Edited by

Wen-Ta Chiu, MD. PhD

Sheng-Jean Huang, MD

Guideline of STBI Development Team

Chief Reviewer

Chin-chang Hung, MD. PhD

Chief Consultant

Ken N. Kuo, MD. PhD

CLINICAL PRACTICE GUIDELINE (CPG) IN

SEVERE TRAUMATIC BRAIN INJURY

National Health Research Institutes
Taiwan Neurotrauma Society
Taiwan Neurosurgical Society
Injury Prevention and Disaster Medicine Research Fundation

Introduction

The principles for managing of TBI have been changed dramatically in recent 20 years. Due to developments of brain monitoring technique in recent years, management focus of severe TBI has been changed from lowering IICP alone to preventing of brain ischemia, elevating of CPP and lowering brain metabolism.

The Need of Guidelines

The incidence of TBI in Taiwan has been decreased gradually after implementing of helmet law. But the mortality rate of severe TBI still remains high as 35%. The management priciples of TBI changes a lot in past 20 years, we have reviewed the benefits and side effects of traditional treatment such as water restrictions, hyperventilation, osmotics diuretics and steroids, etc. In recent years, due to developments of new monitoring technique, the managing severe TBI has been changed from lowering IICP and to the preventing of brain ischemia, elevating of CPP and lowering of brain metabolism. The publications on TBI treatment priciples have been updated rapidly, reviewing all the articles by physician is hard. This guideline is based on the collective knowledge of scholars and all related articles. It is arranged systemically, and concluded for a practical use.

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Methodology

Contributors who have reviewed all the published articles, divided them into eight levels of evidence (1++～4) . Based on the levels of evidence from the articles , the authors gave recommendations of A, B, C and D.

Literature Review

In the pre- and intra-meeting of severe TBI, we have devided the nine topics: ER Treatment, ICP monitoring, CPP, fluid therapy, use of sedatives, nutrition, intracranial hypertension, seizure prophylaxis and second tier therapy. Each topic has one assigned contributor. Contributors have searched the informations from 1966 to 2006 on Medline database for English and Chinese articles. Included was clinical study, and excluded were clinical technical notes, and operative nuances. Each contributor has chosen the keywords used in the literature search.

Levels of Evidence

According to the standards listed in this table, we have divided these articles into eight levels of evidence.

Level	Evidence level
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+	Well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1-	Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.
2++	High quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal.
2+	Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series.
4	Expert opinion.

Making four grades of recommendations

Contributors have reviewed the searched literature articles. Based on above criteria, they have divided all articles into eight levels of evidence, and give four grades of recommendations.

Grades of Recommendations	Description
A	At least one meta analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+.
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++.
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+.

To note, grades C or D still have evidence to support grades of recommendations, but the evidence level is not as strong as grades A or B. Recommendations of grades C or D should not be interpreted as poor clinical managements.

3

ER Treatment

The most important medical work in the emergency room (ER) for a patient with severe brain injury and with a coma scale between 3-8 is to maintain first aid perfusion which has been established on the spot of injury. It is necessary to follow principles of general injury assessment and to proceed with further treatments, stabilization and examination. The main purpose of these steps is to prevent secondary brain injury in such a patient.

Recommendations

Written by Tsu-Yong Chen
Editor: Treatment in ER Guideline Team

C 1. Quick Assessment
   (1) ABC: **A**irway, **B**reathing, **C**irculation, and protection of cervical vertebra.
   (2) Trauma Assessment: cranium, face, cervical vertebra, spine, thoracic cavity, abdominal cavity, pelvic cavity, back, and limbs.

C 2. Basic Treatments
   (1) Endotracheal intubation
   (2) Venous transfusion of normal saline to stabilize blood pressure.

C 3. Neurological Examination
   (1) Glasgow Coma Scale
   (2) Size and reflexes of pupils
   (3) Type of respiration
   (4) Activity of limbs

C 4. Further Assessment (Conditional)
   (1) Use of sedatives (±) : when a patient with endotracheal intubation moves restlessly.
   (2) Anti-epileptic drugs (±) : for treatment and prevention of epilepsy
   (3) Osmotic diuretics (±) : when cranial pressure seems to rise

C 5. Image Examination: feasible only when the vital signs are stable

(1) X-rays

(2) Cranial CT Scan

(3) Others (MRI and angiography) : permissible only when methods above fail.

C 6. Laboratory Examination

(1) General examination of blood, biochemistry and blood coagulative function.

(2) Electrocardiogram

(3) Alcohol and toxin screen (when necessary)

C 7. Final Diagnosis

(1) Consideration of all possibilities in differential diagnosis

(2) Severity assessment

C 8. Final Management

(1) Consultation with neurosurgeons

(2) If there is no licnesed neurosurgeon, it is suggested that the patient be transfered to an appropriate hospital as soon as life sign stays stable.

Introduction

The most important medical work in the emergency room (ER) for a patient with severe brain injury and with a coma scale between 3-8 is to maintain first aid perfusion which has been established on the spot of injury. It is necessary to follow principles of general injury assessment and to proceed with further treatments, stabilization and examination. The main purpose of these steps is to prevent secondary brain injury in such a patient.

Literature Review

There are two possible pathophysiological responses immediately after brain injury: head injury-induced apnea and stress-related massive sympathetic catecholamine discharge, which often lead to hypoxia, hypercarbia, acidosis and rising of blood pressure. Head trauma-induced cardiac injury and gastroduodenal mucosa injury (ulcer) are also common complications. When hypotension or hypoxia results were from cardiorespiratory dysfunction, the mortality or morbidity will exceed 50 %.

Conclusions

1. ER Quick Assessment is mainly based on the guidelines by the ATLS (Advanced Trauma Life Support) principles, which are established by Brain Trauma Foundation and American Association of Neurological Surgeons (AANS).

   (1) ABC (**A**irway, **B**reathing, **C**irculation) :

   ① **A**irway: Patients with severe brain injury are generally believed to be unable to protect their own airway. In addition, vomiting, cranial or facial soft tissue bleeding, and swelling may have blocked the airway. Once ER professionals consider a patient incapable of keeping his/her own airway clear, endotracheal intubation should be carried out in time to help the patient breathe and to lower risks of hypoxia.

   ② **B**reathing: When checking for patency of the airway, it has to be made sure that sufficient oxygen is provided and carbon dioxide

is adequately expelled. More than 35 % of severe head injury patients suffer from hypoxia (PaO_2 < 65 mmHg), and need intubation for respiratory support.

③ **C**irculation: Approximately 15 % of patients with severe brain injury suffer from hypotension (SBP < 95 mmHg), while 12 % of them also have low Hct (Hct < 30 %). Low systolic pressure doubles the death rate. Prompt monitoring of blood pressure, detection of the actual bleeding point and aggressive intravenous transfusion to prevent hypotension will increase the rate of survival.

(2) Trauma assessment: Statistically, 56-60 % of patients with a coma scale lower than 8 suffer from injuries of one or more organs other than the brain, and 25 % of them need immediate surgery. Systemic whole-body trauma assessment helps find out latent but not immediately evident injuries, including:

① Cranial lesions: palpation is necessary to make sure if there is any local swelling, scalp laceration, open skull fracture, or leakage of intracranial contents (brain tissue, cerebrospinal fluid).

② Facial bone fracture: whether the jaw is “floating” , and whether there is an asymmetric facial swelling.

③ Injuries of the spine, especially the cervical spine: 4-5 % of patients with a coma scale lower than 8 suffer from a high (C1-3) cervical fracture. We should first assume that there is a cervical fracture and protect the cervical spine with a cervical collar to prevent head motion until the X-ray or CT scan confirms the absence of fracture.

④ Possible lesions in the thoracic, abdominal or pelvic cavity: In addition to quick palpation and ausculation, X-ray films are re-

quired to ensure that there is no hemothorax, pneumothorax or pelvic fracture.

2. Basic Management:

As patients with severe traumatic brain injury are unable to keep the airway clear, and, in addition, 35 % of them suffer from hypoxia, endotracheal intubation is required for patients with a coma scale lower than 8, along with a ventilator. In view that hypotension results in a greatly reduced survival rate, transfusion of normal saline should be used to maintain blood pressure. Systolic pressure should not be less than 95 mmHg. It is recommended that saline alone be transfused, supplemented with potassium if necessary.

3. Neurological Examination:

After completion of basic examination and stabilization of vital signs, neurological examination should be done at the ER to record neurological functions, including the Glasgow Coma Scale, size of bilateral pupils, light reflex, and limb muscle strength, preferably with a record on the type of respiration before ventilator use.

Table 1: Glasgow Coma Scale

Scale	Eye Opening	V: Language Ability	Best Motor Response
6			obeys
5		oriented and converses	localizes pain
4	spontaneous	disoriented and converses	flexion-withdrawal
3	to speech	inappropriate words	flexion-abnormal
2	to pain	incomprehensible sounds	extension
1	no response	no response	no response

4. Further Assessment — the following are recommended in accordance with the clinical condition of patients:

   (1) Sedation: about 55 % of brain injury patients with GCS Score < 8 suffer from high intracranial pressure,[5] while 53-63 % of those with an abnormal CT scan will suffer from delayed cerebral hemorrhage.[6] Stimulated by intubation, such patients with coma may agitate, and may need adequate sedation to prevent elevation of intracranial pressure, but sedation is allowed only when it is ascertained that the patient has been intubated with proper respiratory support, and that the blood pressure is stable. As regards the details of sedative use, please refer to "Use of Sedatives."

   (2) Use of anti-epileptic drugs: When the patient suffers from an early posttraumatic seizure, anti-epileptic drugs should be used. For those without seizures, the drugs are given to patients according to the "Use of Anti-epileptic Drugs" in the guidelines after the diagnosis of severe traumatic brain injury has been established.

   (3) Osmotic diuretics: about 60 % of actively treated severe traumatic brain injury patients will suffer from intracranial bleeding and intracranial pressure higher than 15 mmHg.[5] Even with a normal initial CT scan, 10-15 % of them may have sequelae of intracranial hypertension. Once the severe traumatic brain injury patients in the ER department begin to have a lowered GCS, slower heartbeats, and pupillary dilation, intracranial hypertension should be suspected, and Mannitol (0.5-1.0 gm/kg) is given when the blood pressure is stable.[7, 13, 14]

5. Image Studies:

   Injury assessments including the lateral view of the chest, pelvis,

and cervical spine (also covering C7-T1), can be done promptly in the ER to eliminate related injuries. For severe traumatic brain injury patients, an emergency CT scan without contrast enhancement may help establish the diagnosis and determine the severity of injury. Generally speaking, MRI is not urgently needed. It has not been universally agreed whether a series of CT scans is advisable or will improve the clinical outcome. In general, angiography and transcatheter embolization are not necessary, unless the bleeding is too massive to be controlled with conservative measures (e.g., bleeding from the nose or mouth cannot be stopped by nasal packing, or pelvic fracture cannot be immediately immobilized with effective means of hemostasis).

6. Laboratory Examinations:

   These include general blood tests commons blood chemistry such as blood sugar, coagulative function of the blood and EKG.

7. Final ER Diagnosis:

   All possibilities should be taken into consideration in the differential diagnosis. Specialists should be consulted from all the fields, e.g. cardiac surgery, chest surgery, general surgery, orthopaedics, and trauma surgery in order to make the best decision.

8. Approximately 55 % of severe brain-injured patients have incranial bleeding with incranial pressure of higher than 15 mmHg. If an immediate pressure-relieving operation cannot be performed, the patient needs the placement of an incranial pressure monitor, endotracheal intubation, and respiratory support with a ventilator. Most patients need a stay in NSICU for continued intensive care. It is suggested that neurosurgeons be consulted in the ER as soon as possible, and join actively in planning and carrying out proper treatment.

Evidentiary Table

Series (ref. No.)	Article title	Evidence level
Chestnut RM, et al. 1993 (1)	The role of secondary brain injury in determining outcome from severe head injury.	2-
The Brain Trauma Foundation. 2000 (2)	The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Initial Management.	2+
American College of Surgeon Committee on Trauma. 2004 (3)	Advanced Trauma Life Support Course for Doctors.	2+
Stocchetti N, Furlan A, Volta F. 1996 (4)	Hypoxia and arterial hypotension at the accident scene in head injury.	2-
Miller JD, Sweet RC, Narayan R, et al. 1978 (5)	Early insults to the injured brain.	2-
Fearnside MR, Cook RJ, McDougall P, et al. 1993 (6)	The West-mead head injury project outcome in severe head injury: A comparative analysis of pre-hospital, clinical and CT variables.	2+
Wald SL, Shackford SR, Fenwick J. 1993 (7)	The effect of secondary insults on mortality and long-term disability after severe head injury in a rural region without trauma system.	2-
Teasdale G, Jennett B. 1974 (8)	Assessment of coma and impaired consciousness: a practical scalet.	2-
Marshall LF, Smith RW, Shapiro HM. 1979 (9)	The outcome with aggressive treatment of in severe head injuries, I: the significance of intracranial pressure monitoring.	2-
Narayan RK, Kishore PR, Becker DP, et al. 1982 (10)	Intracranial pressure: to monitor or not to monitor? An answer to our experience with severe head injuries.	2-
Wen-Ta Chiu, et al. 2006 (11)	Multicenter evaluation of propofol for head-injured patients in Taiwan.	2+

Series (ref. No.)	Article title	Evidence level
Young C, Knudsen N, Hilton A, et al. 2000 (12)	Sedation in the intensive care unit.	2+
Ghajar J. 2000 (13)	Traumatic brain injury.	2++
The Brain Trauma Foundation. 2000 (14)	The Joint Section on Neurotrauma and Critical Care. Intracranial pressure treatment threshold.	1-

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12. Young C, Knudsen N, Hilton A, et al.: Sedation in the intensive care unit. *Crit Care Med* 2000; 28:854-66.
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Members of the ER Treatment Guideline Group

Kuan-Chuan Chang (*Cathay General Hospital*)
Kuo-Sheng Hong (*Taipei Medical University-Wan Fang Hospital*)
Ming-Yang Li (*National Cheng Kung University Hospital*)
Hong-Chang Chang (*Mackay Memorial Hospital Taitung Branch*)
Tzu-Yung Chen (*Chang Gung Memorial Hospital, Linkou*)
Ta-Yu Yang (*Chang Bing Show Chwan Memorial Hospital*)
Hsing-Hang Tsai (*Taipei Medical University-Wan Fang Hospital*)

4

ICP Monitoring

ICP monitoring is now an essential method of management for the intensive care of severe neurotrama. It supplements clinical neurological observation, helps in general evaluation, and protects sedated patients. In addition, it serves as a basic indicator for clinical research by comparison with other brain function monitors, and thus greatly improves the quality of intensive care and the outcome of patients with severe brain injury.

Recommendations

Written by Dr. Kuo-Fan Yu
Editor: ICP Monitor Guideline Team

B 1. The ICP monitor may be used on patients with:

(1) severe traumatic brain injury (GCS Score 3-8) and an abnormal CT scan, e.g. hematomas, contusions, edema, compressed basal cisterns.

(2) severe traumatic brain injury (GCS Score 3-8) and a normal CT scan, but with at least two of the following conditions:

① age of 40 years old or more.

② unilateral or bilateral decerebrate/decorticate rigidity in response to motor posturing.

③ systolic pressure of lower than 90 mmH.

(3) ICP monitoring may be individually considered for mild (GCS Score 13-15) and moderate (GCS score 9-12) brain injury patients in accordance with the actual needs.

B 2. Intracranial Pressure Treatment Threshold

The suggested intracranial pressure treatment threshold is 20-25 mmHg for adults, and 20 mmHg for children.

B 3. ICP Monitor Choice

In standard practice, intraventricular or intraparenchymal monitors are used. Other options depend on resource distribution, location of the district and insurance or various social factors.

Introduction

The first article on ICP monitor application in neurosurgery was written by Guillaure and Janny in France in 1951, which, however, attracted little attention until 1960, when NiL Lundberg made a 193-page publication in English, in which the changes of intracranial pressure in 143 patients were recorded. In the end of this paper, it was concluded that clinical neurological examination could not always predict severe IICP (increased intracranial pressure). In this publication he proposed the famous A waves (plateau waves) and B&C waves. From 1964 to 1969, Langfitt and Kassell of the University of Pennsylvania published a series of articles which recorded IICP causing a pressure gradient arising from trans-tentorial herniation, and introduced the concept of vasomotor paralysis of the terminal stage of IICP. Not until then was the importance of intracranial pressure universally recognized. In 1970, Jennet also published his experience with intracranial pressure monitoring which showed inconsistencies between intracranial pressure changes and clinical neurological observations, and emphasized the significance of changes in intracranial pressure for treatment and prognosis. Based on the results of clinical research for years, the Brain Trauma Foundation and American Association of Neurological Surgeons (AANS) accepted intracranial pressure monitoring as the indispensable procedure in the management of severe traumatic brain injury in 1996 and 2000 guidelines.

However, at present no prospective randomized controlled research is available that proves that ICP monitoring improves the outcome of brain injury patients, mainly because: 1. there is no control group, for fear of possible ethical problems, and 2. a huge project requiring more than 5 million USD and 768 patients would be necessary for such a claim.

According to the articles published in the medical literature, there are three main advantages of ICP monitoring with regard to diagnosis and treatment:

1. It helps in detecting early intracranial changes, making therapeutic decision easier.
2. It helps in use of modes of IICP treatment, e.g. hyperventilation maintaining $PaCO_2 \geq 35$ mmHg, Mannitol, sedation, Barbiturate coma, CSF drainage, etc.
3. It helps determine prognosis.

Literature Review

1. Indications for ICP monitoring

The range of indications depends on risk and cost factors. As the cost of the brain parenchyma monitor is the highest in our country, the criteria are the strictest here. This is also true of the 2000 guidelines of AANS, Brain Trauma Foundation.

(1) Severe traumatic brain injury (GCS score 3-8) and an abnormal CT scan, e.g. one showing hematoma, contusions, edema, compressed basal cisterns

(2) Severe traumatic brain injury (GCS score 3-8) and a normal CT scan but with two or more of the following conditions:

① Age of more than 40 years.

② Unilateral or bilateral decerebrate/decorticate rigidity in motor posturing

③ Systolic pressure lower than 90 mmHg.

(3) For mild (GCS score 13-15) and moderate (GCS score 9-12) brain injury patients, ICP monitoring is not recommended, but may be used with consideration of individual clinical needs.

Patients with severe traumatic brain injury and a normal CT scan were first recognized by Narayan in 1982 as those in need of ICP monitoring according to the guideline with class III data of 207 patients. He found that 13 % of all his patients had IICP and that 60 % of patients with more than two of the conditions mentioned above suffered from IICP, which was present in only 4 % of those who had only one of the conditions. Overall, only 16 % of such patients were entitled to ICP monitoring.

However, many experts maintain that the range of indications should be broader. For reference, the indications proposed in the literature will be mentioned below:

(1) Guidelines for brain injury in children (2003) [5]

- Severe traumatic brain injury (GCS score $\leq$ 8), with or without CT abnormalities.
- Moderate and mild brain injury with mass lesion in CT.

(2) Miller JD (1999) [1]

- All brain injuries with coma, because a normal CT results does not guarantee normal intracranial pressure.

(3) Reilly P. (Guest Book of the National Neurotrauma Society, 1997)

- Same indications as those given by the Brain Trauma Foundation (2000) for severe traumatic brain injury.
- GCS score $\leq$ 10 with CT abnormalities.

— Brain swelling after removal of hematoma.
— Injury other than that on the cranium (especially chest injury), which requires a ventilator.

(4) European Brain Injury Consortium (EBIC, 1997) [7]
— Adult severe traumatic brain injuries requiring early extracranial surgery.

(5) Penetrating Brain Injury (2001) [8]
— if neurosurgical examinations cannot be performed.
— if the indication for removal of the mass lesion can not be established.
— if the CT shows high intracranial pressure.

2. Intracranial Treatment Threshold

Elevation of intracranial pressure with preceding lowered compliance indicates that the compensatory mechanisms have been exhausted. Therefore, the high intracranial pressure should be corrected toward the lower threshold as soon as possible. Suggested thresholds in the literature range from 15 to 25 mmHg, but transtentorial herniation may occur with intracranial pressure of lower than 20 mmHg. It is mandatory, therefore, in addition to clinical neurological examinations covering pupillary changes, to consider whether CPP is adequate and whether the lesion is close to the posterior cranial fossa (15 mmHg is the suggested threshold).

In the Brain Trauma Foundation Guidelines (2000), it is suggested that the upper threshold of intracranial pressure be 20-25 mmHg[2] for adult head injury, and 20mmHg for that in children (according to the 2003 guidelines). [5]

3. ICP Monitor Choice

Clinically, the two most accurate means of ICP monitoring are the intraventricular and intraparenchymal ICP monitors. The former is less expensive and can also drain CSF. However, the rates of bleeding, infection and obstruction are higher. The latter is much easier to operate, but is also much more expensive and is not covered by our health insurance. It is suggested that the neurosurgeon choose between the two according to resource distribution, location of the district, and insurance or other social factors. [2]

Conclusions

After years of experience in clinical research, ICP monitoring is now an essential method of management for the intensive care of severe neurotrauma. It supplements clinical neurological observation, helps in general evaluation, and protects sedated patients. In addition, it serves as a basic indicator for clinical research by comparison with other brain function monitors, and thus greatly improves the quality of intensive care and the outcome of patients with severe brain injury.

Evidentiary Table

Series (ref. No.)	Article title	Evidence level
Miller JD, Piper IR, Statham PF. 1996	ICP monitoring: indications & techniques.	2++
Bullock R, Chestnut RM, Clitton GL, et al. 2000; 17(4)	Guidelines for the management of Severe Traumatic Brain Injury.	2++
Graper JJ, Meagher RJ. 2005	When and how should I monitoring intracranial pressure? Neurotrauma evidence based answers to common questions.	2++
Narayan RK, Kishore PR, Becker DP, et al. 1982 (56)	Intracranial pressure to monitoring or not monitoring? A review of our experience with severe head injury.	2++
Adelson PD, Bratton SL, Laney NA, et al. 2003; suppl V31(6)	Guidelines for the acute medical management of severe traumatic brain injury in infants, children and adolescents.	2++
Reilly P, 1997	Management of intracranial pressure and cerebral perfusion in National Neurotrauma Society Guest Book.	2+
Maas AIR, Dreaden M, Tesdale GM. 1997	GM. EBIC-guidelines for the management of severe brain injury in adults.	2+
Aarahi B, Alden TP, Chestnut RM, et al. 2001; suppl 51(2)	Intracranial pressure in the management of penetrating injury AANS/CNS Penetrating Brain Injury Guidelines.	2+

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Members of the ICP Monitoring Guideline Team

Dr. Kuo-Fang Yu (*Chimei Hospital, Liouying*)
Dr. Tzu-Gan Lin (*Chang Gung Memorial Hospital, Linkou*)
Dr. Ming-Ta Tsai (*Hsin Kuang Hospital*)
Dr. Chi-Wen Chou (*Changhua Christian Hospital*)
Dr. Ta-Ming Lai (*National Taiwan University Hospital*)
Dr. Kuo-Wei Wang (*E-Da Hospital*)
Dr. Yu-Hone Hsu (*Taipei Medical University-Wan Fang Hospital*)
Dr. Kun-Hsing Li (*Chung-Ho Memorial Hospital, Kaohsiung Medical University*)

5

CPP

Cerebral perfusion pressure (CPP) is defined by the value of mean arterial pressure minus intracranial pressure. It is the source of energy for cerebral blood flow and brain metabolism. It has been established in both pathological and biological researches that most patients with severe head injury suffer from brain ischemia. Therefore, in medical care of severe head injury patients, maintenance of normal CPP is of paramount importance.

Recommendations

Written by Hsu-Lin Huang/Jui-Chen Kong
Editor: Cerebral perfusion pressureand Perfusion Guideline Team

B 1. CPP should be maintained between 60 and 70 mmHg.

C 2. CPP < 60 mmHg may be harmful.

C 3. Without evidence of brain ischemia, purposeful elevation of CPP above 70 mmHg may increase the risk of ARDS.

D 4. In both the Lund concept [1] and EBIC (European brain injury consortium) [2] CPP should be maintained between 60 and 70 mmHg.

C 5. Without evidence of brain ischemia, active use of a vasopressor or colloid to raise CPP above 70 mmHg may lead to a rate of ARDS 5-times higher than with CPP kept below 70 mmHg.

Introduction

Cerebral perfusion pressure (CPP) is defined by the value of mean arterial pressure (MAP) minus intracranial pressure (ICP) [CPP = MAP − ICP]. It is the source of energy for cerebral blood flow (CBF) and brain metabolism. It has been established in both pathological and biological researches that most patients with severe head injury (SHI) suffer from brain ischemia. Once the autoregulation of cerebral vessels is damaged, intracranial pressure, cerebral blood flow, and brain metabolism will all be ra-

pidly impaired. Therefore, in medical care of severe head injury patients, maintenance of normal CPP is of paramount importance.

Literature Review

1. In their study of causes of death from severe head injury, Graham et al. found after autopsy that approximately 91% of the patients had ischemic lesions.[3] Also, it was found in other studies that there was a 30 % possibility in cerebral blood flow dropping in the first 6 hours, and the possibility of O_2 saturation in the jugular vein ($SjvO_2$) dropping was 30-35 %.[5,6]

2. Kiening et al. showed that severe head injury may lead to unstable CPP, which decreases $tipO_2$. Once a patient has $tipO_2 < 10$ mmHg for more than 15 minutes, the outcome will be worse. In their research, when CPP was raised from 32 to 67 mmHg, there was a 67 % increase of $tipO_2$. CPP $>$ 60 mmHg was considered to be a critical threshold, and $tipO_2$ adequate with CPP of this value.[7]

3. The research of Cruz et al. shows that when brain autoregulation functions well, cerebral perfusion pressure is kept between 60 and 130 mmHg, and does not affect cerebral blood flow or metabolism. Between CPP and CBF, CPP and $AVdO_2$, or CPP and $CMRO_2$, there is no correlation.[8] Bouma et al. showed that, with intact autoregulation, MAP raised from 92 ± 10 mmHg to 23 ± 8 mmHg did not cause significant changes in ICP ($<$ 1 % CBF change).[4] Bruce et al. also pointed out that whether autoregulation was functioning or not, active raising of SBP by 30 mmHg led only to a slight raising or lowering of ICP. The results of

these researches confirmed that with adequate CPP, a moderate increase in SBP did not cause IICP in most patients. [9]

4. Chan et al. found in transcranial Doppler (TCD) use that $SjvO_2$ decreased but the pulsatility index (PI) increased when CPP was lower than 70 mmHg. On the contrary, neither $SjvO_2$ nor PI changed with CPP > 70 mmHG. [10]

5. In the past, it was advocated that the outcome is worse when CPP > 70 mmHg. In 1995, however, Rosner showed that among patients with CPP > 70 mmHg, 29.5 % died within 10.5 months, and 20 % had moderate disability, while 39 % had a good recovery. [11] In 1989, McGraw investigated the relation between CPP and outcome in animal experiments: when CPP > 80 mmHg, the death rate was approximately 35-40 % , and when CPP decreased by 10 mmHg, the death rate increased by 20 %. When CPP < 60 mmHg, the death rate could be as high as 95 %.[12] In other prospective studies, when CPP was kept around 70 mmHg, the average death rate with GCS 3-7 was approximately 21 % (5-35 %). [13, 14, 15, 16, 17]

6. Robertson et al. used prospective RCT methodology to do a research on severe head injury patients with GCS < 5. He divided the patients into ICP-oriented (CPP > 50 mmHg) and CBF oriented (CPP > 70 mmHg) groups, and found no significant clinical differences between these groups. [18] In analysis of ARDS risks, Contant et al. found that the ARDS rate of the CBF group was five times higher than that of the ICP group. It could be related to the use of more Epinephrine and Dopamine in the former group. In animal experiments, it has been found that ARDS might result from increased sympathetic nerve action via central nervous system lesions. [19] Besides, the rate of uncontrollable ICP for patients with ARDS is 2.5 times higher than that for those who have no ARDS,

while the rate of vegetable state or death within 6 months for the former will be three times higher than with ARDS. [19,20]

Conclusions

Supported by the evidence from the literature, we are convinced that it is adequate to keep cerebral perfusion pressure between 60 and 70 mmHg. However, it is asserted in the literature that CPP $<$ 50 mmHg will lead to severe decrease of tipO_2 and increase the death rate and complication rate. So far, there have been no articles to prove that vasopressor or colloid use which maintains CPP $>$ 60 mmHg increases the death rate, or risk of complications or increased intracranial pressure. With CPP $<$ 70 mmHg, the ARDS rate is five times higher than that without active treatment. On the other hand, the European Lund concept is not yet widely used. In future researches on severe head injury, the increased use of double-blind prospective RCT could be useful in comparison between CPP control and ICP management. With differences between the Lund concept and CPP protocol clarified, the quality of medical care for severe head injury patients would be improved.

Evidentiary Table

Series (ref. No.)	Article title	Evidence level
Grande PO, et al. 2002(1)	Volume-targeted therapy of increased intracranial pressure: the Lund concept unifies surgical and non-surgical treatments.	2-
Maas AIR, et al. 1997(2)	EBIC-Guidelines for management of severe head injury in adults.	2+
Graham DI, et al. 1978(3)	Ischaemic brain damage in fatal non-missile head injuries.	2+
Bouma GJ, et al. 1991 (4)	Cerebral circulation and metabolism after severe traumatic brain injury: the elusive role of ischemia.	2+
De Deyne C, et al. 1996(5)	Analysis of very early jugular bulb oximetry data after severe head injury: implications for the emergency management?	2-
Vigue B, et al. 1999(6)	Early $SjvO_2$ monitoring in patients with severe brain trauma.	2+
Kiening KL, et al. 1997(7)	Brain tissue pO_2-monitoring in comatose patients: implications for therapy.	2-
Cruz J, et al. 1995 (8)	Cerebral blood flow, vascular resistance, and oxygen metabolism in acute brain trauma: redefining the role of cerebral perfusion pressure?	2+
Bruce DA, et al. 1973(9)	Regional cerebral blood flow, intracranial pressure, and brain metabolism in comatose patients.	2-
Chan K-W, et al. 1992(10)	The effect of changes in cerebral perfusion pressure upon middle cerebral artery blood flow velocity and jugular bulb venous oxygen saturation after severe brain injury.	2-
Rosner MJ,et al. 1995(11)	Cerebral perfusion pressure: management protocol and clinical results.	2++

Series (ref. No.)	Article title	Evidence level
McGraw CP. 1989(12)	A cerebral perfusion pressure greater than 80 mm Hg is more beneficial, in Hoff JT, Betz AL (eds): Intracranial pressure VII.	3
Clifton GL, et al. 1993(13)	A phase II study of moderate hypothermia in severe brain injury.	2+
Fortune JB,et al. 1994(14)	Continuous measurement of jugular venous oxygen saturation in response to transient elevations of blood pressure in head-injured patients.	2-
Marion DW, et al. 1997(15)	Treatment of traumatic brain injury with moderate hypothermia.	1-
Rosner MJ, et al. 1990(16)	Cerebral perfusion pressure management in head injury.	2+
Yoshida A, et al. 1993 (17)	Outcome of patients with severe head injury--Evaluation by cerebral perfusion pressure, in Nakamura N, Hashimoto T, Yasue M (eds).	4
Robertson CS, et al. 1999(18)	Prevention of secondary ischemic insults after severe head injury.	1+
Contant CF, et al. 2001(19)	Adult respiratory distress syndrome: A complication of induced hypertension after severe head injury.	2+
Bratton SL, et al. 1997(20)	Acute lung injury in isolated traumatic brain injury.	2-
Eker C, et al. 1998(21)	Improved outcome after severe head injury with a new therapy based on principles for brain Volume regulation and improved microcirculation.	2-
Strandgaard S. et al. 1973(22)	Autoregulation of brain circulation in severe arterial hypertension.	2-

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Members of the Cerebral Perfusion Pressure and Perfusion Guideline Team

Dr. Jui-Chen Kung (*Yuan's General Hospital*)
Dr. Sheng-Chien Huang (*National Taiwan University Hospital*)
Dr. Cheng-Mao Cheng (*Tri-Service General Hospital*)
Dr. Chaun-Fa Su (*Buddhist Tzu Chi General Hospital, Hualien*)
Dr. Sheng-Huang Hsiao (*Taipei City Hospital Jen-ai Branch*)
Dr. Hsu-Lin Huang (*Chung-Ho Memorial Hospital, Kaohsiung Medical University*)

6

Fluid Therapy

The ultimate goal of fluid therapy is to restore vascular capacity, cardiac output and tissue perfusion.

Recommendations

Written by: Hsu-Lin Huang/ Ju-Chen Kung
Editor: Fluid Therapy Guideline Team

D 1. For massive infusion, 0.9 % saline fluid is better than Lactated Ringer's.

C 2. Use of colloid use to maintain osmotic pressure is mentioned in both Rosner et al. [1] and the Lund concept.[2]

I 3. There is no sufficient evidence to show whether colloid use is necessary, but specialists in our country agree that reasonable use of colloid can be helpful, though without agreement on which kind of colloid to be used.

C 4. FFP is indicated only for coagulopathy, and not recommended to be used as a regular volume expander. [3]

D 5. Recently, it has been suggested that hypertonic saline may benefit patients with traumatic brain injury complicated by shock.

C 6. Glucose-containing fluids should be used with caution.

Introduction

The ultimate goal of fluid therapy is to restore vascular capacity, cardiac output and tissue perfusion. Controversy still exists, however, as to the kind and amount of fluid, and the proper intravascular volume monitor in the management of patients with severe traumatic brain injury.

Literature Review

1. Weed et al. found in 1919 that changes in brain volume are related to the tonicity of fluid infused. [4]
2. Hypotonic fluid (e.g. 0.45 % and 5 % glucose), like water, can directly cross BBB, increasing brain water and ICP. [5]
3. All glucose-containing fluids may cause hyperglycemia and worsen outcome. In some researches brain ischemia induced anaerobic respiration, and glucose metabolism in such situations increased the accumulation of lactic acid, induced tissue acidosis, and aggravated neural damage. [6, 7]
4. Some researches showed that pre-hospital use of hypertonic saline on severe traumatic head injury patients with shock restored intravascular volume and lowered ICP. [8, 9]
5. Zornow used colloid (6 % hetastarch or 5 % Albumin) in animal experiemtns, and found that an increase in oncotic pressure did not significantly changed the water volume of the brain. [10]
6. A large amount of isotonic fluid in human and animal experiments has no obvious influence on cerebral edema, but dehydration worsens neurological outcome. [11, 12, 13, 14]

Conclusions

Concrete description of fluid therapy is lacking in most guidelines of foreign countries. Therefore, in our country, in order to promote effective fluid therapy, we have added this item to our Guidelines. The present opin-

ion in the literature favors 0.9 % normal saline, while there is no agreement on colloid use despite the Lund concept confirming its efficacy. On the other hand, FFP is now thought improper as volume-expanding fluid. We hope that in the future more double-blind prospective RCT researches will be done to elucidate proper timing and advantages/disadvantages of crystalloid or colloid use.

Evidentiary Table

Series (ref. No.)	Article title	Evidence level
Rosner MJ, et al. 1990(1)	Cerebral perfusion pressure management in head injury.	2+
Grande PO, et al. 1997(2)	Volume-targeted therapy of increased intracranial pressure: the Lund concept unifies surgical and non-surgical treatments.	2-
Practice guidelines for blood component therapy 2006(3)	Practice Guidelines for Perioperative Blood Transfusion and Adjuvant Therapies. An Updated Report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies.	2+
Weed LH, et al. 1919(4)	Experimental alteration of brain bulk.	4
Zornow MH, et al. 1995(5)	Fluid management in Patients with Traumatic Brain Injury.	4
Dellinger RP, et al. 2004(6)	Surviving sepsis campaign guidelines for management of severe sepsis and septic shock.	2-
Lanier WL, et al. 1987(7)	The effects of dextrose infusion and head position on neurologic outcome after complete cerebral ischemia in primates: Examination of a model.	4

Series (ref. No.)	Article title	Evidence level
Gabriel EJ, et al. 2000 (8)	Guidelines for the pre-hospital Management of Traumatic Brain Injury.	2-
Kramer GC. 2003(9)	Hypertonic resuscitation: physiologic mechanisms and recommendations for trauma care.	3
Zornow MH, et al. 1988(10)	Acute cerebral effects of isotonic crystalloid and colloid solutions following cryogenic brain injury in the rabbit.	4
Fisher B, et al. 1992(11)	Hypertonic saline lowers raised intracranial pressure in children after head trauma.	2+
Morse ML, et al. 1985(12)	Effect of hydration on experimentally induced cerebral edema.	4
Shapira Y, et al. 1992(13)	Brain edema and neurologic status following head trauma in the rat. No effect from large volumes of isotonic or hypertonic intravenous fluids, with or without glucose.	4
Shapira Y, et al. 1995(14)	Brain edema and neurologic status with rapid infusion of 0.9% saline or 5% dextrose after head trauma.	4

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Members of the Fluid Therapy Guideline Team

Dr. Hsu-Lin Huang (*Chung-Ho Memorial Hospital, Kaohsiung Medical University*)
Dr. Sheng-Chien Huang (*National Taiwan University Hospital*)
Dr. Mao-Chen Cheng (*Tri-Service General Hospital*)
Dr. Jui-Chen Kung (*Yuan's General Hospital*)
Dr. Sheng-Huang Hsiao (*Taipei City Hospital Jen-ai Branch*)
Dr. Chuan-Fa Su (*Buddhist Tsu Chi General Hospital*)

7

Use of Sedatives

When safety of respiration is secured for a severe traumatic brain injury patient, sedatives and analgesics may be used for: control of stress response, pain control, better adaptation to endotracheal intubation, reduction of intracranial hypertension resulting from therapeutic or nursing procedures.

Recommendations

Written by: Kuo-Hsing Liao
Editor: Sedatives Use Guideline Team

C 1. In Taiwan, the use of sedatives has been adopted by some intensive care units as an option of treatment for patients with a GCS score of 3-8 and uncontrollable intracranial hypertension or agitation.

C 2. It is recommended that patients with a GCS score of 3-8 have an endotracheal tube in place before sedatives are administered.

Introduction

When safety of respiration is secured for a severe traumatic brain injury patient, sedatives and analgesics may be used for the following purposes: control of stress response, pain control, better adaptation to endotracheal intubation, reduction of intracranial hypertension resulting from therapeutic or nursing procedures.[1,2] Ideal sedatives should be rapidly affective, do not accumulate in the body, producing no cytotoxic metabolites, and do not suppress cardiovascular functions. The sedative effects should rapidly disappear after discontinued use, so that neurological assessment can be easily made. They should be inexpensive and able to lower intracranial pressure as well as brain metabolism.[1,2] Unfortunately, there is no single drug that meets all the criteria mentioned above.

Literature Review

The following sedatives are widely used in NICU currently:

Benzodiazepines

1. Midazolam (Dormicum) : loading doses 0.02-0.3 mg/kg; maintenance dose 0.05-0.1 mg/kg/h [1]
2. Lorazepam (Ativan) : loading dose 0.02-0.05 mg/kg; maintenance dose 0.05-0.5 mg/kg/h [1]
3. Diazepam (Valium) : loading dose 0.03-0.1 mg/kg, not recommended for long use on account of its accumulating effect. [1]

These drugs do not relieve pain, and do not significantly affect intracranial or systemic hemodynamics in small doses. However, they may cause mild hypotension and respiratory suppression with loading doses or large doses. [1,2,4,6,7] Besides, they have moderate effects on $CMRO_2$ and CBF.

Propofol

Loading dose 1-2 mg/kg; maintenance dose 1-3 mg/kg/h. [1] Pharmacologically, like Benzodiazepine, Propofol is a sedative, hypnotic, anticonvulant, and muscle relaxant.[1,3,5] Also, Propofol can suppress respiration almost as rapidly as Midazolam (one of Benzodiazepines), along with similarly short action. Propofol, however, has more suppressive effects on blood pressure.

In a research [9] carried out in our country, Propofol (44 cases) and Midazolam (14 cases) were compared in the management of head injury patients with Glasgow Coma Scales 3-12 with the use of a ventilator and an ICP monitor, and 27.27 % of severe traumatic brain injury patients

using sedatives needed vasopressors at the same time to prevent brain ischemia, while 54.10 % of such patients using no sedatives needed vasopressors ($p < .001$). The ICU intracranial pressure recordings within the first five days after injury, were better for those using sedatives (< 20 mmHg within 3 days) than those using no sedatives. As for cerebral perfusion pressure, patients using sedatives could maintain on the average CPP higher than 70 mmHg within 5 days after injury, while those using no sedatives could keep CPP only around 40 mmHg. Various post-traumatic baseline data (GCS 3-4, 5-6, or above 7), showed that the patients in the GCS 3-4 and 5-6 groups using sedatives also had a lower death rate than those using no sedatives. [9]

Opioids

1. Morphine: 2-10 mg I.V
2. Fentanyl: loading dose 0.25-1.5 μg/kg;
   maintenance dose 0.3-1.5 μg/kg/h
3. Meperidine: hard to control; there are also side effects of cardiac inhibition.[1]

Sedatives by themselves do not relieve pain, and may cause agitation of patients who need analgesia. Thus, sedatives and analgesics should be given at the same time.[1,4,5,7] Since the two usually act synergistically, the goal is achieved with lower doses. This will increase comfort and reduce stress especially for those who also suffer from other injuries.

Neuromuscular blocking agents

These are not recommended. If they are deemed necessary, priority is given to non-depolarizing agents. [1]

Barbiturates

Their use may be considered when intracranial pressure continues to rise, cannot be effectively controlled by most of medical or surgical measures for treatment of IICP. [2] For more details, please refer to *Second Tier Therapy*.

Conclusions

Prevention of brain ischemia is the key of treatment in NICU, [8] and the use of sedatives and analgesics has been more and more widely accepted. However, it still requires further studies to make sure that these drugs lower intracranial pressure, raise cerebral perfusion pressure, improve the prognosis of severe traumatic brain injury, and protect the neural tissue. [1,2,3,4,5] Most scholars are of the opinion that there will be a breakthrough in related researches in early days of the 21st century.

Evidentiary Table

Series (ref. No.)	Article title	Evidence level
F.Procaccio, et al. 2000 (1)	Guidelines for the treatment of adults with severe head trauma.	2+
The Joint Section on Neurotrauma and Critical Care of The Brain Trauma Foundation 2000 (2)	Use of Barbiturates in the control of intracranial hypertension.	2+
Patel HC, et al. 2000 (3)	Specialist neurocritical care and outcome from head injury.	2+
Young C, et al. 2000 (4)	Sedation in the intensive care unit.	2+
Daniel F Kelly, et al. 1999 (5)	Propofol in the treatment of moderate and severe head injury: a randomized, prospective double-blinded pilot trial.	1+
Aitkenhead AR, et al. 1989 (6)	Analgesia and sedation in intensive care.	2-
Mirski MA, et al. 1995 (7)	Sedation for critically ill neurological patients.	2+
Michael F. Stiefel, et al. 2005 (8)	Reduced mortality rate in patients with severe traumatic brain injury treated with brain tissue oxygen monitoring.	2+
Wen-Ta Chiu, et al. 2006 (9)	Multicenter evaluation of propofol for head-injured patients in Taiwan.	2+

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Members of the Sedatives Use Guideline Team

Dr. Wen-Ta Chiu (*Taipei Medical University-Wan Fang Hospital*)
Dr. Tien-Jen Lin (*Taipei Medical University-Wan Fang Hospital*)
Dr. Cheng-Ti Chiu (*Taipei Veterans General Hospital*)
Dr. Cheng-Kuei Chang (*Mackay Memorial Hospital Tanshui Branch*)
Dr. Yi-Long Chen (*Taipei City Hospital Chung-Hsing Branch*)
Dr. Yo-Chi Chang (*Chung Shan Hospital*)
Dr. Wen-Yu Chung (*Taipei Veterans General Hospital*)
Dr. Shu-Hsiung Hsu (*Kaohsiung Veterans General Hospital*)
Dr. Kuo-Hsing Liao (*Taipei Medical University-Wan Fang Hospital*)

8

Nutrition

In early 80's, clinical physicians did not demand too much with regard to nutrition of severe head injury patients. However, later it was found through investigation of energy consumption, nitrogen balance and cardiovascular parameters that there were hypermetabolism and nitrogen wasting in patients with severe head injury. But in the latest researches, evidence shows that Insulin-like Growth Factor-1 (IGF-1) can improve nitrogen balance and outcome.

Recommendations

Written by: Wan-Lin Chen, Yu-Hone Hsu
Editor: Nutrition Guideline Team

B 1. In patients treated with sedatives infusion should provide 100 % of resting metabolic expenditure, and for those without sedation, 140 % should be provided.

B 2. Parenteral and enteral nutrition supplement recipe: at least 15 % of energy source from protein should be provided within 7 days after injury to maintain nitrogen balance.

C 3. Timing for feeding: supplementary nutrition must be started within 24 to 72 hours after injury, with gradually increased doses to meet maximal caloric needs.

Introduction and Literature Review

1. It was commonly thought in early 80's that metabolic needs were lowered in patients with coma than in healthy people, and so clinical physicians did not demand too much with regard to nutrition of severe head injury patients. However, later it was found through investigation of energy consumption, nitrogen balance and cardiovascular parameters that there were hypermetabolism and nitrogen wasting in patients with severe head injury.
2. Currently there are at least 12 articles on nutritional needs of head injury patients at the 2+ or higher level of evidence. Nine are about the amount, means, and route of feeding as well as the influence of steroids on nitro-

gen balance and biochemical changes in blood, but without further comments on clinical outcome. Two deal with the influence of nutritional supplement on outcome. The studies showed that different modes of nutrition did not bring about significant differences in neutrological outcome if the amount of supplement was the same. However, the two articles showed contradictory results about the infection rate and nitrogen balance. In the remaining paper an increased infection rate with malnutrition was reported, but there were some methodological problems in this study.

3. The latest researches show that Insulin-like Growth Factor-1 (IGF-1) can improve nitrogen balance and outcome.

Conclusions

Scientific Foundation

1. Feeding: compared with intravenous infusion, chances for hyperglycemia and infection are decreased, and the costs are lowered with jejunal feeding or gastric feeding.[3,4,5]
2. Timing for feeding: nutritional supplement infusion must be started within 24 to 72 hours after injury, with a gradually increased amount to meet the maximal caloric needs. [1,2]
3. Patients with sedation need 100 % supplement of resting metabolic expenditure, while those without sedation need 140 %. When the patient suffers from vomiting or seizure, the amount of feeding should be accordingly adjusted in time. [6,7,8]
4. Factors for consideration: age, sex, body surface area, use of sedatives

use, muscle tone, gastrointestinal complications (e.g. obstruction, massive bleeding, peritonitis), spinal cord injury, etc.

5. Parenteral or intravenous nutritional supplement recipe: more than 15 % energy should be provided from protein within 7 days after injury in order to maintain nitrogen balance. [9, 10]
6. Weight reduction of more than 30 % leads to increased complication and death rates.
7. Goal for caloric requirement: at least 25 cal/kg.

Directions of Futures Researches

Research on clinical effects of the insulin-like growth factor-1 (IGF-1) with randomized controlled trial.

* : Fick Method of Resting Metabolic Expenditure (REE)

REE (kcal/d) = CO × Hb (SaO_2 − SvO_2) 95.18

CO: cardiac output (L/min)

Hb: hemoglobin concentration (mg/L)

SaO_2 : Oxygen saturation in arterial blood

SvO_2 : Oxygen saturation in mixed venous blood

Evidentiary Table

Series (ref. No.)	Article title	Evidence level
Rapp RP, et al.	The favorable effect of parenteral feeding on survival in severe head-injured patient.	1+
Young B, et al.	Effect of total parenteral nutrition upon intracranial pressure in severe head injury.	1+
Grahm TW, et al.	Nutrition support and neurotrauma: A critical review of early nutrition in forty-five acute head injury patients.	1-
Hausmann D, et al.	Combined-enteral parenteral nutrition versus total parenteral nutrition in brain-injured patients. A comparative study.	1+
Suchner U, et al.	Enteral versus parenteral nutrition:effects on gastrointestinal function and metabolism.	1+
Bruder N, et al.	Evolution of energy expenditure and nitrogen excretion in severe head-injured patients.	2+
Clifton GL, et al.	Assessment of nutritional requirements of head-injured patients.	2+
Clifton GL, et al.	The metabolic response to severe head injury.	2+
Clifton GL, et al.	Enteral hyperalimentation in head injury.	1+
Ott LG, et al.	Comparison of administration of two standard intravenous amino acid formulas to severe brain-injured patients.	1+

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Members of the Nutrition Guideline Team

Dr. Sheng Huang Hsiao （*Taipei City Hospital Jen-ai Branch*）
Kun-Chuan Chang （*Cathay General Hospital*）
Kuo-Sheng Hong （*Taipei Medical University-Wan Fang Hospital*）
Ta-Yu Yang （*Chang Bing Show Chwan Memorial Hospital*）
Dr. Jui-Chen Kung （*Yuan's General Hospital*）
Dr. Kuo-Wei Wang （*E-Da Hospital*）

Intracranial Hypertension

9

Brain ischemia prevention is the main stay of intensive care for severe TBI, and the best way to achieve it is to find the problem and to manage it properly in time. In addition to traditional ICP control means, it is now the focus of intensive care to set up a multiple brain monitor system, and to establish correct concepts of CPP and brain metabolism.

Recommendations

Written by Shen-Chien Huang/Chen Kuei Chang
Editor: Intracranial Hypertension Guideline Team

A Prophylactic hyperventilation is not recommended to be used for treatment of intracranial hypertension.

A Steroids are not recommended for treating intracranial hypertension.

The following are the recommended treatment procedures when ICP ＞ 20 mmHg, aside from due attention to other general factors related to ICP .

Set up the ICP monitor

B Raise the bed head by 30 degrees, keep CVP at 8-12 mmHg and rule out hypornatremia and fever when CPP ＞ 60 mmHg

↓

ICP ＞ 20 mmHg

↓

B CSF drainage (with ventricular drain, if available) of 3-5 cc each time

↓

B Use sedatives and analgesics; use neuromuscular blockade agents when necessary

↓

B Light hyperventilation with $PaCO_2$ 30-35 mmHg

↓

B Mannitol 0.25-1 g/kg/intravenous injection

↓ → Cranial CT-brain edema or ICH

B Craniotomy or decompressive craniectomy

Second Tier Therapy

(Barbiturate coma, hyperventilation ($PaCO_2$ 25-30 mmHg) hypertonic saline)

Introduction

In the past, neurosurgical intensive care for severe traumatic brain injury (TBI) patients was focused on the management of increased intracranial pressure (IICP). Different ways to control IICP, such as fluid restriction, administration of Mannitol or Glycerol, hyperventilation, sedation, hypothermia therapy and use of steroids are, however, being re-assessed. The main target of intensive care for TBI has recently turned from ICP control to brain ischemia prevention. Thus, in addition to lowering ICP, it has become our new concern to increase cerebral perfusion pressure and to slow down brain metabolism in order to prevent ischemia. In this chapter, we discuss important concepts in neurosurgical intensive care and essential principles in the management of IICP.

Literature Review

1. Pathophysiological mechanisms of intracranial hypertension:

Traditionally, ICP control has been the main target in the management of severe TBI. Most scholars agree that ICP ＞ 25 mmHg implies a poor prognosis. [1~7] According to clinical researches, pathological and biological mechanisms of intracranial hypertension due to severe TBI include: intracranial bleeding, cerebral edema, cerebral hyperemia and hydrocephalus, of which massive intracranial bleeding and hydrocephalus require surgical treatment. IICP due to different causes needs different modes of treatment. For instance, hyperventilation should be used for hyperemia, and hypertonic diuretics for cerebral edema. Other common factors to be considered include:

(1) Degrees of bed head raising: when the head of the bed is raised by 15-30 degrees, ICP becomes lower than in the flat position,[2~6] and CPP drops when the bed head is raised by more than 30 degrees.

(2) Fever: high body temperature accelerates brain metabolism, and makes the brain vulnerable to ischemia and IICP. [3~6]

(3) Blood $PaCO_2$: Low $PaCO_2$ leads to constriction of brain vessels and dropping of ICP. On the contrary, high $PaCO_2$ causes IICP. If the $PaCO_2$ is too low, however, compromised cerebral perfusion will lead to brain ischemia. [1~6]

(4) Na^+ concentration in blood : Low Na^+ concentration leads to dropping of osmotic pressure, and thus causes cerebral edema and intracranial hypertension.[3~6]

(5) Neck posture: When jugular venous return is affected, it may lead to intracranial hypertension.[3~6] Neck twist and pressure on jugular veins should therefore be avoided.

(6) Agitation and pain: When the patient "fights" with the ventilator, suction and pain may both lead to IICP, and sedatives and analgesics may be appropriately used. [2~7]

2. Management of IICP:

There are many ways in the treatment of IICP, each with its own advantages and disadvantages. Basically, the principle is not to affect CPP and to avoid brain ischemia. Each way of therapy will be explained below:

(1) CSF Drainage: With ventriculostomy, CSF drainage should be the first choice. [2~6] Effective with few disadvantages, CSF drainage of even only 3-5 c.c. may substantially lower ICP. It is generally suggested that 75 cc. be drained every 8 hours.

(2) Sedatives, analgesics, and neuromuscular blockers: [8~19] Sedatives, analgesics, and neuromuscular blockers make ventilator use more controllable, and may help lower ICP. The most frequently used sedatives are Midazolam, Propofol, and Ketamine. Fetanyl and Morphine are common usual analgesics, and Atracurium and Cis-atracurium, neuromuscular blockers. Through veins these three kinds of drugs can be given continuously, with due caution to the following:

(a) The airway should be patent.

(b) Midazolam, Propofol and Atracurium may have effects on blood pressure.

(c) Neuromuscular blockers can not be used without sedation.

Neuromuscular blockers can not be used without sedation. The main disadvantage is that these agents make it impossible to assess motor reaction and other neurological functions at any time desired. Thus, brain monitoring should be adequate. It is advocated that the smallest effective dose should be used. With ICP < 20 mmHg for more than 24 hours, the dose may be gradually decreased.

(3) Hyperosmotic diuretics:[1~7] Mannitol and Glycerol are most frequently used. Theoretically, increased intravascular osmotic pressure allows extracellular fluid of the brain to enter blood vessels and thus improves cerebral edema and lowers ICP. The effects begin approximately 15-20 minutes after the use of diuretics. Recent research reports show that in addition to the above-mentioned functions, mannitol also lowers blood viscosity as well as hematocrit, and thus accelerating blood flow, causes reactive constriction. As a result, in a few minutes ICP drops on account of the decrease of cerebral blood volume. Bolus, rapid infusion is recommended. Besides, Mannitol can also open the blood-brain barrier. However, Mannitol may accumulate in the brain, and lead to cerebral edema with excessive cerebral osmotic pressure, especially after long use or continuous infusion. Therefore, bolus, rapid infusion should be adopted instead of slow and continuous infusion. The dose suggested is 0.25-1g/Kg/4-6 hrs, and the time interval can be shorter if necessary. It is important that blood volume stays normal with blood osmotic pressure monitored and kept no higher than 320mOsm/L for fear of renal failure. The disadvantages with the traditional methods are hypovolemia, hypotension, electrolyte imbalance, and renal failure. Lasix may be used more effectively along with Mannitol at the dose of 20-40 mg/4-6 hrs. Pay special attention to fluid supplement in or-

der to avoid hypovolemia and hypotension, which may lead to brain ischemia.

(4) Hyperventilation:[1~7] Lowered blood $PaCO_2$ leads to brain vessel constriction and thus lowers ICP. This mode of therapy has been clinically used for more than 20 years. Blood $PaCO_2$ lowered to 25-30 mmHg lowers ICP in seconds, but this effect does not last long. Therefore, it is generally regarded that $PaCO_2$ should stay at 30-35 mmHg, and slight hyperventilation may suffice. As for the timing, the current tendency is to use it for acute IICP, while a reserved attitude is held toward its prophylactic use.

(5) Barbiturate coma: [1~7] Coma induced by a high dose of barbiturate slows down brain metabolism, and thus lowers ICP. In reports from foreign countries, the results of this kind of treatment have varied greatly in the past decades with death rates ranging from 21 to 89 %. Some scholars even think that barbiturate coma therapy actually saves nonfunctioning lives and thus doubt its value. For this reason, some think that the timing of barbiturate coma is of great importance. If the treatment is started too late, brain stem functions may have been impaired, and will produce a nonfunctioning life, even if the IICP has been put under control. It is recommended that barbiturate coma therapy be immediately started when ICP $>$ 30 mmHg and CPP $<$ 70 mmHg, or when CPP $>$ 70 mmHg and ICP $>$ 40 mmHg. Pentobarbital is used for barbiturate coma with the initial loading dose of 10mg/kg by IV infusion for 30 minutes, and then 5mg/kg/hr for 3 hours until electrocerebral silence is reached. If blood pressure is unstable, infusion should be slowed down to 1-3mg/kg/hr, and the plasma concentration maintained at 30-50mg/100ml. When ICP $<$ 20 mmHg for 24 to 48 hours, the drug

should be gradually tapered off. Hypotension is a disadvantage with barbiturate coma, so before the therapy is started, it should be ascertained that body fluid volume is in normal state. In addition, it requires special attention to prevention of pneumonia and septicemia, which need infection monitoring. Now in Taiwan, most scholars do not adopt this mode of therapy.

(6) Hypothermia:[22~23] Fever brings about adverse effects on severe TBI, and hypothermia may counteract such effects. Research reports show that when the body temperature is lowered in 24-96 hours to 33-34℃ and raised back to 37℃ at the rate of 0.3℃ every eight hours, brain metabolism, ICP and blood lactic acid levels are lowered, while CPP remains undisturbed, and the clinical outcome becomes better. Usual complications of hypothermia are: infection, arrhythmia, and prolonged clotting time. This mode of therapy, however, was declared a failure in the 3rd stage clinical experiment in 2001.

(7) Steroids: Steroids are currently considered effective for cerebral edema and ICP due to brain tumor and brain abscess. However, according to the latest reports [24] and guidelines for the management of severe TBI, steroids are not capable of lowering ICP or of improving clinical outcome. Therefore, routine use of steroids is not recommended.

(8) Decompressive Craniectomy: The idea of decompressive craniectomy for severe TBI was proposed first by Horsley and then by Harvey Cushing more than a century ago.[25, 26] Early results failed to show any advantages of such a craniectomy with regard to either mortality or morbidity. Recently, however, the craniectomy outcome has been considerably improved, thanks to advances in neurosurgical intensive care.[27] The American Association of Neurological

Surgeons placed craniectomy in second tier therapy in its 1996 TBI guidelines.[28] Compared with decompressive lobectomy, decompressive craniectomy has been shown to be a better choice as shown by recent evidence.[29] Although some still deem decompressive craniectomy unbeneficial, and possibly even harmful to cats in animal experiments, most agree to put it in second tier therapy.[30] The latest studies on craniectomy have mainly focused their attention to timing and techniques (unilateral/bilateral). Besides, good outcome from craniectomy seems to approve the value of this kind of therapy in pediatric TBI.[31~35] Some of the latest studies have even suggested that decompressive craniectomy be put in first tier therapy.

3. Emergency clinical path and treatment procedure for intracranial hypertension:

The precise threshold of ICP has not yet been determined. Clinically, ICP rising to 20-25 mmHg should be lowered aggressively at once. There are many ways of lowering ICP, and each has its own advantages and disadvantages. Therefore, according to the benefit-risk ratio of each therapy, the emergency path and treatment procedures have been proposed in our country. Before lowering ICP, adjustments should be made, which include: control of body temperature, use of anti-epileptic drugs, head raising by 30 degrees, control of maintenance of smooth bilateral jugular venous return, 100 % blood oxygen saturation, normovolemia, maintenance of central venous pressure at 8-12 mmHg, CPP $>$ 60 mmHg, and $PaCO_2$ at 35-40 mmHg. When these fundamental factors are all secured, the first choice for patients with an intraventricular ventricle ICP monitor is CSF drainage. Release of 3-5 c.c. each time would relieve IICP effectively. If ventricle drainage cannot be done, analgesics and neurovascular blockers should be used to assure

that the patient is kept still and does not fight against the ventilator. In case the procedures mentioned above cannot control ICP well, slight hyperventilation may be used to lower $PaCO_2$ to 30-35 mmHg. If ICP is still too high, hypertonic diuretics such as Mannitol and Glycerol may be used in. A large amount of Mannitol can be used until osmotic pressure reaches 320 Osm/L. Fluid supplement and electrolyte balance should be carefully maintained. In addition to aggressive use of hypertonic diuretics, second tier therapy should also be taken into consideration when all the modes of treatments mentioned above have proven ineffective. However, before using second tier therapy, we should be alert all the time whether or not there is re-bleeding or other situations that require surgery, and a CT scan should be repeated whenever necessary for confirmation. The so-called second tier therapy refers to modes of therapy with relatively great side-effects and uncertain therapeutic effects. Within this category are barbiturate coma, hypothermia, therapeutic hypertension, aggressive hyperventilation ($PaCO_2 < 30$ mmHg), and use of hypertonic saline.

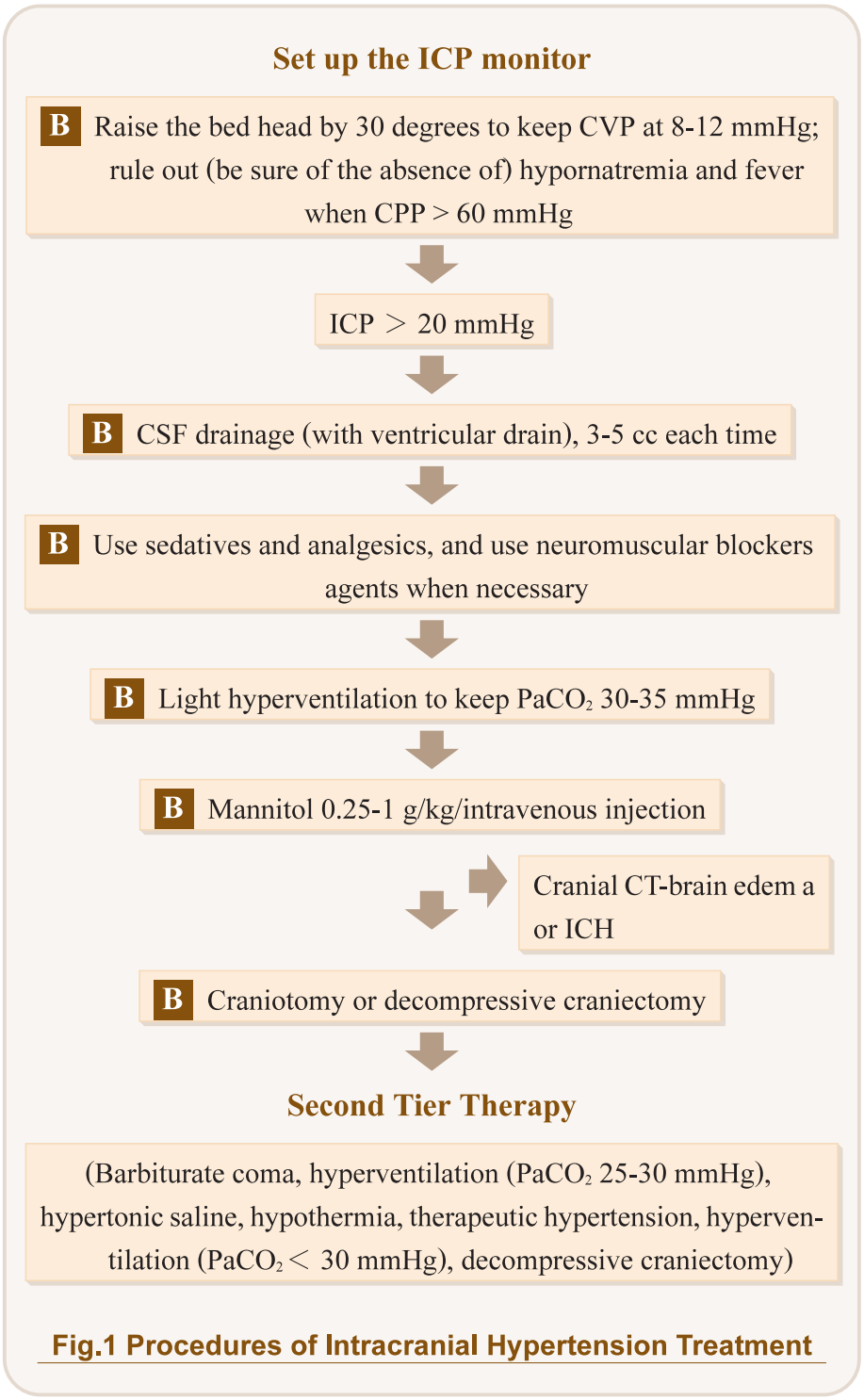

Fig.1 Procedures of Intracranial Hypertension Treatment

Conclusions

Brain ischemia prevention is the main stay of intensive care for severe TBI, and the best way to achieve it is to find the problem and to manage it properly in time. In addition to traditional ICP control means, it is now the focus of intensive care to set up a multiple brain monitor system, and to establish correct concepts of CPP and brain metabolism.

Evidentiary Table

Series (ref. No.)	Article title	Evidence level
Ghajar J. 2000(1)	Traumatic brain injury.	2++
Marion DW, Letarte PB. 1997(2)	Management of Intracranial Hypertension. Conte.	2++
Marion DW, Firlik A, Mclaughlin M. 1995(3)	Hyperventilation and severe traumatic brain injury.	2+
Robertson CS, Cormio M. 1995(4)	Cerebral metabolic management.	2++
Bouma GJ. 1995(5)	Cerebral blood flow in severe clinical head injury.	2++
Chesnut RM. 1995(6)	Medical management of severe head injury: Present and future.	1+
The Brain Trauma Foundation. 2000 (7)	The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Intracranial pressure treatment threshold.	1+
Young C, Knudsen N, Hilton A, et al. 2000(8)	Sedation in the intensive care unit.	2++

Series (ref. No.)	Article title	Evidence level
Kollef MH, Levy NT, Ahrens TS, et al. 1998 (9)	The use of continuous iv sedation is associated with prolongation of mechanical ventilation.	2++
Prielipp RC, Coursin DB. 1995; 3(10)	Sedative and neuromuscular blocking drug use in critically ill patients with head injuries.	2+
Vernon DD, Wooward GA, Skjonsberg AK. 1992(11)	Management of the patient with head injury during transport.	2+
Kornfeld DS, Zimberg S, Malm. 1965(12)	Psychiatric complication of open-heart surgery.	2+
Kanto J, Klotz U. 1982 (13)	Intravenous Benzodiazepines as anaesthetic agents: Pharmacokinetics and clinical consequences.	2+
Ramsay MA, Savege TM. Simpson BR, et al. 1974(14)	Controlled sedation with alphaxalone-alphadolone.	2+
Sigl C, Chamoun CN. 1994(15)	An introduction to bispctral analysis for the EEG.	2+
Malacrida R, Fritz ME, Suter PM, et al. 1991 (16)	Pharmacokinetics of Midazolam administered by continuous intravenous infusion to intensive care patients.	2+
Swart EL, van Schijndel RJ, van Loenen AC, et al. 1999 (17)	Continuous infusion of Lorazepam versus Midazolam in patients in the intensive care unit: sedation with Lorazepam is easier to manage and is more cost-effective.	1-
McCollam JS, O'Neil MG, Norcross ED, et al. 1999(18)	Continuous infusions of Lorazepam, Midazolam, and Propofol for sedation of critically ill surgery trauma patient: A prospective, randomized comparison.	1-
Ostermann ME, Keenan SP, Seiferling RA, et al. 2000; 283 (19)	Sedation in the intensive care unit.	2+

Series (ref. No.)	Article title	Evidence level
Shafer A, White PF, Schuttler J, et al. 1983(20)	Use of a Fentanyl infusion in the intensive care unit: Tolerance to its anesthetic effects.	2+
de Nadal M, Munar F, Poca MA, et al. 2000; 92 (21)	Cerebral hemodynamic effects of Morphine and Fentanyl in patients with severe head injury: absence of correlation to cerebral autoregulation.	2+
Clifton GL, Miller ER, Choi SC, et al. 2001 Feb 22; 344(22)	Lack of effect of induction of hypothermia after acute brain injury.	1+
Clifton GL. 2004(23)	Keeping cool still hot? An update on hypothermia in brain injury.	1-
Edwards P, Arango M, Balica L. 2005(24)	Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury-outcomes at 6 months.	1++
Cushing H. 1905(25)	The establishment of cerebral hernia as a decompressive measure for inaccessible brain tumor; with the description of intramuscular methods of marking the bone defect in temporal and occipital regions.	2+
Cushing H. 1908(26)	Subtemporal decompressive operations for the intracranial complications associated with bursting fractures of the skull.	2+
Brain Trauma Foundation. American Association of Neurological Surgeons, Joint Section on Neurotrauma and critical care 1996(27)	Annonymous: Guidelines for the management of severe head injury.	1-
Albanése J, Leone M, Alliez JR, et al. 2003(28)	Decompressive craniectomy for severe traumatic brain injury: evaluation of the effects at one year.	1-

Series (ref. No.)	Article title	Evidence level
Enblad P, Nilsson P, Chambers I, et al. 2004 (29)	R3-Survey of traumatic brain injury management in European Brain IT centres year 2001.	1-
Schaller B, Graf R, Sanada Y. 2003(30)	Hemodynamic and metabolic effects of decompressive hemicraniectomy in normal brain: An experimental PET-study in cats.	2+
Ruf B, Heckman M, Schroth I, et al. 2003(31)	Early decompressive craniectomy and duroplasty for refractory intracranial hypertension in children: results of a pilot study.	2+
Reithmeier T, Speder B, Pakos P, et al. 2005(32)	Delayed bilateral craniectomy for treatment of traumatic brain swelling in children: case report and review of the literature.	3
Polin RS, Ayad M, Jane J A. 2003(33)	Decompressive craniectomy in pediatric patients.	1-
Hutchinson PJ,Corteen E, Czosnyka M,. 2006 (34)	Decompressive craniectomy in traumatic brain injury: the randomized multicenter RESCUEicp study (www.RESCUEicp.com).	1-
Jiang JY, Xu W, Li WP, et al. 2005(35)	Efficacy of standard trauma craniectomy for refractory intracranial hypertension with severe traumatic brain injury: a multicenter, prospective, randomized controlled study.	1-

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Members of the ICP Hypertension Guideline Team

Dr. Cheng-Kuei Chang (*Mackay Memorial Hospital Tanshui Branch*)
Dr. Hsing-Han Tsai (*Taipei Medical University-Wan Fang Hospital*)
Dr. Cheng-Mao Cheng (*Tri-Service General Hospital*)
Dr. Tien-Jen Lin (*Taipei Medical University-Wan Fang Hospital*)
Dr. Ming-Yang Li (*National Cheng Kung University Hospital*)
Dr. Chuan-Fa Su (*Buddhist Tzu Chi General Hospital*)
Dr. Chi-Wen Chou (*Changhua Christian Hospital*)

Seizure Prophylaxis

10

About 2-10 % of traumatic head injury patients suffer from generalized seizures, which enhance secondary injuries of the brain, such as intracranial hypertension, increased cerebral metabolic rate of oxygen, increased cerebral blood flow, increased cerebral blood volume, decreased mean arterial pressure causing decreased CPP and impaired brain oxygenation.

Recommendations

Written by Kun-Hsing Li
Editor: Seizure Prophylaxis Guideline Team

B 1. Prophylactic use of Phenytoin, Carbamazepine, Phenobarbital or Valproate is not recommended for preventing late post-traumatic seizures.

C 2. Some studies show that Phenytoin and Carbamazepine can prevent early seizures effectively, and may be used on patients with high risks. However, the present evidence does not support that prevention of early seizures improves the outcome of head injury patients.

C 3. High risks include: GCS Score $<$ 10, cortical contusion, depressed skull fracture, subdural hematoma, epidural hematoma, intracerebral hemorrhage, penetrating head injury, and epileptic seizures within 24 hours after injury.

Introduction

About 2-10 % of traumatic head injury patients suffer from generalized seizures. There are two kinds of post-traumatic seizures (PTS): early and late. Early seizures occur within 7 days after injury, and late seizures, later than 7 days thereafter. Seizures enhance secondary injuries of the brain, such as intracranial hypertension, increased cerebral metabolic rate of oxygen ($CMRO_2$), increased cerebral blood flow (CBF), increased cerebral blood volume, decreased mean arterial pressure causing decreased

CPP and impaired brain oxygenation. In addition, seizures also lead to complications such as further brain injury, aspiration pneumonia and nosocomial infection and worsen overall outcome.

American neurosurgeons used to prescribe prophylactic anti-epileptic drugs in 1970s. However, there are some disadvantages in such routine medical orders, which include: side-effects related to the central nervous system and gastrointestinal tract, allergic reactions ranging from mild skin rashes to the Stevens-Johnson syndrome. It is therefore necessary to investigate more deeply the problem of anti-epileptic medication for severe head injury patients.

Literature Review

- Young et al. made a Randomized Controlled Trial (RCT) study whether Phenytoin can prevent early and late seizures. A total of 244 head injury patients were divided at random into two groups: one given Phenytoin, and the other a placebo, and they were followed for two years. A dose of 11 mg/kg was initially administered intravenously, and then intramuscularly or orally, keeping the plasma concentration at 40-80 umol/L (10-20 μg/mL), monitored by daily blood sampling. For early and late post-traumatic epilepsy, there was no significant difference in the incidence rate between both groups. The incidence rate of early post-traumatic epilepsy rate in the phenytoin group was 3.7 % , and for late epilepsy, 12.4 % , while the rates for the placebo group were 3.7 % and 10.8 % , respectively. The validity of this research may be questioned because of the low rate of late post-traumatic epilepsy. One thing is worth noticing; however: no single patient with plasma Phenytoin concentra-

tion higher than 48 umol/L suffered from epilepsy in this study.

- In 1990, Temkin et al. conducted the largest, prospective, randomized, double-blind placebo-controlled trial, in which 404 patients were given at random Phenytoin 20 mg/kg via intravenous injection, followed by regular intravenous injection, or oral or nasogastric tube feeding to maintain therapeutic concentration of Phenytoin at 40-80 umol/L (total) or 3-6 umol/L (free form) according to the results of monitoring by means of blood sampling, which was performed three times a week in ICU and once a week in the general ward, and followed up in the 1st, 3rd, 6th, 9th, and 12th months within 24 months. The dose given intravenously or orally ranged between 200 and 1200 mg/d, and the maximal dose given via the nasogastric tube was 2600 mg/d. The incidence rate of early post-traumatic epilepsy was considerably lower in the phenytoin group than in the control group: 3.6 % (95 % CI: 2.3-4.9) vs 14.2 % (95 % CI:0.12-0.62). The number needed to treat (NNT) for prevention of one attack of early post-traumatic epilepsy was 10 (95 % CI: 8-18). However, there was no significant difference between both groups with regard to late post-traumatic epilepsy prevention.

  The rate of medication termination due to skin rash in the Phenytoin group (8.2 %) was significantly higher than that in the control group (2 %), with $p < .01$. The number needed to harm (NNH) was 17. On the average, 11 epileptic attacks were prevented for every 1,000 patients who received Phenytoin, but 62 patients had to stop medication due to skin rash. The side effect rates in the two groups were similar: 9 % for the treated group, and 6 % for the control group, with $p = .52$. The rate of skin rash occurring within the first week of therapy was 0.6 % for the treated group and 0.1 % for the control group, with $p = 1.0$.

  Temkin et al. concluded that preventive therapy with 7-day use of Phenytoin should be based on done with clinical judgment and overall

neurological examination.

- In 1999, Temkin et al. conducted a research comparing Valproic Acid and Phenytoin in early and late post-traumatic epilepsy prevention. The 379 head injury patients included those with immediate epileptic attacks, those with depressed skull fracture, those with penetrating head wounds, and those with cortical contusion, subdural hematoma, epidural hematoma or intracerebral bleeding. Patients were divided into three groups: (1) Phenytoin for 7 days, (2) Valproic Acid for 30 days, and (3) Valproic Acid for 180 days. The incidence rate of early post-traumatic epilepsy was quite low, without a significant difference between the Phenytoin and pooled Valproic Acid groups (1.5 % : 4.5 % , p = .14, RR = 2.9, 95 % CI: 0.7-13.3).

  Neither was there a significant difference in the incidence of late post-traumatic epilepsy. However, the death rate in the Valproic Acid group appeared to be higher than in the Phenytoin group (13.4 % : 7.2 % , p =.07, RR = 2.0, 95 % CI: 0.9-4.1). Therefore, Valproic Acid is not recommended to be used routinely for prevention of post-traumatic epilepsy.

- The Cochrane Collaboration Group analyzed 10 appropriate RCTs in their meta-analysis, and divided 2,036 patients at random into anti-epileptic drug and placebo groups with regard to post-traumatic epilepsy prevention. Anti-epileptic drugs lowered the early post-traumatic epilepsy rate, but did not lower the incidence rate of late post-traumatic epilepsy or the death rate. Neither the death rate nor neurological disability was reduced by preventive use of Phenytoin or Carbamazepine. Moreover, Carbamazepine appeared to increase both. At present, the results of meta-analysis cannot exclude the possibility that the clinical use of anticonvulsants increases the incidence of skin rash. Preventive use of anti-epileptic drugs is not recommended at present for late post-traum-

atic epilepsy. For prevention of early post-traumatic epilepsy, Phenytoin is currently acceptable. However, there is no evidence that anti-epileptic drugs can reduce the death rate or the incidence of neurological deficits.

- Reference Table: comparison of the anti-epileptic drug group and control group（Data source: Schierhout et al. Anti-epileptic drugs for preventing seizures following acute traumatic brain injury (Cochrane Review), 2000）。

Death	Death and Neurological Disability Rate	Post-traumatic Seizure	Side-effects
Treated Group and Control Group 95/540 78/514 (17.6%)(15.2%) RR = 1.15 (0.89～1.51)	Treated Group and Control Group **Phenytoin** 67/208 66/196 (32.2%)(33.7%) RR = 0.96 (0.72～1.39) **Carbamazepine** 44/75 30/76 (58.7%)(39.5%) RR = 1.49 (1.06～2.08)	Treated Group and Control Group 22/456 65/434 (4.8%) (15%) RR = 0.34 (0.21～0.54) NNT = 10 **Late（> 7 days）** 65/499 49/482 (13%) (10.2%) RR = 1.28 (0.9～1.81)	Treated Group and Control Group **Skin Rash** 30/292 18/276 (10.3%)(6.5%) RR = 1.57 (0.57～39.88)

Conclusions

Based on literature review, prophylactic medication is not recommended for late post-traumatic epilepsy. Though preventive use of anti-epileptic drugs can reduce the incidence of early post-traumatic epilepsy, currently available data do not support that antiepileptic drugs reduce overall mortality and neurological disability rates. They lower neither the inci-

dence of late post-traumatic epilepsy nor death rate. Phenytoin is at present one of the drugs acceptable for prevention of early post-traumatic epilepsy. Some studies show that Phenytoin and Carbamazepine can effectively prevent early epilepsy, and can be used for high-risk patients, including those with GCS Score < 10, cerebral cortical contusion, depressed skull fracture, subdural hematoma, epidural hematoma, intracerebral hemorrhage, penetrating head wounds, and epileptic seizures occurring within 24 hours after injury.

Evidentiary Table

Series (ref. No.)	Article title	Evidence level
Brain Injury Foundation, AANS 1996(1)	Guidelines for the management of severe head injury.	1+
Robertson, et al. 1995(2)	Cerebral metabolic management. New Horizons.	1-
Lang, et al. 1995(3)	Intracranial pressure and cerebral perfusion pressurein severe head injury.	2+
Rapport, et al. 1973 (4)	A survey of attitudes toward the pharmacologic prophylaxis of posttraumatic epilepsy.	2+
Young, et al. 1983(5)	Failure of prophylactically administered Phenytoin to prevent early posttraumatic seizures.	1-
Temkin, et al. 1990 (6)	A randomized, double-blind study of phenytoin for the prevention of posttraumatic seizures.	1+
McKindley, et al. 1997(7)	Effect of acute phase response on Phenytoin metabolism in neurotrauma patients.	2-
Haltiner, et al. 1999 (8)	Side effects and mortality associated with the use of Phenytoin for early posttraumatic seizure prophylaxis.	2++

Series (ref. No.)	Article title	Evidence level
Temkin, et al. 1999 (9)	Valprate therapy for prevention of posttraumatic seizures: A randomized trial.	1+
Schierhout, et al. 2000(10)	Anti-epileptic drugs for preventing seizures following acute traumatic brain injury.	1+
Brain Injury Special Interest Group 1998 (11)	Brain Injury Special Interest Group.	1+

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Members of the Seizure Prophylaxis Guideline Team

Dr. Ming-Ta Tsai	(*Shin-Kong Wu Ho-Su Memorial Hospital*)
Dr. Wen-Yu Chung	(*Taipei Veterans General Hospital*)
Dr. Yo-Chih Wang	(*Chung Shan Hospital*)
Dr. Yu-Hone Hsu	(*Taipei Medical University-Wan Fang Hospital*)
Dr. Tzu-Gan Li	(*Chang Gung Memorial Hospital, Linkou*)
Dr. Shu-Hsiung Hsu	(*Kaohsiung Veterans General Hospital*)
Dr. Kun-Hsing Li	(*Chung-Ho Memorial Hospital, Kaohsiung Medical University*)

Second Tier Therapy

11

When first tier therapy fails and the clinical condition is not improved, second tier may be considered to rescue remaining brain functions. Due to lack of large-scale double-blind studies, currently all second tier therapies remain at the level of options.

Recommendations

D 1. Hypertonic saline

With effects comparable with those of traditional agents used for decreasing IICP, rapidly lowers ICP and effectively increases CPP. Present evidence recommends its single use.

D 2. Barbiturate coma

It slows down brain metabolism and reduces brain activities, and thus lowers ICP. The timing for this therapy is of crucial importance, for it works effectively only before the brain stem function is severely impaired.

C 3. Hyperventilation

(1) Hyperventilation can reduce $PaCO_2$ in blood, so that autoregulation will reduce cerebral blood flow and thus lower ICP.

(2) It is recommended that $PaCO_2$ be kept $\leq$ 30 mm Hg, and that this mode of therapy be used only in emergency for a short time.

C 4. Hypothermia

There is no sufficient clinical evidence that proves its effectiveness.

A 5. Steroids

Steroids prevent intracranial hypertension by reducing cerebral edema caused by brain tumor and brain abscess. However, the latest researches favor the opinion that steroids cannot reduce cerebral edema caused by trauma, and can increase the infection rate. Therefore routine use of steroids is not recommended.

Introduction

The goal of severe head injury treatment is to control ICP, to increase cerebral perfusion, and to slow down brain metabolism in order to prevent ischemia. Second tier therapy, through uses of hypertonic saline, Barbiturate coma, hyperventilation, hypothermia and steroids, aims at rescuing the remaining functions of the brain. This is a mode of therapy that has relatively great side effects and no established therapeutic effects.[1~3] In this chapter, we will discuss the problem from the view point of neurointensive care principles.

Literature Review

Hypertonic saline

As sodium ion is highly selective and hypertonic, hypertonic saline can, with an intact BBB, lower ICP by drawing water away from the brain via a great difference in concentration. It can also create a dehydration-like state in red blood cells and blood vessels, and thus improve blood circulation. In 1999, Qureshi used hypertonic saline in different concentrations (3 % 5.3 ml/kg and 23 % 0.7 ml/kg) and mannitol (1 mg/kg) on patients with acute cerebral hemorrhage, and found that the therapy was quite effective in controlling ICP without significant side effects.[4] In 2002, Schwarz et al. used 10 % 75 ml hypertonic saline 22 times (on 8 acute stroke patients), and found that ICP was reduced by 9.9 mmHg on the average, and that CPP increased significantly. The maximal effects were reached in 35 minutes without serious side effects.[5]

Barbiturate coma

With a high dose, Barbiturate coma diminishes brain metabolism, and thus reduces intracranial pressure, but it has to be done in time. [7] In general, it is recommended that Barbiturate coma be started immediately when ICP > 30 mmHg, BPP < 70 mmHg, or BPP > 70 mmHg and ICP still > 40mm. Phenobarbital is the drug used for this therapy, with the initial dose of 10mg/kg via intravenous injection within 30 min and followed by 5mg/kg/hr for 3 hours until EEG electrocerebral silence is reached. When ICP < 20 mmHg for 24-48 hours, Phenobarbital should be gradually tapered off. Possible side effects include hypotension, pneumonia, and septicemia, and this kind of therapy is rarely used in Taiwan at present.

Hyperventilation

Lowered blood $PaCO_2$ leads to constriction of brain vessels and thus lowers ICP. Blood $PaCO_2$ lowered to 25-30 mmHg causes ICP to drop in seconds, but this effect does not last long. Therefore, the current opinion is that $PaCO_2$ at 30-35 mmHg will be adequate with mild hyperventilation. As for the timing, most scholars tend to think it appropriate to use this mode of therapy for acute intracranial hypertension, [2, 8] but take a reserved attitude toward the use of prophylactic hyperventilation.

Hypothermia

Research reports claim that when the patient's body temperature is lowered to 33-34℃ in 24-96 hours and raised back to 37℃ at 0.3℃ every eight hours, brain metabolism is slowed down, ICP is lowered, and blood lactic acid is reduced, but CPP is kept intact, bringing about considerable clinical improvement. [9, 10] In the 3rd stage clinical experiment in 2001, however, this kind of therapy was declared a failure. [11]

Steroids

It is reported in the latest researches that steroids do not actually lower ICP and improve outcome. Therefore, routine use of steroids is not recommended. [12]

There are insufficient data to support the efficacy of hyperbaric oxygen (HBO) and of the use of metrizamide.

Conclusions

Second Tier Therapy

When first tier therapy fails and the clinical condition is not improved, second tier may be considered to rescue remaining brain functions. Due to lack of large-scale double-blind studies, currently all second tier therapies remain at the level of options.

Evidentiary Table

Series (ref. No.)	Article title	Evidence level
Chesnut RM. 1995(1)	Medical management of severe head injury: Present and future.	2+
Marion DW, Firlik A, McLaughlin MR. 1995(2)	Hyperventilation therapy for severe traumatic brain injury.	2+
Marion DW, Spiegel TP. 2000(3)	Changes in the management of severe traumatic brain injury: 1991-1997.	2-

Series (ref. No.)	Article title	Evidence level
Qureshi AI, Wilsonn DA, Traystman RJ. 1999(4)	Treatment of elevated intracranial pressure in experimental intracerebral hemorrhage: comparison between Mannitol and hypertonic saline.	2+
Schwarz S, Georgiadis D, Aschwab S. 2002(5)	Effect of hypertonic (10 %) saline in patients with raised intracrainial pressure after stroke.	2-
Khanna S, Davis D, Peterson B, et al. 2000 (6)	Use of hypertonic saline in the treatment of severe refractory posttraumatic intracranial hypertension in pediatric traumatic brain injury.	2-
Lee MW, Deppe SA, Sipperly ME, et al. 1994(7)	The efficacy of barbiturate coma in the management of uncontrolled intracranial hypertension following neurosurgical trauma.	2-
Coles JP, Minhas PS, Fryer TD,et al. 2002 (8)	Effect of hyperventilation on cerebral blood flow in traumatic head injury: clinical relevance and monitoring correlates.	2-
Jiang J, Zhu C, Lu Y, et al. 1998(9)	The effects of mild hypothermia on patients with severe traumatic brain injury.	2-
Gal R, Cundrle I, Zimova I, et al. 2002 (10)	Mild hypothermia therapy for patients with severe brain injury.	2-
Clifton GL, Miller ER, Choi SC, et al. 2001(11)	Lack of effect of induction of hypothermia after acute brain injury.	2++
Edwards P, Arango M, Balica L, et al. 2005(12)	Final results of MRC CRASH, a randomized placebo-controlled trial of intravenous corticosteroid in adults with head injury-outcomes at 6 months.	2+

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Members of the Second Tier Therapy Guideline Group

Hong-Chang Chang	(*Mackay Memorial Hospital Taitung Branch*)
Ta-Ming Lai	(*National Taiwan University Hospital*)
Tzu-Yung Chen	(*Chang Gung Memorial Hospital, Linkou*)
Hsu-Lin Huang	(*Chung-Ho Memorial Hospital, Kaohsiung Medical University*)
Kuo-Fang Yu	(*Chimei Hospital, Liouying*)
Cheng-Ti Chiu	(*Taipei Veterans General Hospital*)
Yi-Long Chen	(*Taipei City Hospital Chung-Hsing Branch*)

Abbreviation Table

AANS	American Association of Neurological Surgeons
ARDS	Adult Respiratory Distress Syndrome
$AVdO_2$	Arteriovenous Oxygen Difference
BBB	Blood Brain Barrier
CBF	Cerebral Blood Flow
$CMRO_2$	Cerebral Metabolic Rate of Oxygen
CO	Cardiac Output
CPP	Cerebral Perfusion Pressure
CVP	Central Venous Pressure
CSF	Cerebrospinal Fluid
CT	Computed Tomography
EBIC	European Brain Injury Consortium
EEG	Electroencephalogram
FFP	Fresh Frozen Plasma
GCS	Glasgow Coma Scale
Hb	Hemoglobin
HBO	Hyperbaric Oxygen
Hct	Hematocrit

ICH	Intracerebral Hemorrhage
ICP	Iintracranial Pressure
IGF-1	Insulin-like Growth Factor-1
IICP	Increased Intracranial Pressure
IV infusion	Intravenous infusion
MAP	Mean Arterial Pressure
NNH	Number Needed to Harm
PaO_2	Partial Pressure of Oxygen in Arterial Blood
PI	Pulsatility Index
PTS	Post-Traumatic Seizures
RCT	Randomized Controlled Trial
SaO_2	Arterial Oxygen Saturation
SBI	Severe Brain Injury
SBP	Systolic Blood Pressure
$SjvO_2$	Jugular Venous Oxygen Saturation
SpO_2	Saturation of Pulse Oxygen
STBI	Severe Traumatic Brain Injury
SvO_2	Mixed Venous Oxygen Saturation
TCD	Transcranial Doppler

Guideline of STBI Development Team

Chiu, Wen-Ta 	**Present Position** ● Vice president of Taipei Medical University (TMU) ● Superintendent of Taipei Medical University-Wan Fang Hospital **Background** ● Chairman of Taiwan Neurosurgical Society ● Committee member & secretary of Neurotraumatology Committee, World Federation of Neurosurgical Societies **Education** ● PhD, University of Pittsburgh ● D.M.Sc (Neuroscience) Nihon University School of Medicine, Tokyo, Japan
Huang, Sheng-Chien 	**Present Position** ● Attending Surgeon, National Taiwan University (NTU) Hospital **Background** ● Surgical Resident, NTU Hospital **Education** ● Bachelor's Degree in Physical Therapy, NTU College of Medicine ● Post-graduate program, NTU College of Medicine
Hung, Ching Chang 	**Present Position** ● Honorary Professor of NTU Hospital, Department of Surgery **Background** ● Chairman of Asian Australian Neurological Surgeons ● Chairman of Taiwan Neurological Society **Education** ● MD, National Taiwan University (NTU) College of Medicine

Yu, Kuo-Fan

Present Position
- Attending Neurosurgeon, Chi-Mei Hospital, Liuying

Background
- Attending Neurosurgeon, Kuang Tien General Hospital, Shalu
- Neurosurgical Resident, Shin Kong Wu Ho-Su (WHS) Memorial Hospital

Education
- MD, National Cheng-Kung University

Wang, Yu-Chih

Present Position
- Attending Neurosurgeon, Chung Shan Medical University Hospital
- Professor of Neurosurgery, Chung Shan Medical University Hospital

Background
- Chief of Neurosurgical Dept., Taichung Veterans General Hospital (VGH)
- Chief of Neurosurgical Dept., Tri-Service General Hospital

Education
- MD, National Defense Medical University

Wang, Kuo-Wei

Present Position
- Chief of NICU, Surgical Dept., E-Da Hospital

Background
- Attending Neurosurgeon, Surgical Dept., Feng Shan Hospital, Kaohsiung
- Attending Neurosurgeon, Kaohsiung Chang Gung Memorial Hospital

Education
- MD, National Yang Ming University (NYMU)

Li, Kun-Hsing

Present Position
- Attending Neurosurgeon, Chung-Ho Memorial Hospital, KMU
- Surgery Associate Professor, Kaohsiung Medical University

Background
- Chief Surgical Resident, Chung-Ho Memorial Hospital, KMU
- Attending Neurosurgeon, Chung-Ho Memorial Hospital, KMU

Education
- MD, Kaohsiung Medical University (KMU)

Lee, Ming-Yang

Present Position
- Assistant Professor, Department of Neurosurgery, NCKU Hospital

Background
- Attending Neurosurgeon, NCKU Hospital

Education
- PhD Candidate, Biomedical Engineering, NCKU
- Research Fellow, University of Massachusetts Medical School

Chou, Chi-Wen

Present Position
- Chief of Neurosurgical Dept., Changhua Christian Hospital

Background
- Committee, Taiwan Neurospinal Society
- Associate Chief Secretary, Taiwan Neurosurgical Society

Education
- Master Degree, Graduate Institute of Medicine, China Medical University
- Training Program in Neurosurgery, UCLA, USA

Lin, Tzu-Gan

Present Position
- Attending Neurosurgeon, Chang Gung Memorial Hospital
- Committee, Taiwan Stroke Society

Background
- Chief Secretary, Taiwan Stroke Society

Education
- MD, China Medical University

Lin, Jia-Wei

Present Position
- Chief of Neurosurgical Dept., Teipei Medical University Municipal Wan-Fang Hospital
- Chief of Cyberknife Center, TMU Wan-Fang Hospital

Background
- Chief Secretary, Taiwan Surgical Association
- Attending Neurosurgeon, TMU Wan-Fang Hospital

Education
- PhD, Graduate Institute of Clinical Medicine, TMU
- Master Degree, Graduate Institute of Clinical Medicine, TMU

Lin, Chien-Min

Present Position
- Attending Neurosurgeon, Teipei Medical University Municipal Wan-Fang Hospital

Background
- Chief Neurosurgical Resident, Taipei Medical University Hospital

Education
- Master Degree, Graduate Institute of Injury Prevention and Control, TMU

Lin, Tien-Jen

Present Position
- Attending Neurosurgeon, Teipei Medical University Municipal Wan-Fang Hospital

Background
- Neurosurgical Resident, Mackay Memorial Hospital (MMH)

Education
- Master Degree, Graduate Institute of Injury Prevention and Control, TMU
- MD, China Medical University

Lin, Jui-Feng

Present Position
- Attending Neurosurgeon, Mackay Memorial Hospital, Taipei and Tamshui
- Member of Taiwan Neurosurgical Society

Background
- Chief Neurosurgical Resident, China Medical University Hospital
- Attending Neurosurgeon, Tzu Chi General Hospital, Hualien

Education
- MD, China Medical University
- Master program of Critical Care Medicine, National Yang Ming University

Chiu, Cheng-Ti

Present Position
- Attending Neurosurgeon, Taipei Veterans General Hospital

Background
- Chief Neurosurgical Resident, Taipei Veterans General Hospital

Education
- MD, China Medical University

Hong, Kuo-Sheng

Present Position
- Attending Neurosurgeon, Teipei Medical University Municipal Wan-Fang Hospital

Background
- Attending Neurosurgeon, Chang Gung Memorial Hospital, Kaohsiung
- Associate Professor of Neurosurgery, Taipei Medical University (TMU)

Education
- PhD, Graduate Institute of Medicine, Kaohsiung Medical University
- Research Fellow in Neurosurgery, Stanford University, USA

Chi, Huan-Ting

Present Position
- Attending Neurosurgeon, Emergency Medicine Dept., Taichung VGH
- Member of Council of Medical Policy, Central Taiwan Joint Services Center

Background
- Chief Secretary, Taiwan Society of Emergency Medicine

Education
- Master Degree, Graduate Institute of Injury Prevention and Control, TMU

Chang, Cheng-Kuei

Present Position
- Chief of SICU, Mackay Memorial Hospital, Tamshui (MMH)

Background
- Attending Neurosurgeon, Mackay Memorial Hospital (MMH)

Education
- PhD, Physiology, School of Medicine, National Yang Ming University
- Master Degree, Graduate Institute of Clinical Medicine, TMU

Chang, Hong Chang

Present Position
- Chief of Neurosurgical Dept., Mackay Memorial Hospital Taitung Branch
- Chief of Surgery Dept., Mackay Memorial Hospital Taitung Branch

Background
- Attending Neurosurgeon, Emergency & Intensive Care Unit, MMH
- Surgical Resident, Mackay Memorial Hospital (MMH)

Education
- MD, Chung Shan Medical University

Chang, Kun-Chuan

Present Position
- Committee, Formosa Association for Surgery of Trauma
- Chief of 2 nd SICU, Cathay General Hospital

Background
- Chief of Emergency Medicine Dept., Cathay General Hospital
- Attending Neurosurgeon, Cathay General Hospital

Education
- MD, National Defense Medical University

Hsu, Yu-Hone

Present Position
- Attending Neurosurgeon, Teipei Medical University Municipal Wan-Fang Hospital

Background
- Neurosurgical Resident, Taipei Veterans General Hospital

Education
- MD, Taipei Medical University

Hsu, Shu-Hsiung

Present Position
- Chief of Neurosurgical Dept., Kaohsiung Veterans General Hospital

Background
- Attending Neurosurgeon, Kaohsiung Veterans General Hospital
- Attending Neurosurgeon, Kaohsiung Armed Forces General Hospital

Education
- MD, National Defense Medical University
- Research Fellow, Division of Neurosurgery, University of Toronto, Canada

Chen, Tzu-Yung

Present Position
- Chief of Neurosurgical Dept., Chang Gung Memorial Hospital, Keelung
- Committee, Taiwan Neurosurgical Society

Background
- Vice-Superintendent, Buddhist Tzu Chi General Hospital, Taichung
- Chief of NICU, Chang Gung Memorial Hospital, Linko
- Vice-Professor Qualified by Ministry of Education

Education
- MD, China Medical University
- Training Program in Neurosurgery, Chicago University, USA

Chen-Yi Long

Present Position
- Chief of Neurosurgical Dept., Taipei City Hospital, Zongxing Branch

Background
- Attending Neurosurgeon, Taipei City Hospital, Zhongxing Branch

Education
- MD, National Taiwan University College of Medicine

Chen, Wan-Lin

Present Position
- Neurosurgeon, Lotung Poh-Ai Hostital

Background
- Neurosurgical Resident, Taipei City Hospital Renai Branch

Education
- Master Degree, Graduate Institute of Injury Prevention and Control, TMU

Huang, Hsu-Lin

Present Position
- Chief of NICU, Chung-Ho Memorial Hospital, KMU
- Professor of Surgery, KMU

Background
- Attending Neurosurgeon, Chung-Ho Memorial Hospital, KMU
- Qualified Neurosurgeon

Education
- PhD, Graduate Institute of Clinical Medicine, KMU
- MD, Kaohsiung Medical University (KMU)

Yang, Ta-Yu

Present Position
- Vice-Superintendent, Education Division, Chang Bing Show Chwan Memorial Hospital

Background
- Neurosurgeon

Education
- MBA, National Yunlin University of Science and Technology
- Research Fellow, Tokyo University, Japan

Liao, Kuo-Hsing

Present Position
- Attending Neurosurgeon, Teipei Medical University Municipal Wan-Fang Hospital

Background
- Chief Neurosurgical Resident, Taipei Veterans General Hospital (VGH)
- Neurosurgical Resident, Taipei Veterans General Hospital (VGH)

Education
- MD, National Yang Ming University (NYMU)

Chiang, Yung-Hsiao

Present Position
- Chief of Neurosurgical Dept., Taipei Medical University Hospital
- Vice-Professor of Neurosurgery,Taipei Medical University

Background
- Chief of NICU for Sever Patients, Tri-Service General Hospital
- Chief of NICU, Tri-Service General Hospital

Education
- PhD in Medical Neurobiology, Indiana University, USA
- Master Degree in Health Administration, Tulane University, USA

Chiang, Ming-Fu

Present Position
- Attending Neurosurgeon, Mackay Memorial Hospital

Background
- Member, American Association of Neurological Surgeons
- Member, German Association of Neurosurgery and Neurology

Education
- PhD, Free University of Berlin, Germany
- MD, Kaohsiung Medical University

Tsai, Shin-Han

Present Position
- Professor and Director, Graduate Institute of Injury Prevention and Control,TMU
- Executive Medical Director, National Aeromedical Counseling Center, MOH

Background
- Professor and Chairman, Department of Medical Affair, Department of Emergency and Critical Care Medicine, Taipei Medical University WanFang Hospital
- Chief of Neurosurgical Dept., TMU Hospital

Education
- PhD, College of Medicine, University of Cincinnati
- MD,College of Medicine, National Defense Medical University

Tsai Ming-Ta

Present Position
- Chief of Teaching and Research Dept., Shin Kong WHS Memorial Hospital
- Attending Neurosurgeon, Shin Kong WHS Memorial Hospital

Background
- Attending Neurosurgeon, Chang Gung Memorial Hospital

Education
- PhD Candidate, Clinical Medicine, NTU College of Medicine
- Master Degree, Clinical Medicine, NTU College of Medicine

Cheng, Cheng-Maw

Present Position
- Attending Neurosurgeon, Tri-Service General Hospital

Background
- Research Fellow and Lecturer in Skull Base Surgery and Neuroradiology, Oregon Health & Science University, USA

Education
- MD, National Defense Medical University

Hsiao, Sheng Huang

Present Position
- Chief of Neurosurgical Dept., Taipei City Hospital

Background
- Chief of Neurosurgical Dept., Taipei City Hospital Renai Branch
- Member of Taiwan Neurosurgical Society

Education
- PhD Candidate, Physiology, National Yang Ming University (NYMU)
- Research Fellow, UCLA Medical Center, USA

Lai, Ta-Ming

Present Position
- Attending Neurosurgeon, NTU Hospital

Background
- Research Fellow, University of Texas Southwestern Medical Center at Dallas, USA

Education
- MD, Kaohsiung Medical University (KMU)

Chung, Wen-Yu

Present Position
- Chief of NICU, Taipei Veterans General Hospital (VGH)

Background
- Attending Neurosurgeon, Taipei Veterans General Hospital (VGH)

Education
- MD, National Taiwan University College of Medicine
- Training Program, Tokyo University, Japan

Su, Chuan-Fa

Present Position
- Chief of Neurosurgical Dept., Buddhist Tzu Chi General Hospital, Hualien
- Vice-Professor of Neurosurgery, Tzu Chi University College of Medicine

Background
- Attending Neurosurgeon, Tri-Service General Hospital

Education
- MD, National Defense Medical University
- Research Fellow in Neurosurgery, University of Missouri, Columbia, USA

Kung, Sui-Sum

Present Position
- Attending Neurosurgeon, ICU, Yuan's General Hospital

Background
- Research Fellow, Klinikum Hannover Nordstadt and University Hospital of Cologne, Germany
- Chief Resident, Neurosurgical Dept., KMU Hospital

Education
- MD, Kaohsiung Medical University (KMU)

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