| 3 | 84 (98.8%) | 1 (1.2%) | <0.001 | 81 (98.8%) | 1 (1.2%) | <0.001 |
| 4 | 34 (91.9%) | 3 (8.1%) | | 33 (91.7%) | 3 (8.3%) | |
| 5 | 18 (90.0%) | 2 (10.0%) | | 16 (80.0%) | 4 (20.0%) | |
| 6 | 32 (65.3%) | 17 (34.7%) | | 26 (56.5%) | 20 (43.5%) | |
| 7 | 18 (42.9%) | 24 (57.1%) | | 17 (41.5%) | 24 (58.5%) | |
| 8 | 19 (61.3%) | 12 (38.7%) | | 15 (48.4%) | 16 (51.6%) | |
| ICP monitoring | | | | | | |
| Yes | 81 (72.3%) | 31 (27.7%) | 0.236 | 70 (63.6%) | 40 (36.4%) | 0.012 |
| No | 135 (78.5%) | 37 (21.5%) | | 128 (77.6%) | 37 (22.4%) | |
| ICP | | | | | | |
| <20 mmHg | 41 (56.2%) | 32 (43.8%) | <0.001 | 33 (47.1%) | 37 (52.9%) | <0.001 |
| ≥20 mmHg | 40 (93.0%) | 3 (7.0%) | | 37 (86.0%) | 6 (14.0%) | |
| CPP | | | | | | |
| <60 mmHg | 15 (88.2%) | 2 (11.8%) | 0.035 | 15 (88.2%) | 2 (11.8%) | 0.007 |
| ≥60 mmHg | 53 (69.3%) | 30 (36.1%) | | 46 (55.4%) | 37 (44.6%) | |
| <70 mmHg | 31 (79.5%) | 8 (20.5%) | 0.045 | 29 (74.4%) | 10 (25.6%) | 0.026 |
| ≥70mmHg | 37 (60.7%) | 24 (39.3%) | | 32 (52.5%) | 29 (47.5%) | |

High lighted data were the *p*-values without significant difference.
Poor prognosis: GOS 1–3.
Good prognosis: GOS 4–5.

Table 3. *GCS severity, ICP level, and CPP value influencing the mortality*

| | Mortality before discharge | | | Mortality in 3 months F/U | | |
|---|---|---|---|---|---|---|
| | Death | Survive | *p* value | Death | Survive | *p* value |
| GCS 3–5 | | | | | | |
| CPP <60 mmHg | 7 (100.0%) | 0 (0.0%) | <0.001 | 7 (100.0%) | 0 (0.0%) | <0.001 |
| CPP ≥60 mmHg | 7 (26.9%) | 19 (73.1%) | | 7 (28.0%) | 18 (72.0%) | |
| CPP <70 mmHg | 10 (62.5%) | 6 (37.5%) | 0.022 | 10 (62.5%) | 6 (37.5%) | 0.030 |
| CPP ≥70 mmHg | 4 (23.5%) | 13 (76.5%) | | 4 (25.0%) | 12 (75.0%) | |
| GCS 6–8 | | | | | | |
| CPP <60 mmHg | 6 (60.0%) | 4 (40.0%) | <0.001 | 6 (60.0%) | 4 (40.0%) | <0.001 |
| CPP ≥60 mmHg | 3 (6.5%) | 43 (93.5%) | | 3 (6.7%) | 42 (93.3%) | |
| CPP <70 mmHg | 6 (31.6%) | 13 (68.4%) | 0.028 | 6 (31.6%) | 13 (68.4%) | 0.031 |
| CPP ≥70 mmHg | 3 (8.1%) | 34 (91.9%) | | 3 (8.3%) | 33 (91.7%) | |
| ICP >20 mmHg | | | | | | |
| CPP <60 mmHg | 3 (60.0%) | 2 (40.0%) | 0.026 | 3 (60.0%) | 2 (40.0%) | 0.026 |
| CPP ≥60 mmHg | 9 (14.3%) | 54 (85.7%) | | 9 (14.3%) | 54 (85.7%) | |
| CPP <70 mmHg | 4 (28.6%) | 10 (71.4%) | 0.251 | 4 (28.6%) | 10 (71.4%) | 0.251 |
| CPP ≥70 mmHg | 8 (14.8%) | 46 (85.2%) | | 8 (14.8%) | 46 (85.2%) | |
| ICP >20 mmHg | | | | | | |
| CPP <60 mmHg | 10 (83.3%) | 2 (16.7%) | <0.001 | 10 (83.3%) | 2 (16.7%) | <0.001 |
| CPP ≥60 mmHg | 3 (15.8%) | 16 (84.2%) | | 3 (15.8%) | 16 (84.2%) | |
| CPP <70 mmHg | 13 (52.0%) | 12 (48.0%) | 0.006 | 13 (52.0%) | 12 (48.0%) | 0.006 |
| CPP ≥70 mmHg | 0 (0.0%) | 6 (100.0%) | | 0 (0.0%) | 6 (100.0%) | |

High lighted data were the *p*-values without significant difference.
Mortality: GOS 1.
Survival: GOS 2–5.

Table 4. *GCS severity, ICP level, and CPP value influencing the outcome and prognosis*

| | Outcome before discharge | | | 3 months F/U outcome | | |
|---|---|---|---|---|---|---|
| | Poor | Good | *p*-value | Poor | Good | *p*-value |
| GCS 3–5 | | | | | | |
| CPP <60 mmHg | 7 (100.0%) | 0 (0.0%) | 0.219 | 7 (100.0%) | 0 (0.0%) | 0.099 |
| CPP ≥60 mmHg | 23 (88.5%) | 3 (11.5%) | | 20 (80.0%) | 5 (20.0%) | |
| CPP < 70 mmHg | 16 (100.0%) | 0 (0.0%) | 0.039 | 15 (93.8%) | 1 (6.3%) | 0.033 |
| CPP ≥70 mmHg | 14 (82.4%) | 3 (17.6%) | | 12 (75.0%) | 4 (25.0%) | |
| GCS 6–8 | | | | | | |
| CPP < 60 mmHg | 8 (80.0%) | 2 (20.0%) | 0.121 | 8 (80.0%) | 2 (20.0%) | 0.036 |
| CPP ≥60 mmHg | 25 (54.3%) | 21 (45.7%) | | 20 (44.4%) | 25 (55.6%) | |
| CPP < 70 mmHg | 12 (63.2%) | 7 (36.8%) | 0.644 | 11 (57.9%) | 8 (42.1%) | 0.451 |
| CPP ≥70 mmHg | 21 (56.8%) | 16 (43.2%) | | 17 (47.2%) | 19 (52.8%) | |
| ICP <20 mmHg | | | | | | |
| CPP <60 mmHg | 3 (60.0%) | 2 (40.0%) | 0.847 | 3 (60.0%) | 2 (40.0%) | 0.593 |
| CPP ≥60 mmHg | 35 (55.6%) | 28 (44.4%) | | 30 (47.6%) | 33 (52.4%) | |
| CPP < 70 mmHg | 7 (50.0%) | 7 (50.0%) | 0.620 | 7 (50.0%) | 7 (50.0%) | 0.902 |
| CPP ≥70 mmHg | 31 (57.4%) | 23 (42.6%) | | 26 (48.1%) | 28 (51.9%) | |
| ICP >20 mmHg | | | | | | |
| CPP <60 mmHg | 12 (100.0%) | 0 (0.0%) | 0.153 | 12 (100.0%) | 0 (0.0%) | 0.038 |
| CPP ≥60 mmHg | 17 (89.5%) | 2 (10.5%) | | 15 (78.9%) | 4 (21.1%) | |
| CPP < 70 mmHg | 24 (96.0%) | 1 (4.0%) | 0.311 | 22 (88.0%) | 3 (12.0%) | 0.766 |
| CPP ≥70 mmHg | 5 (83.3%) | 1 (16.7%) | | 5 (83.3%) | 1 (16.7%) | |

High lighted data were the *p*-values without significant difference.
Poor prognosis: GOS 1–3.
Good prognosis: GOS 4–5.

lower chances to survive ($p<0.001$). The CPP values maintained at levels higher than 60 or 70 mmHg both had better survival rates ($p<0.001$), and no significant difference in CPP was seen between the 60 and 70 mmHg groups.

As to the outcome before the discharge of patients from the hospital and the condition 3 months after the hospital stay, the results were quite similar (Table 2). For the patients age <50 Y/O, a higher GCS score, and ICP value maintained at level lower than 20 mmHg, it was enough to maintain CPP values of higher than 60 mmHg for a better prognosis ($p<0.05$ or 0.001). There was no further benefit in keeping a still higher CPP (≥70 mmHg) for such patients. However, the use of ICP monitoring showed no significant benefit for short term prognosis, while for the long term follow-up at 3 months, incorporation of ICP monitoring appeared to bring about better outcome ($p<0.05$).

We also classified the GCS severity into two groups: GCS 3–5 and 6–8 (Table 3). We found that maintenance of the CPP ≥60 or ≥70 mmHg both produced some benefits shown by higher survival rates no matter how severe the GCS was ($p<0.001$ or 0.05). For the CPP of higher than 70 mmHg, no further help was noted with regard to mortality. On the other hand, when we classified the patients according to ICP values of higher or lower than 20 mmHg, we found that to produce a lower mortality rate for he patients with ICP <20 mmHg, CPP ≥60 mmHg was enough ($p<0.05$) and the treatment with CPP ≥70 mmHg produced no better results. But if the ICP level was ≥20 mmHg, the CPP ≥70 mmHg did reduce the mortality further both during admission and at 3 months of follow-up ($p<0.001$ or 0.05).

Finally in Table 4, maintenance of the CPP value higher than 70 mmHg, for patients with GCS 3–5 produced a better prognosis than the CPP value maintained only higher than 60 mmHg ($p<0.05$). For patients with GCS 6–8, maintenance of CPP higher than 60 mmHg was good enough for long term follow-up ($p<0.05$). Therefore, it did not appear necessary to keep CPP ≥70 mmHg for patients with GCS 6–8. For patients with ICP <20 mmHg, nothing important was gained if the CPP level went beyond 70 mmHg. If the ICP level was ≥20 mmHg, maintenance of the CPP ≥60 mmHg was enough for long term outcome only, as with the patients with GCS 6–8 ($p<0.05$).

## Discussion

Younger patients or the patients with less severe TBI should have better outcome and lower mortality [1, 2].

Implantation of an ICP monitor can reduce mortality for STBI patients, but in this study the outcome turned out better only in long term follow-up. However, if the ICP monitor was implanted for the STBI patient, the maintenance of ICP below 20 mmHg still helped the patients both in mortality and morbidity. ICP-oriented treatment for TBI patients has been the major principle of treatment in the past 10 years. The guidelines of head injury suggested the intracranial pressure threshold to be between 20 and 25 mmHg [13]. The results of our study showed that patients who were implanted with an ICP monitor improved both the survival rate and Glasgow Outcome Scale (Tables 1, 2). The results were comparable with regard to the previous report [3]. Therefore, it is still very important to implant an ICP monitor and to control ICP below 20–25 mmHg for STBI patients.

There was relative high mortality rate for the low GCS patients, around 80% [9]. Patients with GCS 3–5 are believed to have severe brain stem damages. We specifically divided patients into two subgroups: GCS 3–5 and GCS 6–8. In the GCS 3–5 subgroup, high CPP of $\geq$70 mmHg still improved the mortality rate both for the short term and long term outcome (Tables 3, 4) [9, 10]. For patients in the GCS 6–8 subgroup, CPP maintenance of $\geq$60 mmHg appear sufficient. It is obvious that the maintenance of CPP above 70 mmHg for patients with severe brain stem damage brought about significant improvement in outcome. In other words, the lower the GCS level, the higher the CPP should be.

In patients with ICP $\geq$ 20 mmHg, the benefits of high CPP ($\geq$70 mmHg) maintenance appear even more obvious as regards mortality. The aim of our study was focused on the CPP threshold in severe TBI patients. We divided the patients into two subgroups, according to ICP above or below 20 mmHg. In the ICP $<$ 20 mmHg group, maintenance of CPP $\leq$ 60 mmHg improved the survival rate, but not the functional aspect [8]. There was no additional benefit for patients with ICP $<$20 mmHg to maintain CPP of $\geq$70 mmHg. In addition, if the ICP was greater than 20 mmHg maintenance of CPP above 60 mmHg improved survival only ($p <$ 0.001). However the survival rate for these increased ICP patients was higher when CPP was kept $\geq$70 mmHg. The results were somewhat similar to Those of Lannoo *et al.* [6]. This suggests that the importance of maintaining CPP above 60 mmHg in increased ICP patients; maintenance of CPP at or above 70 mmHg for such IICP patients produced even better mortality control.

What is the optimal CPP? In 2000, cerebral perfusion pressure-orientated treatment for TBI suggested that adequate CPP must be kept greater than 70 mmHg, which however, was prone to produce adult respiratory distress syndrome because of excessive use of fluid and inotropic drugs for maintaining CPP [4]. The 2003 head injury treatment guidelines recommend that CPP has only to be maintained at a level greater than 60 mmHg. This study shows that maintenance of CPP higher than 70 mmHg was really necessary in some instances, such as low GCS and high ICP. Our results may help amend or recommendations in the 2003 guidelines for treatment of severe traumatic brain injury.

## Conclusions

The maintenance of CPP above 60 mmHg was enough to prevent cerebral ischemia and further damages in most situations. But for patients with lower GCS 3–5, the CPP should be kept higher than 70 mmHg to produce lower mortality and better functional results. If complications of CPP maintenance at higher level can be avoided, the maintenance of CPP above 70 mmHg still should considered benefits of TBI patients.

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