計 畫 編 號：NHRI-EX95-9106PN

國家衛生研究院整合性醫藥衛生科技研究計畫

嚴重頭部外傷處理準則對病患存活情形及健康相關生活品質之影響

計畫名稱

95年度成果報告

執 行 機 構： 台北醫學大學

計 畫 主 持 人： 邱文達 教授

本年度執行期間 95 年 1 月 1 日 至 95 年 12 月 31 日

壹、95年度計畫研究成果摘要

計 畫 名 稱：嚴重頭部外傷處理準則對病患存活情形及健康相關生活品質之影響

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執 行 機 構：台北醫學大學

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關 鍵 字：嚴重頭部外傷病患、顱內壓監測、腦灌流壓照護管理、生活品質、嚴重頭部外傷處理準則

成 果 分 類：

- ☐ 癌症基礎與臨床研究(可複選，最多三項)
- ☐ 分子與基因醫學研究
- ☑ 臨床研究
- ☐ 生物技術與藥物研究
- ☐ 生物統計與生物資訊研究
- ☑ 醫療保健政策研究
- ☐ 環境衛生與職業醫學研究
- ☐ 醫學工程研究
- ☐ 老年醫學研究
- ☐ 精神醫學與藥物濫用研究
- ☐ 疫苗研究
- ☐ 幹細胞研究
- ☐ 奈米醫學研究
- ☑ 其他重要疾病或醫藥衛生問題研究

（1）中文摘要

一、　本年度研究重點及進度

九十五年度本研究計畫之執行方向可分成四個方向：

（一）上半年持續進行頭部外傷病例登錄，本計畫已完成建立國內最完備之頭部外傷登錄資料庫。(a)頭部外傷病患登錄共收集有效問卷 3,804 筆；(b)嚴重頭部外傷有效問卷共 297 筆。(c)頭部外傷後病患之生活品質追蹤有效問卷共 488 筆。研究結果：(1) 研究中發現，頭部外傷病患同時使用顱內監測器及腦灌流壓療法及使用鎮定劑，均有較高的存活率。(2)持續運用 WHOQOL-BREF 台灣版及針對頭部外傷後病人之腦部傷害病患生活品質問卷之評估，並以 GOS 及 GOSE 追蹤已收案病患評估其恢復狀態及癒後情形，結果證明 GOSE 的病患評估與腦部傷害病患的生活品質有較高相關性。

（二）透過多次的頭部外傷治療共識會議與研討會，持續進行國內神經外科及相關醫療人員頭部外傷處理準則之共識與教育訓練。邀請台灣地區神經科學領域北、中、南、東的專家學者，共同制訂台灣版嚴重頭部外傷處理準則 (Guidelines) 之共識。經過多次的專家會議以及外部書面審查，修正後結果如下：

（1）急診處置 Management in ER (ER: Emergency Room)：

建議：1.迅速評估 2.基本處置 3.神經學檢查 4.進一步評估－視

情況使用(a)鎮靜劑（Sedation）的使用(? ：當病人躁動，有氣管內插管。(b)抗癲癇藥物之投予(? ：已有癲癇發生或作預防時。(c)高滲透性利尿劑(? ：疑有顱內壓升高時。5.影像檢查一當生命徵象穩定時，方可進行下列檢查：(a)X 光。(b)腦部斷層檢查。(c)其他（核磁共振造影、血管攝影）一視特殊情況需要，如上述檢查無法証實時，方可行之。6.實驗室檢查：7.急診之最終診斷：(a)考慮所有可能之鑑別診斷。(b)評估嚴重度。8.最後處置:會診神經外科醫師。

（2）顱內壓監測 ICP monitor：

指引:1.下列情況下得使用顱內壓監測器：(a)嚴重頭部外傷電腦斷層檢查異常。(b)嚴重頭部外傷電腦斷層檢查正常，至少有下列二項條件：40 歲以上、肢體動作出現單側或雙側之去大腦強直或去皮質強直反射及收縮壓 90mmHg 以下。(c)輕度頭部外傷與中度頭部外傷可依病情需要個別考慮使用顱內壓監測。2.顱內壓治療閾值：建議成人頭部外傷之顱內壓治療閾值為 20-25mmHg，而小兒頭部外傷之顱內壓治療閾值則為 20mmHg。3.顱內壓監測器之選擇：最標準之顱內壓監測方法乃腦室與腦間質顱內壓監測。

（3）腦灌流壓與輸液之原則 **CPP and Fluid management**：

指引：**1.**宜維持大腦灌流壓，至少 **60-70mmHg**。**2.**大腦灌流壓，小於 **60mmHg** 可能有害。**3.**在沒有證明腦缺血的狀態下，刻意提昇血壓使大腦灌流壓大於 **70mmHg** 引起成人呼吸窘迫症候群（**ARDS**）的機會增高。建議：**1.Lund concept** 及 **EBIC**（**European brain injury consortium**）均認為 **CPP** 維持於 **60-70mmHg** 已足夠。**2.**在沒有證明腦缺血的狀態下，使用積極手段如昇壓劑或膠質液維持大腦灌流壓大於 **70mmHg** 出現成人呼吸窘迫症候群之機會較大腦灌流壓小於 **70mmHg** 之病患高 **5** 倍。

（4）鎮定劑之使用 **Sedation**：

建議：(a)針對昏迷指數 **3-8** 分，顱內壓不易控制或是躁動的病人，目前國內、外有些加護單位已經把鎮靜劑的使用列為治療項目之一。(b)建議昏迷指數 **3-8** 分的病人，須有氣管內插管，再行使用鎮定劑。

（5）營養 **Nutrition**：

指引：(a)在接受鎮靜劑治療之病患，需補足靜態能量消耗量之 **100%**；在未接受鎮靜劑治療之病患，應補足靜態能量消耗量之

140%。(b)經腸道或經靜脈給予之營養製劑配方：應於受傷後 7 天內給予含至少 15% 蛋白質之熱量來源，以維持氮平衡。建議：灌食時間：二十四至七十二小時以內一定要開始補充營養，並逐漸增加至最大所需熱量。

（6）顱內壓上升之處置 Management of intracranial hypertension：

指引：(a)不建議使用預防性過度換氣治療顱內壓升高。(b)不建議使用類固醇治療顱內壓升高。

（7）癲癇之預防治療 Seizure Prophylaxis：

標準程序：遲發性癲癇不建議預防性藥物投予。建議：有些研究顯示：Phenytoin 和 Carbamazepine 能有效預防早發性癲癇發作，可在某些高危險群病患中使用。但目前的證據並不支持預防早發性癲癇發作，可以改善頭部外傷病患的預後。

（8）二線療法 Second tier therapy:

建議：(a)高張性食鹽水可快速降低顱內壓，且其效果相當於傳統降腦壓藥物，進而有效提昇腦灌流壓，目前証據均建議單一使用。(b)巴比妥鹽昏迷可降低腦代謝率，減少腦部活動，而達到降低腦壓的目的。使用時機相當重要，在腦幹功能尚未受損嚴重之前使用，才能有實質的功效。(c)過度換氣：(1)

可因降低血中之二氧化碳濃度，經由腦血流自動控制機轉達到減少腦血流量，進而降低腦壓的目的。(2)建議 $PaCO_2$ 小於 30 mm Hg，只用在緊急神經症狀惡化時，而且時間要短。(d)低溫療法：目前臨床上仍無証據顯示有效。(e)類固醇：類固醇可降低腦瘤及腦膿瘍所引起之腦水腫，而降低顱內壓之昇高。但依照最新研究報告，認為類固醇並不能降低因外傷所引起之腦水腫，且有增加感染率之虞，臨床功效不佳，因此不建議例行使用。

研究結果：已完成建立台灣版嚴重頭部外傷及輕度頭部外傷治療共識。國內健康照護者更瞭解國際間與國內之差異，並加入本土性之研究結果，區隔本土與國際之治療差異，提供國內醫療照護人員、病患及一般名眾充分瞭解頭部外傷之治療目標。推動應用依循嚴重頭部外傷處理準則，分析結果發現嚴重頭部外傷病患處理準則介入前後，對社會大眾及節省社會成本的重大貢獻。

（三）根據計畫多年收集之頭部外傷病患資料、生活品質追蹤及神經外科醫師對腦灌流壓治療意見，進行資料處理與分析，依研究成果提出具成本效益且降低社會成本之建議。

（四）舉辦大型研討會，透過與會專家學者的討論，進行目前國內頭部外

傷治療共識之評比，期提升治療共識嚴謹度，最後公告國內制訂頭部外傷治療共識之研究成果於網路上，提供國內醫療照護人員最好的教育機會，促使國內臨床應用上有一共同醫療處置之依循。

二、 結果與討論

（一）已完成建立國內最完備之頭部外傷登錄資料庫。並可提供日後相關研究者之參考。頭部外傷病患有持續下降的趨勢，其中嚴重頭部外傷問卷分析的結果，發現嚴重頭部外傷病患在妥善地治療處理之下，生活品質比輕度的病患好（已刊登於 **Journal of Neurotrauma 2006(23), 1609-20**）。

（二）本研究證實，接受腦灌流壓療法之嚴重頭部外傷病患，確實能獲得較佳之存活率，同時也使得醫療照護成本降低。

（三）使用鎮定劑，特別是 **Propofol**，對腦部傷害病患的存活率有些幫助（已刊登於 **Journal of Surgical Neurology 2006(66), 37-42**）。

（四）台灣版嚴重頭部外傷治療共識，八大主題加入了本土研究，切合國內神經外科醫療需要，也已解除部分國內專家學者對台灣版之治療共識之疑慮，將進一步與全球實證臨床診療指引接軌，發展國際化之頭部外傷相關指引。（已刊登於 **Journal of Surgical Neurology 2006(66), 3-7**）

（1）Abstract:

I. Focus and Process

There are four main parts of research project this year:

1. Head injury registry system is one of the most complete head injury database in Taiwan: (a) 3,804 valid entries to head injury questionnaire registry system are collected; (b) 297 valid severe head injury questionnaires are collected. (c) 488 valid quality of life after head injury questionnaires are collected. Findings: (1) Survival rate of head injury patients is relatively high with ICP monitor, CPP treatment and sedation at the same time. (2) It is proven that GOSE assessment is related to quality of life of brain injury patients.

2. We continued to work on education for neurosurgeons and related professionals, and invitee neurosurgical experts from all over Taiwan were to write severe head injury guidelines Taiwan version. Following are the summarized contents:

（1）Management in ER (ER: Emergency Room):

Options: 1. Quick Assessment (a) ABC-Airway, clavicle protection, Breathing, Circulation. (b)Trauma Assessment - cranium, face, clavicle, spin, chest, abdomen, pelvis, back and limbs. 2. Basic Treatments (a) Endobroncial intubation (b) Venous transfusion of normal saline to stabilize blood pressure. 3. Neurological examination. (a) Glasgow coma Scale (b) pupil size and reflection (c) Respiratory type (d) Activity of limbs 4. Further Assessment - Conditional (a) Sedation (? : for patients with agitation and endobroncial intubation (b) Anti-Epileptic

Drugs (? : for epilepsy treatment and prevention (c) C. Osmotic diuretics(? : for intracranial hypertension 5. Image Examinations - only when the sign of life is stable (a) X-ray (b) Brain CT scan (c) Others (MRI, angiography) - only when methods above fail. 6. Laboratory Examinations(a) General examinations of blood, biochemistry and blood coagulative function. (b) Electrocardiogram (c) Alcohol and toxin screen (when necessary) 7. Final Diagnosis (a) Consideration of all differential diagnoses (b) Severity Assessment 8. Final Treatments: Consultation with neurosurgical physicians

(2) ICP monitor:

Guideline: 1. ICP monitor may be used for the following situations: (a) Severe head injury (GCS Score 3-8), abnormal CT scan results (hematomas, contusions, edema, and compressed basal cisterns) (b) Severe head injury (GCS Score 3-8), normal CT scan results, and addition of at least two of the following situations: the patient older than 40, unilateral or bilateral decerebrate/decorticate rigidity in motor posturing, and systolic pressure<90mmHg. (c) ICP monitor could also be used on mild (GCS Score 13-15) and medium (GCS Score 9-12) head injury. 2. Treatment Threshold: It is suggested that intracranial pressure treatment threshold for adults be 20-25mmHg, while that for children be 20. 3. Choice: Conventionally, ventricle and brain parenchyma monitors are used, while other options may be adopted due to resource distribution, region, insurance or other

social factors.

（3）CPP and Fluid management:

Cerebral Perfusion Pressure (a) Guideline: 1. should be 60-70mmHg。2. CPP<60mmHg indicates dangerous state. 3. Without brain ischemia, purposeful raising blood pressure driving CPP over 70mmHg increases ARDS rate. (b) Options: 1. Both Lund concept and EBIC (European brain injury consortium) think that CPP should stay 60-70mmHg. 2. Without brain ischemia, of vasopressor or colloid use driving CPP over 70mmHg may lead to ARDS rate five times more than that of patients with CPP<70. Fluid (a) Guideline: 0.9% saline is better than Lactate Ringer . (b) Options: Rosner et al and Lund concept recognize Colloid for maintaining swelling pressure. (b) No evidence supports Colloid, but experts and professionals have reached the agreement that reasonable use is helpful, but there is no recognized type yet. (c) FFP is useful for Coagulopathy only, and is not suggested for routine volume expander. (d) Patients with coma are not to be treated with hypertonic saline. (e) Carbohydrate containing fluids should be used very carefully.

（4）Sedation:

Options: (a) For patients with GCS Score 3-8, hardly controllable intracranial pressure, or agitation, some ICU have defined sedation as part of standard treatment. (b) It is suggested that GCS Score 3-8 patients should have endobroncial intubation before sedation.

(5) Nutrition:

Guideline: (a) Patients with sedation should be provided with 100% of sufficient resting metabolic expenditure; others should be provided with 140%. (b) Parenteral and enteral nutrition supplement recipe: more than 15% energy source of protein should be provided within 7 days after injury to maintain nitrogen balance. Option: nutrition supplement has to begin within 24 to 72 hours after injury, and the amount should grow gradually to maximum necessary calorie.

(6) Management of intracranial hypertension:

Guideline: (a) Preventive hyperventilation treatment is not suggested for intracranial hypertension. (b) Steroid treatment is not suggested to be used for intracranial hypertension.

(7) Seizure Prophylaxis:

Standard: Preventive drugs, like Phenytoin, Carbamazepine, Phenobarbital or Valproate, are not suggested to be used for late seizure. Option: some studies show that Phenytoin and Carbamazepine could prevent from early seizure effectively, and may be used on patients with high risks. However, it is not supported by present evidence that prevention of early seizure could consequently improve outcome of head injury patients. Patients with high risks include: GCS Score<10, cortex contusion, depressed cranial fracture, subdural hematoma, epidural hematoma, brain bleeding, penetrating head injury, and epileptic seizures within 24 hours after injury.

（8）Second Tier Therapy:

Options: (a) Hypertonic saline decreases intracranial pressure rapidly, and consequently raise CPP. It suggested that no combination with other drugs should be used. (b) Barbiturate coma slows brain metabolism as well as decrease brain activity, and thus reduces intracranial pressure. This treatment isn feasible without brain stem not severely damaged. (c) Hyperventilation: (1) Hyperventilation can lower blood carbon dioxide density so that autoregulation would reduce cerebral blood flow and decrease intracranial pressure. (2) It is suggested that $PaCO_2 \leqq 30$ mmHg only be used for short duration when the patient neurosurgical condition worsens. (d) Hypothermia: There is no positive clinical evidence. (e) Steroids: steroids can reduce brain swelling caused by brain tumor and brain abscess, and consequently prevent from intracranial hypertension. However, it claimed in recent studies that steroids not only do not reduce brain swelling caused by head injury, but would increase infection rate. Thus, steroids are not suggested to be used.

Conclusion: With the guideline, difference between domestic and international situations and ideas are understood better. In addition, with reference of local research, the guideline is serves as region-oriented, and allows the public and patients to understand treatment purposes. Analysis shows that implementation of the guideline has contributed to the society and to saving social costs.

3. Cost-effective and useful to reduce social costs, the suggestions are made based on data accumulated for the project, record of quality of life of head injury patients, neurosurgeons?opinions on cerebral perfusion pressure treatment, and data process as well as analysis.

4. Final version of guideline is posted on the Internet to educate medical professionals, and to serve as a standard guideline for neurosurgeons.

II. Discussion

(1)As the most complete head injury database in Taiwan, the registry system serves as a reference for future research. In addition, it found that there is significant reduction in number of severe head injury cases, and severe head injury patients have better average outcome than mild ones due to good medical care (published in Journal of Neurotrauma 2006(23), 1609-20).

(2)It proven that fluid treatment does increase survival rate of severe head injury patients, and reduce medical costs.

(3)Sedation, especially Propofol, increase survival rate of head injury patients moderately (published in Journal of Surgical Neurology 2006(66), 37-42).

(4)The next goal of the project is to connect this guideline to international research by translation (published in Journal of Surgical Neurology 2006(66), 3-7).

貳、95年度計畫著作一覽表

Journal

序號	計畫產出名稱	產出型式	Impact factor	致謝對象
1	Ming-Fu Chiang, Jasmine Chao, Shu-Fen Chu, Shiu-Jau Chen, Wen-Ta Chiu, Ching-Chang Hung, Shin-Han Tsai Head injuries in adolescents in Taiwan: a comparison between urban and rural groups. Surgical Neurology 2006;66:14-19. Supported by NHRI-EX95-9106PN (SCI) Accepted	Foreign	1.142	NHRI
2	Ming-dar Tsai, Wen-Ta Chiu, Jia-Wei Lin, Chun-Fu Chen, Sheng-Jean Huang, Cheng-Kuei Chang, Wan-Lin Chen, Shin-Han Tsai Current experiences in the use of the severe head-injury guidelines in Taiwan. Surgical Neurology 2006;66:3-7. Supported by NHRI-EX95-9106PN (SCI) Accepted	Foreign	1.142	NHRI
3	Wen-Ta Chiu, Sheng-Jean Huang, Hei-Fen Hwang, Jau-Yih Tsauo, Chun-Fu Chen, Shih-Han Tsai, Mau-Roung Lin Use of the WHOQOL-BREF for Evaluating Persons with Traumatic Brain Injury. Journal of Neurotrauma 2006;23:1609-1620. Supported by NHRI-EX95-9106PN (SCI) Accepted	Foreign	2.574	NHRI
4	Wen-Ta Chiu, Jia-Wei Lin, Muh-Shi Lin, Wan-Lin Chen, Chien-Min Lin, Shu-Fen Chu, Tien-Jen Lin, Shin-Han Tsai Clinical correlation between CT numbers and Nakaguchi classifications of chronic subdural hematoma. Surgical Neurology 2006;Supported by NHRI-EX95-9106PN (SCI) Accepted	Foreign	1.142	NHRI
5	Shin-Han Tsai, Wan-Lin Chen, Che-Ming Yang, Li-Hua Lu, Ming-Fu Chiang, Long-Jin Chi, Wen-Ta Chiu Emergency air medical services for head injury patients. Surgical	Foreign	1.142	NHRI

	Neurology 2006;66:32-36. Supported by NHRI-EX95-9106PN (SCI)			
6	Ming-Fu Chiang, Wen-Ta Chiu, Shih-Han Tsai, Chun-Jen Huang, Peterus Thajeb Multiparametric Analysis Of Cerebral Substrates And Nitric Oxide Delivery In Cerebrospinal Fluid In Patients With Intracerebral Haemorrhage: Correlation With Hemodynamics and Outcome. Acta Neurochirurgica. 2006;6:615-621. Supported by NHRI-EX95-9106PN (SCI)	Foreign	1.064	NHRI
7	Che-Ming Yang, Wen-Ta Chiu The risk of malpractice litigation in caring of head injury patients in Taiwan: a population-based epidemiological study. Surgical Neurology 2006;66:43-47. Supported by NHRI-EX95-9106PN (SCI)	Foreign	1.142	NHRI
8	Wen-Ta Chiu, Tien-Jen Lin, Jia-Wei Lin, Sheng-Jean Huang, Cheng-Kuei Chang, Hsiang-Yin Chen Multi-centers evaluation of propofol for head-injured patients in Taiwan. Surgical Neurology 2006;66:37-42. Supported by NHRI-EX95-9106PN (SCI)	Foreign	1.142	NHRI
9	Jia-Wei Lin, Shih-Han Tsai, Wan-Chen Tsai, Wen-Ta Chiu*, Shu-Fen Chu, Chien-Min Lin, Che-Ming Yang, Ching-Chang Hung Survey of traumatic intracranial hemorrhage in Taiwan. Surgical Neurology 2006;66:20-25. Supported by NHRI-EX95-9106PN (SCI)	Foreign	1.142	NHRI
10	Wen-Ta Chiu, Sheng-Jean Huang, Shin-Han Tsai, Jia-Wei Lin, Ming-Da Tsai, Tien-Jen Lin, William CW Huang Traumatic Brain Injury: The Impact Of Time, Legislation And Geography On Epidemiology. Journal Of Clinical Neuroscience 2006;Supported by NHRI-EX95-9106PN (SCI) Accepted	Foreign		NHRI
11	Sheng-Jean Huang, MD, Yuan-Shen	Foreign	1.142	NHRI

	Chen, MD, Wei-Chen Hong, MD, Lin Chang, MD, Yin-Yi Han, MD, Li-Ming Lien, MD, Yong-Kwang Tu, MD, PhD Clinical experience of hydroxyethyl starch (10% HES 200/0.5) in cerebral perfusion pressure protocol for severe head injury. Surgical Neurology 2006;66:26-31. Supported by NHRI-EX95-9106PN (SCI)			
12	Wei-Chen Hong, MD, Yong-Kwang Tu, PhD, Yuan-Shen Chen, MD, Li-Ming Lien, MD, Sheng-Jean Huang, MD Subdural intracranial pressure monitoring in severe head injury: Clinical experience with Codman MicroSensor. Surgical Neurology 2006;66:8-13. Supported by NHRI-EX95-9106PN (SCI)	Foreign	1.142	NHRI
13	Ming-Chao Huang MD, PhD, Pei-The Chang, PhD, May-Jywan Tsai, PhD, Huai-sheng Kuo, PhD, Wen-Chun Kuo, Meng-Jen Lee PhD, Ming-Jei Lo, MMS, I-Hui Lee MD, PhD, Wen-Cheng Huang, MD, Liang-Ming Lee, MD ,Yang-Hsin Shih, MD, Liang-Shong Lee, MD, and Henrich Cheng, MD, PhD Sensory and motor recovery after repairing transected cervical roots. Surgical Neurology 2006;Supported by NHRI-EX95-9106PN (SCI) Accepted	Foreign		NHRI

Patent

序號	計畫產出名稱
	無

Book

序號	計畫產出名稱
	無

Conference Paper

序號	計畫產出名稱

1	Wen-Ta Chiu (Taiwan) Rapid Decline Of Traffic Injury Deaths In A Developing Country. APACPH, Taiwan, 11/19-23, 2005. (Keynote Speaker) NHRI-EX95-9160PN 2005
2	Min-Huei Hsu, Wen-Ta Chiu, Yu-Chuan Li: Trends In Road Traffic Injury Mortality Taiwan, 1991-2003. APACPH, Taiwan, 11/19-23, 2005.NHRI-EX95-9160PN 2005
3	Tien-Jen Lin, Wen-Ta Chiu, Jia-Wei Lin, Chien-Min Lin, Shin-Han Tsai, Wan-Chen Tsai: Infantile Traumatic Brain Injury: Its Clinical Features And Related Early Post-Traumatic Seizures. APACPH, Taiwan, 11/19-23, 2005.NHRI-EX95-9160PN 2005
4	Cheuk-Sing Choy, Wen-Ta Chiu, Jia-Wei Lin, Chien-Min Lin, Tien-Jen Lin, Wan-Chen Tsai, Shih-Han Tsai: Mild Traumatic Brain Injury, MTBI, Intracranial Hematoma. APACPH, Taiwan, 11/19-23, 2005.NHRI-EX95-9160PN 2005
5	Wen-Ta Chiu, Wan-Chen Tsai, Hung-Yi Chiou, Cheuk-Sing Choy, Shin-Han Tsai: Pediatric Traumatic Brain Injuries In Taiwan. APACPH, Taiwan, 11/19-23, 2005.NHRI-EX95-9160PN 2005
6	Wen-Ta Chiu And Yuh-Shan Ho: An Overview Of Traumatic Brain Injury Research During The Year 1991-2004. APACPH, Taiwan, 11/19-23, 2005.NHRI-EX95-9160PN 2005

Technical Report

序號	計畫產出名稱
	無

參、95年度計畫重要研究成果產出統計表

註：群體計畫(PPG)者，不論是否提出各子計畫資料，都必須提出總計畫整合之資料

(係指執行95年度計畫之所有研究產出結果)

科技論文篇數			技術		
	國　內	國　外	類　型	經　費	項　數
期　刊 論　文	篇	13篇	技　術 輸　入	千元	項
研討會 論　文	篇	6篇	技　術 輸　出	千元	項
專　著	篇	篇	技　術 擴　散	千元	項
專　利	項	項	技　術 報　告	千元	項
			技　術 創　新	千元	項

〔註〕：

期刊論文：指在學術性期刊上刊登之文章，其本文部份一般包含引言、方法、結果、及討論，並且一定有參考文獻部份，未在學術性期刊上刊登之文章（研究報告等）與博士或碩士論文，則不包括在內。

研討會論文：指參加學術性會議所發表之論文，且尚未在學術性期刊上發表者。

專　　著：為對某項學術進行專門性探討之純學術性作品。

技術報告：指從事某項技術之創新、設計及製程等研究發展活動所獲致的技術性報告且未公開發表者。

技術移轉：指技術由某個單位被另一個單位所擁有的過程。我國目前之技術轉移包括下列三項：一、技術輸入。二、技術輸出。三、技術擴散。

技術輸入：藉僑外投資、與外國技術合作、投資國外高科技事業等方式取得先進之技術引進國內者。

技術輸出：指直接供應國外買主具生產能力之應用技術、設計、顧問服務及專利等。我國技術輸出方包括整廠輸出、對外投資、對外技術合作及顧問服務等四種。

技術擴散：指政府引導式的技術移轉方式，即由財團法人、國營事業或政府研究機構將其開發之技術擴散至民間企業之一種單向移轉（政府移轉民間）。

技術創新：指研究執行中產生的技術，且有詳實技術資料文件者。

肆、95年度計畫重要研究成果

註：群體計畫(PPG)者，不論是否提出各子計畫資料，都必須提出總計畫整合之資料

計畫之新發現、新發明或對學術界、產業界具衝擊性(impact)之研究成果，請依性質勾選下列項目。

☐1. 研發或改良國人重要疾病及癌症的早期診斷方式及治療技術

☑2. 發展新的臨床治療方式

☐3. 發展新生物製劑、篩檢試劑及新藥品

☐4. 瞭解常見疾病及癌症之分子遺傳機轉

☐5. 瞭解抗癌藥劑對癌細胞之作用機制

☐6. 提供有效的疾病預防策略

☐7. 利用生物統計與生物資訊研究，推動台灣生技醫藥研究，促進生物技術與基因體醫學之發展

☑8. 醫療保健政策相關研究

☐9. 瞭解環境毒理機制及重金屬對人體健康的影響

☐10. 研發適合臨床使用的人造器官及生醫材料

☐11. 縮短復健流程並增加復健效果的醫療輔助方式或器材之研究應用

☐12. 改進現有醫療器材的功能或增加檢驗影像的解析能力

☑13. 其他重要疾病或醫藥衛生問題研究

<u>發展國內頭部外傷病患之治療共識，應用於國內神經外科臨床治療具有重大影響。</u>

一、 計畫之新發現、新發明或對學術界、產業界具衝擊性（impact）之研究成果，請敘述其執行情形。

（一）本計畫已完成建立國內最完備之頭部外傷登錄資料庫，為世界最大的頭部外傷資料庫之一。將依不同嚴重程度之病患建立生活品質及癒後之追蹤。並期許進一步完成線上電子登錄系統，提供遠距即時的登錄資料庫。

（二）本研究證實，研究中發現，頭部外傷病患同時使用顱內監測器及腦灌流壓療法，是最好的治療指標。同時，使用鎮定劑對病患也會有較好的癒後。而高度過度換氣，則未達統計上之顯著意義。

（三）透過台灣地區神經科學領域之專家學者及實證臨床診療指引專家的共同努力，已完成制訂台灣版嚴重及輕度頭部外傷處理共識，以嚴重頭部外傷八大主題及輕度頭部外傷四大主題，為目前國內之醫療照護人員對台灣版之治療共識，提供國內頭部外傷照護應用依循嚴重頭部外傷處理共識的重要性，及嚴重頭部外傷病患處理準則介入前後，對社會大眾及節省社會成本具重大貢獻。同時將以本計畫之研究成果公告於國家衛生研究院衛生政策研究中心之實證臨床指引平台，提供國、內外相關診療指引之互動，進一步達到與國際接軌。

二、 計畫對民眾具教育宣導之研究成果（此部份將為規劃對一般民眾教育或宣導研究成果之依據，請以淺顯易懂之文字簡述研究成果，內容以不超過300字為原則）

本計畫主要是希望能針對神經外科醫師及相關照護人員進行教育宣

導的目的，除了將美國版之嚴重頭部外傷病患照護準則引入台灣，強化國內神外照護之新觀念，此項照護準則(**Guidelines of management in severe head injury**)將能大大提昇頭傷病患之存活率。且由本土之研究成果，制訂了台灣版嚴重頭部外傷治療共識，為國內神經外科之一大貢獻，透過訪視神經外科醫師，來瞭解本計畫介入後，國內使用台灣版嚴重頭部外傷治療準則的情形，並藉此提昇國內頭部外傷治療水準，故本計畫研究成果為很好的指標與教育。

三、 簡述年度計畫成果之討論與結論，如有技術移轉、技術推廣或業界合作，請概述情形及成效

已確立台灣版嚴重及輕度頭部外傷治療共識，以實證醫學為基礎，將八大主題依證據等級及建議等級分列陳述於各個主題中，並且將研究結果公告於台灣神經創傷學會網站，未來將可提供國內專家學者與民眾互動之平台。唯國內之專家學者對台灣版之治療共識，仍多採取認同但較保守的態度，需進一步推廣與教育本研究結果。

四、 成效評估（技術面、經濟面、社會面、整合綜效）

本計畫於將致力於嚴重頭部外傷病患之收集與追蹤上，並加強與各家醫院之聯繫等。透過與各個醫院的交流，已建立國內最完整之頭部外傷病患資料庫。同時，本土性研究也證實，美國版之嚴重頭部外傷病患照護準則此項照護準則(**Guidelines of management in severe head injury**)運用於台灣，將能大大提昇頭傷病患之存活率，確實也已更正國內神經外科照護之新觀念，已將台灣之神經外科照護能力提昇至世界水準。本計畫成果完成及推廣台灣版嚴重和輕度頭部外傷之治療共

識，將大幅提昇頭部外傷病患之預後情形，增加良好復健的人數，降低社會成本。

五、 下年度工作構想及重點之妥適性

本年度為五年計畫之第五年，最終的目標是將制訂完成的台灣版嚴重頭部外傷治療共識推廣至整個台灣地區，讓全國神經外科照顧水準能再提升，降低國家對頭部外傷病患醫療上的負擔，並降低嚴重程度及死亡率。同時，進一步達到與國際接軌，將本計畫之研究成果公告於國家衛生研究院衛生政策研究中心之實證臨床指引平台，提供國際相關診療指引之互動。

六、 檢討與展望

經過五年來的研究，將美國頭部外傷治療準則觀念引進國內，目前接受情形以相當高，藉由本研究之積極推動介入之下，此研究計畫之成效已成功展現，並不斷提昇國內治療之水準。未來應更積極舉辦國內外神經外科照護之研討活動，並針對神經外科醫師、相關醫療人員及一般民眾，全面性宣導新的照護觀念，推動台灣版頭部外傷治療共識。必將更大幅提昇頭傷病患之預後情形，降低社會成本負擔。

伍、95年度計畫所培訓之研究人員

註：群體計畫(PPG)者，不論是否提出各子計畫資料，都必須提出總計畫整合之資料

種類				人數	備註
專任人員	1.	博士後研究人員	訓練中		
			已結訓		
	2.	碩士級研究人員	訓練中		
			已結訓	2	
	3.	學士級研究人員	訓練中	1	
			已結訓		
	4.	其他	訓練中		
			已結訓		
兼任人員	1.	博士班研究生	訓練中	4	
			已結訓		
	2.	碩士班研究生	訓練中	6	
			已結訓		
醫師			訓練中	6	
			已結訓	3	

特殊訓練課程（請於備註欄說明所訓練課程名稱）

陸、參與95年度計畫所有人力之職級分析

註：群體計畫(PPG)者，不論是否提出各子計畫資料，都必須提出總計畫整合之資料

職級	所含職級類別	參與人次
第一級	研究員、教授、主治醫師	13 人
第二級	副研究員、副教授、總醫師、助教授	3 人
第三級	助理研究員、講師、住院醫師	6 人
第四級	研究助理、助教、實習醫師	2 人
第五級	技術人員	0 人
第六級	支援人員	0 人
合計		24 人

〔註〕：

第一級：研究員、教授、主治醫師、簡任技正，若非以上職稱則相當於博士滿三年、碩士滿六年、或學士滿九年之研究經驗者。

第二級：副研究員、副教授、助研究員、助教授、總醫師、薦任技正，若非以上職稱則相當於博士、碩士滿三年、學士滿六年以上之研究經驗者。

第三級：助理研究員、講師、住院醫師、技士，若非以上職稱則相當於碩士、或學士滿三年以上之研究經驗者。

第四級：研究助理、助教、實習醫師，若非以上職稱則相當於學士、或專科滿三年以上之研究經驗者。

第五級：指目前在研究人員之監督下從事與研究發展有關之技術性工作，且具備下列資格之一者屬之：具初（國）中、高中（職）、大專以上畢業者，或專科畢業目前從事研究發展，經驗未滿三年者。

第六級：指在研究發展執行部門參與研究發展有關之事務性及雜項工作者，如人事、會計、秘書、事務人員及維修、機電人員等。

柒、參與95年度計畫所有人力之學歷分析

註：群體計畫(PPG)者，不論是否提出各子計畫資料，都必須提出總計畫整合之資料

類別	學　　歷　　別	參與人次
1	博士	10 人
2	碩士	10 人
3	學士	5 人
4	專科	0 人
5	博士班研究生	0 人
6	碩士班研究生	6 人
7	其他	0 人
	合計	31 人

捌、參與95年度計畫所有協同合作之研究室

註：群體計畫(PPG)者，不論是否提出各子計畫資料，都必須提出總計畫整合之資料

機構	研究室名稱	研究室負責人
無		

玖、九十五年度計畫執行情形

註：群體計畫(PPG)者，不論是否提出各子計畫資料，都必須提出總計畫整合之資料

一、請簡述原計畫書中，九十五年預計達成之研究內容

九十五年度本研究計畫之執行方向可分成五個方向：(一)上半年持續進行頭部外傷病例登錄，其中依不同嚴重程度之頭部外傷的患者，持續運用 **WHOQOL-BREF** 台灣版及針對頭部外傷後病人之腦部傷害病患生活品質問卷之評估，並以 **GOS** 及 **GOSE** 追蹤已收案病患評估其恢復狀態及癒後情形。建立國內完整且精確之頭部外傷資料庫。(二)持續進行國內神經外科及相關醫療人員之教育訓練，提供國內相關領域之醫療照護人員瞭解國際間與國內之差異，並提出相關治療建議，提倡國內頭部外傷照護推動應用嚴重頭部外傷處理準則的重要性，及訂定台灣版處理準則的必要性。(三)延續上一年度之重要發展，繼續修訂台灣版頭部外傷治療共識，並加入本土性之研究結果，區隔本土與國際之治療差異，提供國內醫療照護人員、病患及一般名眾充分瞭解頭部外傷之治療目標。(四)根據計畫多年收集之頭部外傷病患資料、生活品質追蹤及神經外科醫師對腦灌流壓治療意見，進行資料處理與分析，依研究成果提出具成本效益且降低社會成本之建議。(五)舉辦的大型研討會，透過與會專家學者的討論，進行目前國內頭部外傷治療共識之評比，期提升治療共識嚴謹度。並證明嚴重頭部外傷病患處理準則介入前後，對社會大眾及節省社會成本的重大貢獻。最後公告國內制訂頭部外傷治療共識之研究成果於網路上，促使國內神經外科相關醫療人員應用於臨床上有一共同醫療處置之依循。

二、請詳述九十五年度計畫執行情形，並評估是否已達到原預期目標（請註明達成率）

九十五年度計畫執行情形，評估已達到原預期目標（達成率：100%）。本計畫已完成建立國內最完備之頭部外傷登錄資料庫。本年度收集頭部外傷病患有效問卷共 3804 筆；其中嚴重頭部外傷有效問卷共 297 筆；及頭部外傷後病患之生活品質追蹤有效問卷共 488 筆。研究中發現，頭部外傷病患同時使用顱內監測器及腦灌流壓療法，是最好的治療指標。同時，使用鎮定劑對病患也會有較好的癒後。而高度過度換氣，則為達統計上之顯著意義。同時，透過多次的頭部外傷治療共識會議與研討會，消彌國內腦灌流（CPP）相關治療的爭議，藉此邀集國內神經外科專家學者，已完成制訂台灣版嚴重頭部外傷及輕度頭部外傷治療共識，建立國內健康照護者更瞭解國際間與國內之差異，並提供相關治療建議，對國內頭部外傷照護推動應用依循嚴重頭部外傷處理準則的重要性。嚴重頭部外傷病患處理準則介入前後，對社會大眾及節省社會成本的重大貢獻。同時將以本計畫之研究成果公告於國家衛生研究院衛生政策研究中心之實證臨床指引平台，提供國、內外相關診療指引之互動，進一步達到與國際接軌之目的。

拾、附錄

附錄一

嚴重頭部外傷治療共識：

急診處置

（**Management in ER**）

<u>原則</u>

甲.標準程序（**Standard**）：

目前並沒有 Level I 的研究可提供足夠資料作為標準程序。

乙.指引（**Guideline**）：

目前並沒有 Level I 的研究可提供足夠資料作為指引。

丙.建議（**Options**）：

1. 迅速評估。

(1) ABC－維持氣道暢通（<u>A</u>irway）、保護頸椎、呼吸（<u>B</u>reathing）、循環（<u>C</u>irculation）。

(2) 創傷評估－顱骨-顏面、頸椎、脊椎 、胸腔、 腹腔、骨盆腔、背部及四肢。

2. 基本處置。

(1) 氣管內插管。

(2) 靜脈輸液，建議給予足量生理食鹽水靜脈輸液維持血壓穩定。

3. 神經學檢查。

(1) 昏迷指數（Glasgow Coma Scale）。

(2) 瞳孔大小及反射。

(3) 呼吸型態。

(4) 四肢活動力。

4. 進一步評估－視情況使用。

(1) 鎮靜劑 （Sedation） 的使用(? ：當病人躁動，有氣管內插管。

(2) 抗癲癇藥物之投予 (? ：已有癲癇發生或作預防時。

(3) 高滲透性利尿劑 (? ：疑有顱內壓升高時。

5. 影像檢查一當生命徵象穩定時，方可進行下列檢查。
   (1) X 光 。
   (2) 腦部斷層檢查 。
   (3) 其他（核磁共振造影、血管攝影）一視特殊情況需要，如上述檢查無法証實時，方可行之。
6. 實驗室檢查。
   (1) 動脈氣體分析、一般血液、一般生化、凝血功能檢查。
   (2) 心電圖。
   (3) 有必要時，加入酒精及毒藥物篩檢。
7. 急診之最終診斷。
   (1) 考慮所有可能之鑑別診斷。
   (2) 評估嚴重度 。
8. 最後處置
   (1) 會診神經外科醫師。

撰寫人：陳子勇
制訂委員:急診處置共識小組

■ 前言

面對一個嚴重腦外傷、昏迷指數介於**3-8**分的病人急診室醫護人員最主要的工作為確保並延續院外及事故現場所建立的腦部急救、灌流步驟，雖有少數病患的第一急救現場為急診室，不論如何，皆需遵行一般外傷原則進行病患的評估及進一步的處置，穩定及檢查，目的在避免嚴重腦外傷病患出現腦部的二次傷害。

■ 文獻回顧

頭部受傷後引起之呼吸暫停(**Head injury ? induced apnea**)及外傷壓力併發之交感神經異常升高(**Stress-related massive sympathetic (catecholamine) discharge**)為嚴重頭部外傷後之**2**個立即引發之生理病理現象，常可導致**Hypoxia, Hypercarbia, acidosis**及血壓升高產生。而**Head trauma-induced cardiac injury**和**Gastroduodenal mucosa injury (ulcer)**也是在嚴重頭部外傷後常併發的疾病。**Hypotension**或**Hypoxia**若在急性期因心肺功能不張發生，也會使此類病患之**Mortality**或**Morbidity**升高至**50%**以上。

■ 結論

1. 急診室的迅速評估包括？主要依據美國外傷組織所制定的ATLS原則迅速評估[1]

   (1) ABC（<u>A</u>irway, <u>B</u>reathing, <u>C</u>irculation）:

   I. 呼吸道暢通：嚴重腦外傷病患已陷入嚴重昏迷，一般認為已經喪失保護呼吸道暢通的能力。再加上嘔吐物、頭臉部軟組織出血，腫脹物可能堵塞呼吸道。一但急診處置人員認為病患無能力維護己身的呼吸道時，及早進行氣管內插管有助於幫助換氣，並降低缺氧可能性。

II. 正常呼吸：檢查呼吸道是否通暢的同時，並檢查呼吸情形，換氣需確保身體足夠的氧氣供應並排出二氧化碳，在嚴重腦傷病患有＞35％病人會出現缺氧（PaO_2＜65mmHg），故以插管病人需藉助呼吸器輔助呼吸。

III.循環並控制出血：在嚴重腦外傷之病人，約 15％會出現低血壓的現象（SBP＜95mmHg）而 12％會伴隨低血容比（Hct＜30％）。[2] 低收縮血壓的出現，會升高嚴重腦傷病患死亡率達一倍。[3] 迅速監測血壓及找到實際出血點，積極給予靜脈輸液，避免低血壓，可有效提升病患存活率。

(2) 創傷評估：在昏迷指數小於或等於 8 分的病人統計上，56-60％會伴隨一個以上之其他器官損傷，其中 25％需要手術治療。全身性的創傷評估有助於發現潛在但立即的創傷，包括

I. 顱骨：需觸診是否頭部撞擊腫塊、頭皮撕裂傷、開放性顱骨骨折及顱內內容物（腦組織、腦脊髓液）是否外漏。

II. 顏面骨折：下顎骨是否浮動，是否有不對稱顏面腫脹等。

III.頸椎、脊椎評估：昏迷指數小於等於 8 分的病人，約 4-5％具有高位(C1-3)頸椎骨折，面對這類病患，需先假設具有頸椎骨折，以頸圈保護，不可隨意搬動頭部，直到 X 光或電腦斷層檢查證實無頸椎骨折方可移除頸圈。

IV.胸腔、腹腔、骨盆腔，除迅速觸診、聽診外，並需 X 片排除無血胸、氣胸或骨盆骨折。

2. 基本處置：

完成迅速評估之後，由於嚴重腦外傷病人都無法保護呼吸道，

且35%有缺氧的危險，在昏迷指數小於或等於8分的病患，需儘快進行氣管內插管，輔以呼吸器通氣輔助為必要的基本處置。由於低血壓造成存活率大幅下降，穩定血壓、維持基本灌流可以快速靜脈生理食鹽水輸液來維持血壓。注射量調整到足夠維持收縮血壓超過95mmHg為準，輸液建議只給生理食鹽水，並適度補充鉀離子。

3. 神經功能檢查：

完成基本檢查及穩定生命徵象的同時，急診需進行神經學檢查，需記錄基礎神經學功能，包括昏迷指數（Glasgow Coma Scale）[4]（表一）、雙側瞳孔大小及光反射、四肢肌力，最好有插管前的呼吸型態。

表1：昏迷指數對照表

分數	E：睜開眼睛	V：語言能力	M：運動功能
6			可依照檢查者命令動作
5		對答如流,邏輯正常	僅可定位疼痛點
4	自動睜開眼睛	言語內容混淆	僅可閃躲外來疼痛刺激
3	聽聲音睜眼	言語短促，不恰當	去大腦皮質型僵直反射
2	在疼痛下睜眼	呻吟聲，聽不懂	去腦幹型僵直反射

1	完全不睜開眼睛	完全無言語反應	不論如何刺激，全無動作

4. 進一步評估？ 視病人的臨床狀況可給予以下的處置：

(1) 鎮定劑：在昏迷指數小於等於 **8** 分的腦外傷病患，約 **55%** 會產生顱內高壓，[5] 若已知電腦斷層檢查不正常者，**53-63%** 會出現遲發性腦出血。[6] 這類昏迷病人在氣管內管刺激之下，可能會出現燥動現象，可適度給予鎮定劑以防腦壓升高，但需確定病人已有氣管內插管並適度的呼吸器輔助及穩定的血壓，方可給予。鎮定劑的給予可參考「鎮定劑使用」的描述。

(2) 抗癲癇藥物的投予：若出現外傷性早發性癲癇時，需給予本類藥物。若無癲癇發作者，待嚴重腦外傷之診斷確立後，按準則中「抗癲癇藥物之投予」的方式給予。

(3) 高滲透壓利尿劑報告，在積極治療的嚴重腦傷病人中，約 **60%** 會出現顱內出血，且顱內壓會上升超過 **15mmHg**。[5] 縱使起初的電腦斷層檢查為正常，亦有 **10-15%** 可能出現顱內壓上升的後遺症。面對急診室中，嚴重腦外傷的病患，一但出現昏迷指數下降、心跳下降、血壓上昇，瞳孔放大等現象，則須懷疑顱內壓升高，可在血壓穩定的情況下先給予 **Mannitol**（劑量為 **0.5-1g/kg**）。[7]

5. 影像學檢查：

急診室中可迅速進行外傷相關檢查，主要包括胸腔、骨盆、頸椎側照（包括 **C7-T1**），以排除相關的損傷。在嚴重腦外傷病患，

緊急電腦斷層檢查，可幫助建立診斷並進行嚴重度評估，不需注射顯影劑，即可進行完整的評估。至於磁振造影，一般不須緊急施行。不過是否須進行一系列電腦斷層檢查，以及一系列電腦斷層檢查是否可改善病人預後，尚無確定的結論及準則。嚴重腦部外傷病患一般不需施行血管攝影及血管內栓塞術，除非大量出血無法以保守療法控制，如口鼻部出血無法藉鼻腔填塞或骨盆骨折無法立即固定止血時，需考慮實施血管攝影栓塞術。

6. 實驗室檢查：

   包括一般血液；一般生化血糖值、凝血功能及心電圖。

7. 急診之最後診斷：

   所有有可能的鑑別診斷皆須納入考慮並延請外傷相關科系如心臟、胸腔、一般外傷、外傷骨科、外傷整形科迅速到現場會診並協商必要的處理方法。

8. 嚴重腦外傷病患中，約 **55%** 會出現顱內出血，且顱內壓會上升超過 **15mmHg**。若未立即接受手術降低腦壓，都需接受顱內壓監測器植入，插氣管內管並呼吸器輔助。絕大部分需入住神經外科加護病房，接受加護照顧。建議盡速會診神經外科醫師，於急診完整提供第一線諮詢，並積極參與臨床治療計劃擬定與實施。

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■ 急診處置共識小組

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附錄二

嚴重頭部外傷治療共識：

顱內壓監測

(ICP monitoring)

原則

甲. 標準程序（Standard）：

目前並沒有 Level I 的研究可提供足夠資料作為標準程序。

乙. 指引（Guideline）：

1. 下列情況下得使用顱內壓監測器
   (1) 嚴重頭部外傷（GCS Score 3-8 分）電腦斷層檢查異常，如 hematomas, contusions, edema, compressed basal cisterns.
   (2) 嚴重頭部外傷（GCS Score 3-8 分）電腦斷層檢查正常，至少有下列二項條件：
      I. 40 歲以上。
      II. 肢體動作出現單側或雙側之去大腦強直或去皮質強直反射。
      III. 收縮壓 90mmHg 以下。
   (3) 輕度頭部外傷（GCS Score 13-15 分）與中度頭部外傷（GCS Score 9-12 分）可依病情需要個別考慮使用顱內壓監測。
2. 顱內壓治療閾值(Treatment Threshold)
   建議成人頭部外傷之顱內壓治療閾值為 20-25mmHg，而小兒頭部外傷之顱內壓治療閾值則為 20mmHg。
3. 顱內壓監測器之選擇
   最標準之顱內壓監測方法乃腦室與腦間質顱內壓監測。可因資源分佈、地域、保險或其他社會因素之考量選擇使用。

丙. 建議（Options）：

撰寫人：于國藩醫師
制訂委員：顱內壓監測共識小組

■ 前言

神經外科醫師於臨床使用顱內壓監測最早發表文獻乃於1951年法國之Guillaure 與 Janny，但未引起注意，直至1960年，NiL Lundberg以英文發表193頁之巨作，紀錄143位病人之顱內壓變化，其發現嚴重之顱內高壓（IICP）無法完全由臨床之神經學檢查來預測，其並提出著名之A waves（plateau waves）與B&C waves。1964-1969年，美國賓州大學Langfitt & Kassell發表一系列文章紀錄顱內壓升高，造成tentorial herniation 之 pressure gradient。並提出顱內壓升高末期之asomotor paralysis□，至此顱內壓監測之重要性才廣泛影響全美與全世界。英國於1970年Jennet 也發表顱內壓監測的經驗，發現顱內壓之變化與臨床神經學之觀察有不一致之現象，並認為其對治療與預後有重要價值。[1] 經過多年的臨床研究證實，美國 Brain Trauma Foundation與American Association of Neurological surgeons(AANS)於1996年與2000年guidelines 把顱內壓監測列為嚴重頭部外傷治療不可或缺之步驟。[2,3]

顱內壓監測是否可以改善頭部外傷病人之預後，事實上目前並無前瞻性隨機對照研究證實，主要原因是：1. 未放置顱內壓之對照組病人產生倫理學上之爭議。 2. 此大型研究所需經費過於龐大，超過5百萬美金，病人最少要768人。[4]

顱內壓監測之重要性，從已發表之臨床文獻，在診斷、治療、預後三方面有如下之價值：1. 有助於早期偵測顱內的變化，以決定治療方針。2. 有助於某些治療顱內高壓(IICP)方式之使用，如適當過度換氣（Hyperventilation，維持 $PaCO_2 \geq 35mmHg$），Mannitol，鎮靜劑（Sedation）與Barbiturate coma，CSF 引流. 等。3. 有助於預測病

人的預後。[2]

■ 文獻回顧

1. 顱內壓監測之適應症

適應症的寬與窄，取決於風險（risk）與成本花費（cost）的考量評估，由於腦間質顱內壓監測之成本在國內較高，因此採取最嚴格的適應症，也就是美國 Brain Trauma Foundation/AANS 2000 年的 guideline：[2]

(1) 嚴重頭部外傷（GCS Score 3-8 分）電腦斷層檢查檢查異常，如 hematoma, contusions, edema, compressed basal cisterns。

(2) 嚴重頭部外傷（GCS Score 3-8 分）電腦斷層檢查正常，但有下列二項條件以上：

I. 40 歲以上。

II. 肢體動作出現單側或雙側之去大腦強直或去皮質強直反射（motor posturing）。

III. 收縮壓 90mmHg 以下。

(3) 輕度頭部外傷（GCS Score 13-15）與中度頭部外傷（GCS Score 9-12）不建議例行使用顱內壓監測，但可依病情需要個別考慮使用。

其中嚴重頭部外傷而電腦斷層檢查正常之病人，乃依 Narayan（1982）class III data 207 位病人之研究結論成為 guideline，[4] 其發現全體病人有 13%有 IICP，而若具上述二項條件以上，則高達 60%病人有 IICP，相反的若只有合乎一項條件，則只有 4%病人有 IICP，而整體來說此類病人有 16%合乎顱內壓監測之資格。

但從文獻回顧中，仍有許多專家主張有較寬的適應症，在此也列出其他文獻有關之適應症：

(1) 小兒頭部外傷之 **guideline**（**2003**）[5]

- 嚴重頭部外傷（**GCS Score≦8** 分），不論 **CT** 有無異常。
- 輕度與中度頭部外傷其 **CT** 有 **mass lesion**。

(2) **Miller JD**（**1999**）[1]

- 所有昏迷(**coma**)之頭部外傷，因 **CT** 正常不代表顱內壓不高。

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

- 嚴重頭部外傷與美國 **Brain Trauma Foundation**（**2000**）之適應症相同。
- **GCS Score≦10** 且 **CT** 有異常。
- 術中血塊移除後出現腦腫。
- 其他顱外外傷（特別是胸部外傷）需呼吸器支持。

(4) **European Brain Injury Consortium**（**EBIC, 1997**）[7]

- 成人嚴重頭部外傷需早期作顱外外傷手術。

(5) **Penetrating Brain Injury**（**2001**）[8]

- 無法作神經學檢查。
- 無法確定是否要移除 **mass lesion**。
- **CT** 顯示有顱內高壓。

2. 顱內壓治療閾值（**Treatment Threshold**）

顱內壓升高，顱內 **compliance** 已先行下降，表示顱內代償性機制以耗盡。因此積極治療顱內高壓必須在較低的治療閾值時儘早進行，文獻上建議之閾值從 **15-25mmHg** 都有，但是顱內壓可在 **<20mmHg** 發生經小腦天幕疝脫，所以除了臨床神經學檢查與瞳孔

變化，必須考慮 CPP 是否足夠，lesion 是否靠近後顱窩（文獻建議 15mmHg 較安全）作綜合研判。

依美國 Brain Trauma Foundation 之 guideline（2000）建議成人頭部外傷顱內壓治療閾值之上限為 20-25mmHg，[2] 而美國小而頭部外傷之 guideline（2003）[5] 則為 20mmHg。

3. 顱內壓監測器之選擇

臨床上最準確之顱內壓監測方法乃腦室引流（ventricular drainage）顱內壓監測與腦間質（parenchymal）顱內壓監測。前者成本花費較低，可引流 CSF，但出血率、感染率與堵塞異常率較高，後者操作方便，只是成本花費高且健保並未給付。建議神經外科醫師可依資源分布、地域、保險或其他社會因素之考量選擇使用。[2]

■ 結論

經過多年臨床研究經驗，顱內壓監測已成為神經重症加護不可或缺之處置，其對顱內壓高壓之監測不但可輔助臨床神經學之觀察，作病情綜合研判，且對於需鎮靜之病人提供了安全上之保障。另外在臨床研究上也是基本之評量指標，可與其他腦部功能監測器作對照之比較，使得嚴重頭部外傷病人之重症照護品質與結果得到顯著提升。

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■ 顱內壓監測共識小組

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附錄三

嚴重頭部外傷治療共識:

腦灌流壓之原則

（**Cerebral perfusion pressure, CPP**）

原則

丙. 標準程序（**Standard**）:

針對此題目並沒有 Level I 的研究，可提供足夠資料作標準程序。

丁. 指引（**Guideline**）:

1. 宜維持大腦灌流壓，至少 60-70mmHg。
2. 大腦灌流壓，小於 60mmHg 可能有害。
3. 在沒有證明腦缺血的狀態下，刻意提昇血壓使大腦灌流壓大於 70mmHg 引起成人呼吸窘迫症候群（ARDS）的機會增高。

戊. 建議（**Options**）:

1. Lund concept [1] 及 EBIC（European brain injury consortium）[2] 均認為 CPP 維持於 60-70mmHg 已足夠。
2. 在沒有證明腦缺血的狀態下，使用積極手段如昇壓劑或膠質液（colloid）維持大腦灌流壓大於 70mmHg 出現成人呼吸窘迫症候群（ARDS）之機會較大腦灌流壓小於 70mmHg 之病患高 5 倍。

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■ 前言

大腦灌流壓（Cerebral perfusion pressure,CPP）定義為平均動脈壓（Mean arterial pressure,MAP）減去顱內壓（Intracranial pressure, ICP） [CPP = MAP ? ICP]。它是大腦血流量（Cerebral blood flow, CBF）及大腦代謝活動的原動力。在病理學及生理學研究中，可證實嚴重頭部外傷（SHI）患者大都有腦部缺血的情況，如果當腦部血管自主調控機制（Autoregulation）在受損時會加速惡化，腦內壓、大腦血流量及大腦代謝等。所以嚴重頭部外傷的病患維持適當的大腦灌注壓力實為重要。

■ 文獻回顧

1. 嚴重頭部外傷致死病患的研究中，Graham et al.，經病理解剖發現約91%的病例可見腦部缺血性病變。[3] 同時其它的研究中發現頭部外傷後，前6小時中出現CBF血流量下降的機會約30%，[4] 而頸靜脈氧氣飽和度（$SjvO_2$）下降的機會約30-35%。[5,6]

2. Kiening et al.研究顯示嚴重頭部外傷後會引起CPP不穩，使腦部組織含氧量$tipO_2$下降，超過15分鐘$tipO_2$<10mmHg的病患，其預後會變差。研究中把CPP從32mmHg提昇到67mmHg時，$tipO_2$增加67%。他們認為CPP>60mmHg為重要的臨界值（critical threshold），超逾此值時$tipO_2$便會足夠。[7]

3. Cruz et al.研究顯示，當腦部自主調控機轉正常時，腦灌注壓維持在一定範圍中（60-130mmHg），並沒影響到腦血流或腦部代謝。當中CPP和CBF，或CPP和$AVdO_2$，或CPP和$CMRO_2$間並沒有相關。[8] Bouma et al.研究發現在自主調控完整下，把MAP從92+/-10mmHg

提升到123+/-8mmHg，並沒有使ICP明顯改變（<1%CBF改變）。[4] 而Bruce et al.也指出無論自主調控正常與否，主動調昇SBP30mmHg，ICP只有微量上昇或下降。上述研究進一步證實了維持足夠的CPP而中度增加SBP，此舉並沒有使大部份病患的ICP上昇。[9]

4. Chan et al.在使用Transcranial Doppler（TCD）的研究中，發現CPP<70mmHg時$SjvO_2$會下降，同時Pulsatility Index（PI）會增加，反之CPP>70mmHg時上述$SjvO_2$及PI均不變。[10]

5. 在過去的論證中CPP>70mmHg時患者預後較差。1995，Rosner提出CPP>70mmHg時，發現患者10.5月後的死亡率約29.5%；中度殘障約20%，良好復原約39%。[11] 1989，McGraw在動物實驗中找出CPP跟預後的關係，在CPP大於80mmHg時其死亡率約35-40%，而CPP每減低10mmHg時，死亡率會隨著增加20%。最後當CPP<60mmHg時，死亡率可高達95%。[12] 其它prospective研究中CPP維持約70mmHg時，患者（GCS 3-7間）的平均死亡率約21%（5-35%）。[13, 14, 15, 16, 17]

6. Robertson et al.以Prospective RCT方法研究GCS<5的嚴重頭部外傷患者。它將患者分為ICP為導向之治療組(CPP>50mmHg)及CBF為導向之治療組（CPP>70mmHg）兩組。最後發現臨床上並沒有明顯之差別。[18] Contant et al.分析上述研究中有關ARDS的風險率時，發現CBF組之ARDS出現率比ICP組大5倍。此現象可能因前者使用較多的腎上腺素及dopamine等藥物的關係。因為在動物實驗中發現ARDS或許因交感神經活動增加而經中樞神經病變所引起。[19] 再者，有ARDS的病患比沒有ARDS者多2.5倍之機會出現無法控制之

ICP，而有ARDS者變為植物人或於創傷後6個月內死亡之機會也會多出3倍。[20, 19]

■ 結論

根據上述文獻的支持下，本原則認為腦灌流壓維持放60-70mmHg間已足夠。但是腦灌流壓小於50mmHg在文獻支持下認為會嚴重降低大腦組織氧分壓，同時會增加嚴重頭部外傷後之死亡率及合併症。直到現在仍沒有文獻可證明，使用膠質液或升壓劑以維持腦灌流壓大於60mmHg會增加死亡率、合併症或腦內壓升高等。維持腦灌流壓於70mmHg以上時，引起成人呼吸窘迫症候群的機會較沒有使用積極手段之病患高五倍。另一方面，歐洲的Lund concept仍沒有廣泛使用。在未來嚴重頭部外傷的研究中，增加使用雙盲隨機控制試驗（Prospective RCT）的方法，去比較控制腦灌流壓或腦內壓之處理以何者較理想。最後找出Lund concept 及CPP protocol 之差異，促使嚴重頭部外傷病患之照護可獲提昇。

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■ 腦灌流壓與輸液之原則共識小組

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嚴重頭部外傷治療共識：

輸液之原則

（**Fluid Therapy**）

原則

己. 標準程序（**Standard**）：

針對此題目並沒有 Level I 的研究，可提供足夠資料作標準程序。

庚. 指引（**Guideline**）：

作為大量輸液時 0.9%生理食鹽水（Saline），較乳酸林格氏液（Lactate Ringer ）佳。

辛. 建議（**Options**）：

1. Rosner et al [1] 及 Lund concept [2] 中皆提到使用膠質液（Colloid）以維持血中之膨脹壓。
2. 有關膠質液（Colloid）是否應該使用目前沒有足夠證據。但依國內專家學者共識嚴重頭部外傷患者認為膠質液（Colloid）可適當使用。至於使用那一類膠質液（colloid）仍未有共識。
3. FFP 只適合凝血性病變（Coagulopathy），不建議使用在例行性容積擴張劑（Volume expander）。[3]
4. 頭部外傷併發休克的病患，最近的趨勢建議可使用高張食鹽水（Hypertonic saline）。
5. 含醣類輸液應謹慎使用。

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制訂委員: 腦灌流壓與輸液之原則共識小組

■ 前言

輸液治療（Fluid Therapy）之最終目標為恢復血管內容積，心輸出量（Cardiac Output）及組織血流灌注（Tissue Perfusion）。目前對於輸液的種類、用量及適當的血管內容積監測法(Intravascular Volume Monitor）仍有爭論，對於嚴重頭部外傷病患的輸液治療，迄今仍無共識。

■ 文獻回顧

1. 於1919時Weed et al發現腦容積會隨輸液之張力而改變。[4]
2. 低張輸液（如0.45%及5%葡萄糖）等視同純水及可直接穿過BBB，造成腦部水份和ICP增加。[5]
3. 所有含葡萄糖的輸液可能引起血糖過高（Hyperglycemia）及預後變差，在一些研究中腦部缺血時進行厭氧呼吸（Anaerobic Respiration），血糖代謝會增加乳酸的堆積進而引致組織酸化及加重神經破壞。[6,7]
4. 有些研究顯示於嚴重頭部外傷併休克時，到院前使用高張鹽水（Hypertonic Saline）可恢復血管內容積及使ICP下降。[8,9]
5. Zornow的動物實驗中使用Colloid（6% hetastarch或5% albumin），在（Oncotic Pressure）增加下並不影響腦部水份的含量。[10]
6. 在人及動物實驗中使用多量之等張輸液（Isotonic Fluid），對於腦水腫並沒有明顯的影響，但脫水會使病患之神經預後較差。[11,12,13,14]

■ 結論

在國外之嚴重頭部外傷治療指引中，並沒有把輸液之使用作特別的描述。因此本委員會增加此項以強化醫護人員對病患作出更有效之輸液治

療。現時文獻中以0.9%生理食鹽水之使用為佳，而膠質液使用仍沒有共識。但是在 Lund concept 已證實其效果。另一方面，血漿（FFP）的使用在指引中已認為不適合作容積擴張液。希望未來有更多之雙盲隨機控制試驗（Prospective RCT）研究，以澄清晶質液（Crystalloid）或膠質液之使用時機及優缺點。

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■ 腦灌流壓與輸液之原則共識小組

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附錄四

嚴重頭部外傷治療共識：

鎮定劑之使用

（Sedation）

原則

甲. 標準程序（Standard）：

針對此題目並沒有 Level I 的研究,可提供足夠資料作標準程序。

乙. 指引（Guideline）：

針對此題目並沒有 Level I 的研究，可提供足夠資料作指引。

丙. 建議（Options）：

1. 針對昏迷指數 GCS Score 3-8 分，顱內壓不易控制或是躁動的病人，目前國內、外有些加護單位已經把鎮靜劑的使用列為治療項目之一。
2. 建議 GCS Score 3-8 分的病人，須有氣管內插管，再行使用鎮定劑。

撰寫人：廖國興
制訂委員: 鎮定劑之使用共識小組

■ 前言

於嚴重頭部外傷中，若病人已確保呼吸安全，則鎮靜劑與止痛劑給予之目的有以下幾種：對壓力反應之控制（stress response）、疼痛控制、增加對氣管內管之耐受性及呼吸器之調適、降低因醫療或護理照護所形成之顱內壓增加[1,2]。而理想之鎮靜劑需具以下之特點：作用快速、藥效無累積性且無活化性代謝產物、無心血管之抑制、停藥後能快速回復以利神經功能之評估、不昂貴且能降低顱內壓及腦部代謝[1,2]。然迄今為止，並無單一藥物可符合上述各點。

■ 文獻回顧

就當前於神經加護病房所廣泛使用之鎮靜劑，茲分述如下：

Benzodiazepines

1. **Midazolam (Dormicum): loading doses 0.02-0.3 mg/kg; maintain doses 0.05-0.1 mg/kg/h[1]**
2. **Lorazepam (Ativan): loading doses 0.02-0.05 mg/kg; maintain doses 0.05-0.5 mg/kg/h[1]**
3. **Diazepam (Valium): loading doses 0.03-0.1 mg/kg,** 不建議持續給予，因易導致藥物劑量累積[1]。

此類藥物並無止痛效果。於低劑量使用時，對顱內或全身之血流動力影響不大。但當**loading doses**及大劑量給予時，可能會產生輕度低血壓及呼吸抑制[1,2,4,6,7]。另此類藥物對腦細胞代謝率（**CMRO2**）及腦部血流量（**CBF**）有中度之影響。

Propofol

Loading doses 1-2 mg/kg; maintain doses 1-3 mg/kg/h[1]。在藥理學上，**Propofol**可以造成鎮靜，安眠，抗痙攣，肌肉鬆弛的作用[1,3,5]。這

和Benzodiazepine相當類似。而Propofol也同樣會造成呼吸抑制。其效果產生快速，作用時間短的特性，更是和Benzodiazepine類中的Midazolam十分雷同。只是Propofol對血壓的抑制比Midazolam顯著。

於一本土性研究[9]比較Propofol（44例）及Midiazolam（14例）於頭部受創致昏迷指數（Glasgow Coma Scale）3-12分之患者、須使用呼吸器及植入顱內壓監測器之比較中，使用鎮靜劑須利用升壓劑預防腦部缺血的腦部外傷重症病患約為27.27%，但未使用鎮定劑者則有54.10%的比例須使用升壓劑（P<0.001）。加護病房的前五日顱內壓的記錄上，使用鎮靜劑的患者其在個別天數的顱內壓的平均值皆比未使用者理想（傷後前三日ICP小於20mmHg）。在腦灌流壓方面，使用鎮靜劑患者傷後前五日之平均腦灌流壓均可維持在70mmHg以上，反觀未使用者其平均腦灌流壓僅可維持在40mmHg左右。在各種受傷後的基準昏迷指數 (Baseline GCS 3-4分，5-6分及7分以上) 其日後死亡率的數據顯示，使用鎮靜劑的患者其死亡率在基準昏迷指數3-4分及5-6分皆比未使用者佳。

Opioids

1. **Morphin: 2-10 mg I.V**
2. **Fentanyl: loading doses 0.25-1.5 痢/kg; maintain doses 0.3-1.5 痢/kg/h**
3. **Meperidine:** 不易掌控且有心臟抑制之副作用[1]

鎮靜劑本身並沒有止痛的效果，對於需要施予止痛的病人，如果只給予鎮靜劑，反而會增加病人煩躁不安，因此必須同時施予止痛劑及鎮靜劑[1,4,5,7]，二者常有加成作用，可降低彼此劑量即可達到雙重效果，尤其在頭部外傷合併其他外傷的病人，可以使得病人處在較舒適、

壓力較少之狀態下。

Neuromuscular blocking agents

不建議常規使用肌肉鬆弛劑。若需使用，則優先考慮**non-depolarizing**類之肌肉鬆弛劑[1]。

Barbiturates

於顱內壓持續升高，且對大多數之內科及外科之降顱內壓方法反應不佳者，可考慮使用[2]。詳見後續章節：二線療法(**Second Tier Therapy**)之所述。

■ 結論

在神經加護病房中，如何避免腦部缺血是治療中心主軸[8]。而鎮靜劑及止痛劑之使用也愈來愈被廣泛接受。此類藥物所能提供之降低顱內壓、提高腦灌流壓及是否改善嚴重頭部外傷病患之預後及是否具有神經保護作用，仍須進一步的發展與研究[1,2,3,4,5]。不過，多數學者均認為 **21** 世紀初期，有關研究將會有所突破。

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■ 鎮定劑之使用共識小組

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附錄五

嚴重頭部外傷治療共識:

營養

（Nutrition）

原則

甲. 標準程序（Standard）:

目前並沒有 Level I 的研究可提供足夠資料作為標準程序。

乙. 指引（Guideline）:

丁.在接受鎮靜劑治療之病患，需補足靜態能量消耗量（Resting Metabolic Expenditure）之 100%；在未接受鎮靜劑治療之病患，應補足靜態能量消耗量之 140%。

戊.經腸道或經靜脈給予之營養製劑配方：應於受傷後 7 天內給予含至少 15% 蛋白質之熱量來源，以維持氮平衡。

丙. 建議（Option）:

灌食時間：二十四至七十二小時以內一定要開始補充營養，並逐漸增加至最大所需熱量。[1,2]

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制訂委員：營養共識小組

前言及文獻回顧

1. 1980年代早期，一般認為意識昏迷的病患代謝需求較正常人低，當時臨床醫師對嚴重頭部外傷病患的營養需求要求較寬鬆。但後來的研究藉由測量能量消耗量、氮平衡以及心血管系統相關參數發現在嚴重頭部外傷病患有代謝增加（Hypermetabolism）及氮消耗（Nitrogen Wasting）的現象。

2. 目前至少有12個關於營養需求Level I的研究。其中九篇探討灌食量、灌食方法及途徑、類固醇對氮平衡的影響以及血液中生化值的變化，但並未對病患臨床結果加以探討。另外兩篇針對營養供給量對病患預後的研究，發現在相同的營養供給量下，營養供給的方式對病患神經學預後沒有影響，但這兩篇研究關於感染率與氮平衡的關係卻有相衝突的結果。最後一篇報告發現營養缺乏會增加病患感染率。但此篇在方法學上有些疑點。

3. 新的研究結果顯示給予Insulin-like Growth Factor-1（IGF-1）可以改善氮平衡以及病患的預後。

結論

◆ 科學基礎

1. 灌食方法：空腸灌食（Jejunal Feeding）或胃管灌食（Gastric Feeding）與靜脈營養相比較，可以減少血糖升高和感染的機率，成本也較低。[3,4,5]

2. 灌食時間：二十四至七十二小時以內一定要開始補充營養，並逐漸增加至最大所需熱量。[1,2]

3. 在接受鎮靜劑治療之病患，需補足靜態能量消耗量（Resting

Metabolic Expenditure*）之 100%；在未接受鎮靜劑治療之病患，應補足靜態能量消耗量之 140%。當病患有嘔吐或癲癇時，需適時調整灌食量。[6,7,8]

4. 需列入考慮因素：病患年齡、性別、體表面積、是否接受鎮靜劑治療、肌肉張力、是否合併腸胃疾病（如：阻塞、大量出血、腹膜炎）、脊髓受傷等。

5. 經腸道或經靜脈給予之營養製劑配方：應於受傷後七天內給予含至少 15%蛋白質之熱量來源，以維持氮平衡。[9,10]

6. 體重下降超過 30%會增加合併症及死亡率。

7. 目標熱量需求：每公斤體重至少 25 大卡。

◆ 未來研究方向

以隨機對照實驗(Randomized Controlled Trial)研究 Insulin-like Growth Factor-1（ IGF-1）的臨床效果。

***: 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

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附錄六

嚴重頭部外傷治療準則：

顱內壓升高之處置

（**Intracranial Hypertension**）

<u>原則</u>

甲. 標準程序（Standard）：

目前並沒有 Level I 的研究可提供足夠資料作為標準程序。

乙. 指引（Guideline）：

1. 不建議使用預防性過度換氣治療顱內壓升高。
2. 不建議使用類固醇治療顱內壓升高。

丙. 建議（Options）：

當顱內壓大於 20 mmHg 時，一般影響顱內壓因素需注意之外，建議處理如下圖：

裝置顱內壓監測器

↓

CPP > 60mmHg，床頭抬高 30 度，CVP 8-12mmHg，排除低血鈉及發燒

↓

顱內壓升高 ICP>20 mmHg

↓

腦脊髓液引流（如果有腦室引流）3-5 cc/次

↓

使用鎮靜劑、止痛劑，必要時使用神經肌肉阻斷劑

↓

輕度過度換氣 $PaCO_2$ 30-35mmHg

↓

Mannitol 0.25 ? g/kg/靜脈注射

↓ → 頭部 CT、腦水腫 or ICH

開顱術或減壓性顱骨切除術

第二線治療法

（Barbiturate Coma，過度過度換氣（$PaCO_2$ 25-30mmHg），高張性食鹽水）

撰寫人：黃勝堅 / 張承圭
制訂委員: 顱內壓升高之處置共識小組

■ 前言

在嚴重頭部外傷的神經加護照顧以往將治療的目標專注在處理顱內壓升高，例如: 限水（**Fluid Restriction**）、高張利尿劑（**Mannitol, Glycerol**）、過度換氣（**Hyperventilation**）、鎮靜劑（**Sedation**）、低溫療法及類固醇等使用均被重新再評估。目前腦部重症加護照顧的中心目標已經由顱內壓的控制轉為缺血的預防，因此，除了降低顱內壓之外，如何提升腦部的灌流（**Cerebral Perfusion**）及降低腦部代謝以避免缺血，已成為另一注意的焦點。本文將針對神經加護照顧當中重要的觀念，顱內壓升高的處理原則加以討論。

■ 文獻回顧

1. 顱內壓升高的病生理機轉：

傳統以來，嚴重頭部外傷的治療都是以顱內壓的控制為目標。學者大多認為顱內壓大於 **25mmHg** 者其預後均屬不良。[1-7] 根據臨床的研究，嚴重頭部外傷病患顱內壓升高主要的病理生理機轉包括：顱內出血、腦水腫、腦過度充血（**Hyperemia**）及水腦症。其中大量顱內出血與水腦症必須以外科手術治療；除此，不同的原因造成的顱內壓升高，則必須選用不同的方法解決。例如: 顱內壓升高是由於腦過度充血引起，則應使用過度換氣，若是腦水腫引起，則應使用高張利尿劑。除了上述之病理機轉外，尚有其它因素會影響顱內壓，常見之影響因素包括:

(1) 床頭部抬高度數：床頭部抬高 **15-30** 度顱內壓較平躺低，[2-6] 若大於 **30** 度時會使 **CPP** 下降。

(2) 發燒：體溫上升會增加腦部代謝，容易造成腦部缺血及顱內壓升高。[3-6]

(3) 血中二氧化碳分壓：血中二氧化碳分壓降低會引起腦血管收縮，顱內壓下降。反之，顱內壓升高。但過度降低血中二氧化碳分壓會影響腦部灌流造成缺血。[1-6]

(4) 血中鈉離子濃度：血中鈉離子降低會引起滲透壓下降引起腦水腫增加及顱內壓升高。[3-6]

(5) 頸部姿勢：當頸靜脈回流受到影響會引起顱內壓升高。[3-6]避免頸部過度扭轉及壓迫影響頸靜脈回流。

(6) 躁動不安與疼痛：當病患與呼吸器拮抗、抽痰或疼痛均會引起顱內壓升高，可適當使用鎮靜劑（Sedatives）及止痛劑（Analgesics）。[2-7]

2. 顱內壓升高的處理：

治療顱內壓升高的方法有許多種，各有其優缺點。基本上以不應影響腦灌流而造成腦部缺血為原則。以下對各種方法加以說明：

(1) 腦脊髓液引流(CSF Drainage)：如果有腦室引流導管（Ventriculostomy），腦脊髓液引流是第一個應考慮的方法。[2-6]此法有效而且缺點少，即使少量（3-5c.c.）的腦脊髓液，也能有效的降低顱內壓。一般建議每8小時引流75cc.屬安全範圍。

(2) 鎮靜劑止痛劑及神經肌肉阻斷劑(Neuromuscular Blockade)：[8-19]鎮靜劑、止痛劑及神經肌肉阻斷劑的使用，一方面使得呼吸器的使用容易控制，另一方面可降低顱內壓。常用的鎮靜劑如Midazolam、Propofol、Ketamine。止痛劑如Fetanyl、Morphine。中短效神經肌肉阻斷劑如 Atracurium、 Cis-atracurium。這三類藥物均可連續靜脈給藥，但應特別注意: (a) 呼吸道安全、(b)

Midazolam Propofol 及 Atracurium 會影響血壓、(c) 神經肌肉阻斷劑不可單獨使用，必須合併鎮靜劑一起使用。主要缺點是無法隨時評估病人的運動反應及神經學檢查，因此須要足夠的腦部監測。學者主張使用時，應以有效之最低劑量為原則，當顱內壓小於 20mmHg 超過 24 小時，則可以將藥量逐漸降低。

(3) 高滲透壓高張利尿劑（Hyperosmotic Diuretics）：[1-7] 常用的藥物是 Mannitol 及 Glycerol，其降低顱內壓的理論是增加血管內滲透壓，而使腦部細胞外的水進入血管，如此能改善腦水腫而降低顱內壓。這種效果約在給藥 15-20 分鐘後開始作用。最近的研究報告顯示，Mannitol 除了以上的作用之外，還有減低血液黏稠度、降低血比容，使得血液流速變快，引起反應性的血管收縮，如此能減少腦部血液的體積而降低顱內壓。這樣的效果約在給藥後數分鐘內開始。建議使用方法是單次靜脈快速給藥（Bolus, Rapid Infusion)。此外，Mannitol 有打開血腦障礙（Opening of Blood-Brain Barrier）的作用，因此，在多次劑量使用之後，Mannitol 可能聚集在腦內，反而使得腦內滲透壓過高而產生腦水腫的現象。這樣的情形，在長期使用或者是連續給藥（Continuous Infusion）容易發生。因此給藥的方式應該是單次靜脈快速給藥（Bolus, Rapid Infusion），而不是連續慢速的給藥（Continuous Infusion）。建議使用劑量為 0.25-1g/Kg/4-6 hrs，必要時可以縮短使用間隔，使用時應保持正常血容積，應監測血中滲透壓，避免滲透壓大於 320mOsm/L，以免造成腎衰竭。傳統上主要的缺點是會造成低容積量（Hypovolemia）、低血壓（Hypotension）、電解質不平衡及腎衰竭。利尿劑 Lasix 可和 Mannitol 合併使用

效果更好。使用劑量：**20-40 mg/4-6 hrs**，特別要注意的是液體的補充以免造成低容積量及低血壓而產生腦部缺血。

(4) 過度換氣（**Hyperventilation**）：[1-7] 利用降低血中二氧化碳分壓，使得腦部血管收縮以達到降低顱內壓的效果。臨床上的使用已經超過二十年的歷史。將血中二氧化碳分壓降到 **25** 至 **30 mmHg**，數秒鐘內即有降顱內壓效果，但時效短暫。因此近年來大多主張將 $PaCO_2$ 維持在 **30** 至 **35 mmHg**，輕微過度換氣即可。至於使用的時機，目前則比較偏向於針對急性顱內壓升高的處理。對於預防性過度換氣的使用則採較保留的態度。

(5) 巴比妥鹽昏迷（**Barbiturate Coma**）：[1-7] 利用高劑量的巴比特酸昏迷來降低腦部的代謝，以達到降低顱內壓的目的。從過去十幾年的國外報告來看，結果相當的不一致，死亡率在 **21%** 至 **89%**。有學者甚至認為巴比特酸昏迷治療的結果，往往是救活了沒有功能的生命，而質疑此療法的價值。因此有人認為實施巴比特酸昏迷治療的時機相當的重要，如果開始使用的時間太晚，腦幹功能已受損，縱使顱內壓能夠控制，結果也是沒有功能的生命。所以建議，當顱內壓大於 **30 mmHg**，腦灌流壓小於 **70 mmHg** 或者是腦灌流壓大於 **70 mmHg** 而顱內壓仍大於 **40mmHg** 時，即應該實施巴比特酸昏迷療法。使用的藥物為戊基巴比特魯（**Pentobarbital**），起始劑量為 **10mg/kg loading**，**30 min** 靜脈注射(**IV Infusion**)，然後 **5mg/kg/hr** 持續 **3** 小時直到腦波沉寂(**EEG Electrocerebral Silence**)。如果血壓不穩定，則注射速度應減慢，接著以 **1-3mg/kg/hr** 的劑量維持，並測定血漿濃度使之維持在 **30-50mg/100ml**。在顱內壓小於 **20mmHg**，**24** 至 **48** 小時藥物即

逐漸徹離。巴比特酸昏迷療法的缺點是低血壓，因此實施之前應確定體液為正常容積量狀態。特別要注意的是肺炎和敗血症的發生，應針對感染加以監測。目前國內學者大多不採此法。

(6) 低溫療法（**Hypothermia**）：[22-23] 對於腦部重症，高溫發燒會引起不好的結果。相反的，低溫療法（**Hypothermia**）卻有其效果。研究報告顯示，將病人在 **24-96** 小時內體溫降至 **33** 至 **34**℃，之後再以每八小時攝氏 **0.3** 度的速度回溫至 **37**℃，此法可降低腦代謝、顱內壓及血液中乳酸值，而不引影響到腦灌流壓，且臨床結果的確進步。常見的併發症是：感染、心律不整、及凝血時間延長（**Prolonged Clotting Time**）。此方法已於 **2001** 年第三期臨床實驗宣告失敗。

(7) 類固醇（**Steroid**）：目前認為類固醇對於腦瘤及腦膿瘍（**Brain Abscess**） 所引起腦水腫、顱內壓升高有效。依照目前的最新之國際性研究報告 [24] 及嚴重頭部外傷處理指引，認為類固醇並不能降顱內壓，而使得臨床結果更好，因此不建議例行性使用。

(8) 減壓性顱骨切除術（**Decompressive Craniectomy**）：用於治療嚴重腦外傷（**TBI**）的概念早於第一次世界大戰前即由 **Harvey Cushing** 所提出 [25,26] 早期顱骨切除術手術的結果，不論 **Mortality or Morbidity** 均無法顯示較其他治療方法有顯著的優點。近年來因為神經加護照顧的進步，使得顱骨切除術的預後有令人鼓舞的提昇。[27] **1996** 年的 **American Association of Neurological Surgeons**，使用顱骨切除術於嚴重 **TBI** 的原則，將顱骨切除術定位在第二線療法。[28] 治療顱內高壓的手術方法，顱骨切除術與顳葉切除減壓術（**Decompressive Lobectomy**）比較，最近的證據

顯示顱骨切除術是較好的選擇。[29]雖然有研究仍視顱骨切除術無法改善，甚至可能使腦傷老鼠的更惡化。[30]多數研究將顱骨切除術視為第二線療法。許多推廣顱骨切除術的中心所做最新的研究，多著重在顱骨切除術的使用時機及技術（單側、雙測)。同時顱骨切除術使用在小兒頭部外傷結果，似乎有較多的正向結論，[31,-33]甚至最新的研究及國內學者亦建議將顱骨切除術視為第一線治療的位置。

3. 處理顱內壓升高的危急路徑及步驟：

到底顱內壓多高才是底限，目前尚未有定論。臨床上，當顱內壓升高至 20 至 25mmHg 時，即為應當積極處理的時機。降低顱內壓的方法有許多種，各有其適用的情況及不良的反應，因此依照各種治療的益處與危險比（Benefit Risk Ratio)，國內學者專家們提出了處理顱內壓升高的危急路徑及步驟。在使用降低顱內壓的方法之前，病人的基本狀況必須先調整好，其中包括體溫的控制、抗癲癇藥物的使用、頭部抬高 30 度、避免兩側頸靜脈回流受到影響、血氧飽和度為 100%、體液為正常容積狀態（Normovolemia)、中心靜脈壓維持在 8 至 12 mmHg、腦灌流壓大於 60mmHg，及血中二氧化碳分壓 35-40mmHg。在所有基本條件安全無虞的狀態下，如果病人使用的是腦室內顱內壓監測，則第一個考慮方法是腦脊髓液引流，每次引流 3 至 5 c.c.可達到良好的降壓效果。如果無法執行腦室引流，則應使用鎮靜止痛劑及神經肌肉阻斷劑，確定病人是處於安靜的狀態與呼吸器沒有拮抗的情形。如果顱內壓仍然居高不下，如果仍然無法有效的控制顱內壓，則可考慮輕微的過度換氣，將血中二氧化碳分壓降至 30-35mmHg。倘若仍然無法有效的控制顱內壓則應考慮使用高張利

尿劑（Mannitol, Glycerol），Mannitol 可以大量的使用，直到滲透壓 320 Osm/L 為止。當中特別要注意液體的補充，及電解質的平衡。如果仍然無法有效的控制顱內壓，除了更積極高張利尿劑之外，則應考慮第二線的治療法。在進入第二線的療法之前，隨時應該想到是否有再出血或者是須要外科手術情形。因此應重複電腦斷層檢查以確定之。所謂第二線的療法，是指副作用較大，或者是效果尚未確定的療法。其中包括巴比特酸昏迷、低溫療法（Hypothermia）、高血壓療法、高度的過度換氣（$PaCO_2$＜30mmHg）、高張性食鹽水（Hypertonic Saline）等。

裝置顱內壓監測器

↓

CPP > 60mmHg，床頭抬高 30 度,CVP 8-12mmHg, 排除低血鈉及發燒

↓

顱內壓升高 ICP>20 mmHg

↓

腦脊髓液引流(如果有腦室引流)

3-5 cc/次

↓

使用鎮靜劑,止痛劑,必要時使用神經肌肉阻斷劑

↓

輕度過度換氣 $PaCO_2$ 30-35mmHg

↓

Mannitol 0.25 ?   g/kg

靜脈注射

↓ → 頭部 **CT,**腦水腫 **or ICH**

開顱術或減壓性顱骨切除術

第二線治療法

Barbiturate coma,高度過度換氣(PaCO2 25-30mmHg),高張性食鹽水

圖一、處理顱內壓升高之步驟

■ 結論

在嚴重頭部外傷神經加護病房中,如何避免腦部缺血是治療中心主軸。最好的方法就是早期發現問題適時的處理。除了傳統的顱內壓控制之外,如何建立多方面的腦部監測系統、正確的腦灌流及代謝觀念以避免腦缺血的發生,為目前加護照顧的重點。

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■ 顱內壓升高之處置共識小組

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附錄七

嚴重頭部外傷治療共識：

癲癇之預防治療

（**Seizure prophylaxis**）

原則

甲. 標準程序（Standard）：

遲發性癲癇不建議預防性藥物投予，如: Phenytoin、Carbamazepine、Phenobarbital 或 Valproate。

乙. 指引（Guideline）：

針對此題目並沒有 Level I 的研究，可提供足夠資料作指引。

丙. 建議（Option）：

有些研究顯示：Phenytoin 和 Carbamazepine 能有效預防早發性癲癇發作，可在某些高危險群病患中使用。但目前的證據並不支持預防早發性癲癇發作，可以改善頭部外傷病患的預後。

其中高危險群病患包括：昏迷指數 GCS Score 10 分以下、腦皮質挫傷、凹陷性顱骨骨折、硬腦膜下血腫、硬腦膜上血腫、腦內出血、穿透性頭部外傷、外傷後 24 小時內出現癲癇者。

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■ 前言

頭部外傷後的病人，約有 2%至 10%會有全身性的癲癇發作。而外傷後癲癇（Post-traumatic Seizures, PTS）可區分為早發性與遲發性。早發性癲癇是指受傷 7 天內發生，而遲發性癲癇是指受傷 7 天以後才發生的。頭部外傷後，癲癇發作會更加重腦部繼發性的損害（Secondary Injury），如：腦壓上升、腦氧氣代謝率（Cerebral Metabolic Rate of Oxygen, $CMRO_2$）增加、腦血流量（Cerebral Blood Flow, CBF）增加、腦血液容量（Cerebral Blood Volume）增加、降低平均動脈壓，使得腦部灌注壓下降，進而惡化腦部的氧氣和合（Oxygenation）。此外，癲癇也會產生一些併發症，如：進而加重腦部傷害、吸入性肺炎、院內感染等，使得整體的結果變差。

在美國 1970 年代，神經外科醫師常常開立癲癇藥物之預防治療。然而，常規性的醫囑卻會有一些缺點，包括：中樞神經系統與胃腸道的副作用，以及藥物特異體質的反應，輕微的皮膚紅疹到嚴重的史帝芬-強生症候群。所以對於嚴重頭部外傷患者，如何開立癲癇藥物之預防治療，是一項值得探討的議題。

■ 文獻回顧

1. Young et al. 早期的 RCT（Randomized Controlled Trials）研究 Phenytoin 是否能預防早發性與遲發性的外傷後癲癇發作。其結果顯示 244 位頭部外傷的病患，隨機分成投予 Phenytoin 與安慰劑兩組，並追蹤 2 年。病人接受 11 mg/kg 靜脈注射的負荷劑量，之後肌肉注射或口服劑量，根據每天抽血以達目標血漿藥物濃度 40-80 umol/L (10-20 㮊/mL)。對於早發性與遲發性的外傷後癲癇，其發生率，在投予 Phenytoin 與安慰劑兩組比較並無明顯差別，在投予藥物組：早發性外

傷後癲癇 3.7%，遲發性的外傷後癲癇 12.4%；對照組：早發性外傷後癲癇 3.7%，遲發性的外傷後癲癇 10.8%。此現象可能是對照組其外傷後癲癇的發生率太低而影響本研究的效度。但是有一點值得注意的是：病人的 **Phenytoin** 血漿濃度大於 **48 umol/L**，沒有人會有癲癇發作。

2. 於西元 1990 年 Temkin et al.對於嚴重頭部外傷病患，操作一最大型的、前瞻的、隨機的、雙盲的、安慰劑對照的試驗。404 位病患隨機接受 Phenytoin 20 mg/kg 靜脈注射的負荷劑量，之後靜脈注射、口服或鼻胃管給予，以達維持劑量，根據抽血監測目標血漿藥物濃度 Phenytoin 40-80 umol/L (total) 或 3-6 umol/L（free）。在加護病房中抽血每星期三次、病房中抽血每星期一次，並追蹤 24 個月，在第 1、3、6、9、12 個月抽血。靜脈注射或口服的每天的藥物劑量範圍是 200-1200 mg/d，最高達鼻胃管給予的 2600 mg/d。早發性外傷後癲癇的發生率在治療組與對照組比較有明顯下降，分別是 3.6%（95% CI:2.3-4.9）比 14.2%（95% CI:0.12 to 0.62）。而預防一次早發性外傷後癲癇的 NNT（Number Needed to Treat）是 10（95% CI:8-18）。但是對於遲發性外傷後癲癇的預防，這兩組並無明顯差異。

因為皮膚紅疹而停藥的發生率，在投予 Phenytoin 藥物組是比對照組顯著上升，分別是 8.2%比 2%，p<0.01。而 NNH（Number Needed to Harm）是 17。接受 Phenytoin 者，每 1,000 人，可預防 111 次癲癇的發作；但是有 62 人因為皮膚紅疹而停止藥物治療。整體副作用的比例，兩組相似，分別是藥物組 9% 比對照組 6%，p=0.52。而第一星期發生皮膚紅疹的比例，分別是藥物組 0.6% 比對照組 0.1%，p=1.0。

Temkin et al.其結論：使用 7 天的 Phenytoin 預防治療必須根據

臨床的判斷與整體的神經學結果來衡量投予。

3. Temkin et al 於西元 1999 年比較 Valproic Acid 與 Phenytoin 預防早發性與遲發性的外傷後癲癇的研究。379 位頭部外傷的患者，包括：立即性癲癇發作、顱骨凹陷性骨折、腦部穿刺傷、電腦斷層檢查發現有大腦皮質挫傷、硬腦膜下血腫、硬腦膜外血腫、腦內出血者。病人分成投予 Phenytoin 藥物七天、Valproic Acid 治療 30 天、Valproic Acid 治療 180 天三組。早發性外傷後癲癇的發生率相當低，在 Phenytoin 藥物組與 Pooled Valproic Acid 治療組比較無明顯差別，（1.5% 比 4.5%, p=0.14），RR=2.9（95% CI:0.7-13.3）。

   遲發性的外傷後癲癇的發生率亦無明顯差別，但是接受 Valproic Acid 治療組似乎比 Phenytoin 藥物組有較高死亡率之傾向（13.4%比 7.2%，p=0.07，RR=2.0，95% CI:0.9-4.1）。因此，Valproic Acid 不建議常規使用來預防外傷後癲癇。

4. Cochrane Collaboration Group 的 Meta-analysis 分析 10 個合適的 RCT，共 2,036 個病例隨機分組投予抗癲癇藥物與安慰劑兩組來預防外傷後癲癇的發生。抗癲癇藥物可以降低早發性外傷後癲癇的發生率，但是無法降低遲發性外傷後癲癇的發生率，也無法降低死亡率。不管有無使用抗癲癇藥物或者是預防給 Phenytoin 或 Carbamazepine 均無法減少死亡與神經殘障。但是接受 Carbamazepine 治療組似乎可能增加死亡與神經殘障。Meta-analysis 分析的結果，無法排除臨床上是否增加皮膚紅疹的情形。預防性使用抗癲癇藥物目前並不建議應用於遲發性外傷後癲癇。預防早發性外傷後癲癇，Phenytoin 是目前可以接受的治療。然而，現今的資料並不支持使用抗癲癇藥物可以降低整體的死亡率與

神經殘障。

5. 附表比較：抗癲癇藥物治療組與對照組之比較(資料來源：Schierhout et al. Anti-epileptic drugs for preventing seizures following acute traumatic brain injury (Cochrane Review), 2000）。

死亡	死亡率與神經殘障	外傷後癲癇	副作用
治療組比對照組 **95/540　78/514** **(17.6%) (15.2%)** **RR=1.15** **(0.89-1.51)**	治療組比對照組 **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)**	治療組比對照組 **Early (< 7 days)** **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)**	治療組比對照組 **Skin Rash** **30/292　18/276** **(10.3%) (6.5%)** **RR=1.57** **(0.57-39.88)**

■ 結論

根據以上文獻回顧，預防遲發性外傷後癲癇，是不建議預防性藥物投予。預防性給予抗癲癇藥物，可以降低早發性外傷後癲癇的發生率，但是，對於嚴重頭部外傷患者，現今的資料並不支持使用抗癲癇藥物可以降低整體的死亡率與神經殘障。無法降低遲發性外傷後癲癇的發生率，也無法降低死亡率。預防早發性外傷後癲癇，**Phenytoin** 是

目前可以接受的治療之一。有些研究顯示：**Phenytoin** 和 **Carbamazepine** 能有效預防早發性癲癇發作，可在某些高危險群病患中使用。其中高危險群病患包括：昏迷指數 **GCS Score 10** 分以下、腦皮質挫傷、凹陷性顱骨骨折、硬腦膜下血腫、硬腦膜上血腫、腦內出血、穿透性頭部外傷、外傷後 **24** 小時內出現癲癇者。

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■ 癲癇之預防治療共識小組

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附錄八

嚴重頭部外傷治療準則：

二線療法

（**Second Tier Therapy**）

原則

甲. 標準程序（**Standard**）：

針對此題目並沒有 Level I 的研究，可提供足夠資料作標準程序。

乙. 指引（**Guideline**）

針對此題目並沒有 Level I 的研究，可提供足夠資料作指引。

丙. 建議（**Options**）：

1. 高張性食鹽水（Hypertonic saline）
   可快速降低顱內壓，且其效果相當於傳統降腦壓藥物，進而有效提昇腦灌流壓，目前証據均建議單一使用。
2. 巴比妥鹽昏迷（Barbiturate coma）
   可降低腦代謝率，減少腦部活動，而達到降低腦壓的目的。使用時機相當重要，在腦幹功能尚未受損嚴重之前使用，才能有實質的功效。
3. 過度換氣（Hyperventilation）
   (1)可因降低血中之二氧化碳濃度，經由腦血流自動控制機轉（autoregulation）達到減少腦血流量，進而降低腦壓的目的。
   (2)建議 $PaCO_2 \leq 30$ mm Hg，只用在緊急神經症狀惡化時，而且時間要短。
4. 低溫療法（Hypothermia）
   目前臨床上仍無証據顯示有效。
5. 類固醇（Steroid）
   類固醇可降低腦瘤及腦膿瘍所引起之腦水腫，而降低顱內壓之昇高。但依照最新研究報告，認為類固醇並不能降低因外傷所引起之腦水腫，且有增加感染率之虞，臨床功效不佳，因此不建議例行使用。

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■ 前言

嚴重頭部外傷的治療都是以顱內壓的控制，提升腦部的灌流(cerebral perfusion)及降低腦部代謝以避免缺血為目標，第二線治療法如高張性食鹽水（Hypertonic saline）、巴比妥鹽昏迷（Barbiturate coma）、過度換氣（Hyperventilation）、低溫療法（Hypothermia）及類固醇（Steroid）的使用可來搶救剩餘的腦部功能，是副作用較大，或是效果尚未確定的療法，[1-3] 本文將針對上述神經加護照顧的觀念及原則加以討論。

■ 文獻回顧

高張性食鹽水（Hypertonic saline）

鈉離子具有高選擇性及高滲透性，高張性食鹽水可以在 BBB 完整的地方產生相當高的濃度差利用減少腦組織水分的方式降低顱內壓，也可以使紅血球及血管內皮產生類似脫水的情形使血液循環改善。1999 年 Qureshi 等在急性腦出血病人使用不同濃度的高張性的食鹽水（3% 5.3ml/kg 以及 23% 0.7ml/kg）和 Mannitol（1mg/kg）發現降顱內壓效果相當，且無明顯副作用。[4] 2002 年 Schwarz 等使用 10% 75ml 的高張性食鹽水處理 22 次（急性腦中風病人 8 人），發現顱內壓平均下降 9.9mmHg，腦灌流壓明顯增加，達到最大效果的時間為 35 分鐘，沒有出現嚴重副作用。[5]

巴比妥鹽昏迷（Barbiturate coma）

利用高劑量的巴比妥鹽昏迷來降低腦部的代謝，以達到降低顱內壓的目的，但必須及早使用才可能有效。[7] 一般建議使用時機為當顱內壓大於 30 mmHg，腦灌流壓小於 70 mmHg 或者是腦灌流壓大於 70

mmHg 而顱內壓仍大於 **40mmHg** 時，即應該實施。使用的藥物為戊基巴比妥(**Phenobarbital**)，起始劑量為 **10mg/kg**，**30 min** 靜脈注射，然後 **5mg/kg/hr** 持續 **3** 小時直到腦波沉寂(**EEG electrocerebral silence**)。在顱內壓小於 **20mmHg**，**24** 至 **48** 小時藥物即應逐漸徹離。巴比妥鹽昏迷療法的缺點有低血壓、肺炎和敗血症，目前國內學者大多不採此法。

過度換氣（**Hyperventilation**）

利用降低血中二氧化碳分壓，使得腦部血管收縮以達到降低顱內壓的效果。將血中二氧化碳分壓降到 **25** 至 **30 mmHg**，數秒鐘內即有降顱內壓效果，但時效短暫。因此近年來大多主張將 $PaCO_2$ 維持在 **30** 至 **35 mmHg**，輕微過度換氣即可。至於使用的時機，目前則比較偏向於針對急性顱內壓升高的處理。[2,8] 對於預防性過度換氣的使用則採較保留的態度。

低溫療法（**Hypothermia**）

研究報告顯示，將病人在 **24-96** 小時內體溫降至 **33** 至 **34**℃，之後再以每八小時攝氏 **0.3** 度的速度回溫至 37℃，此法可降低腦代謝、顱內壓及血液中乳酸值，而不引影響到腦灌流壓，且臨床結果的確進步。[9,10] 此方法已於 **2001** 年第三期 臨床實驗宣告失敗。[11]

類固醇（**Steroid**）

依照目前的最新之國際性研究報告及嚴重頭部外傷處理指引，認為類固醇並不能降顱內壓，而使得臨床結果更好，因此不建議例行性使用。[12]

其它療法例 **Hyperbaric oxygen (HBO)** , **Metrizamide** 等，皆無證據顯示有明顯療效。

■ 結論

第二線治療法：

定位於當第一線療法無效或臨床病況沒有明顯進展時，即可考慮使用第二線療法，目的在搶救殘留的腦部功能。因缺乏大規模雙盲之研究，所以第二線治療法均歸於建議（Options）之範疇。

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■ 二線療法共識小組

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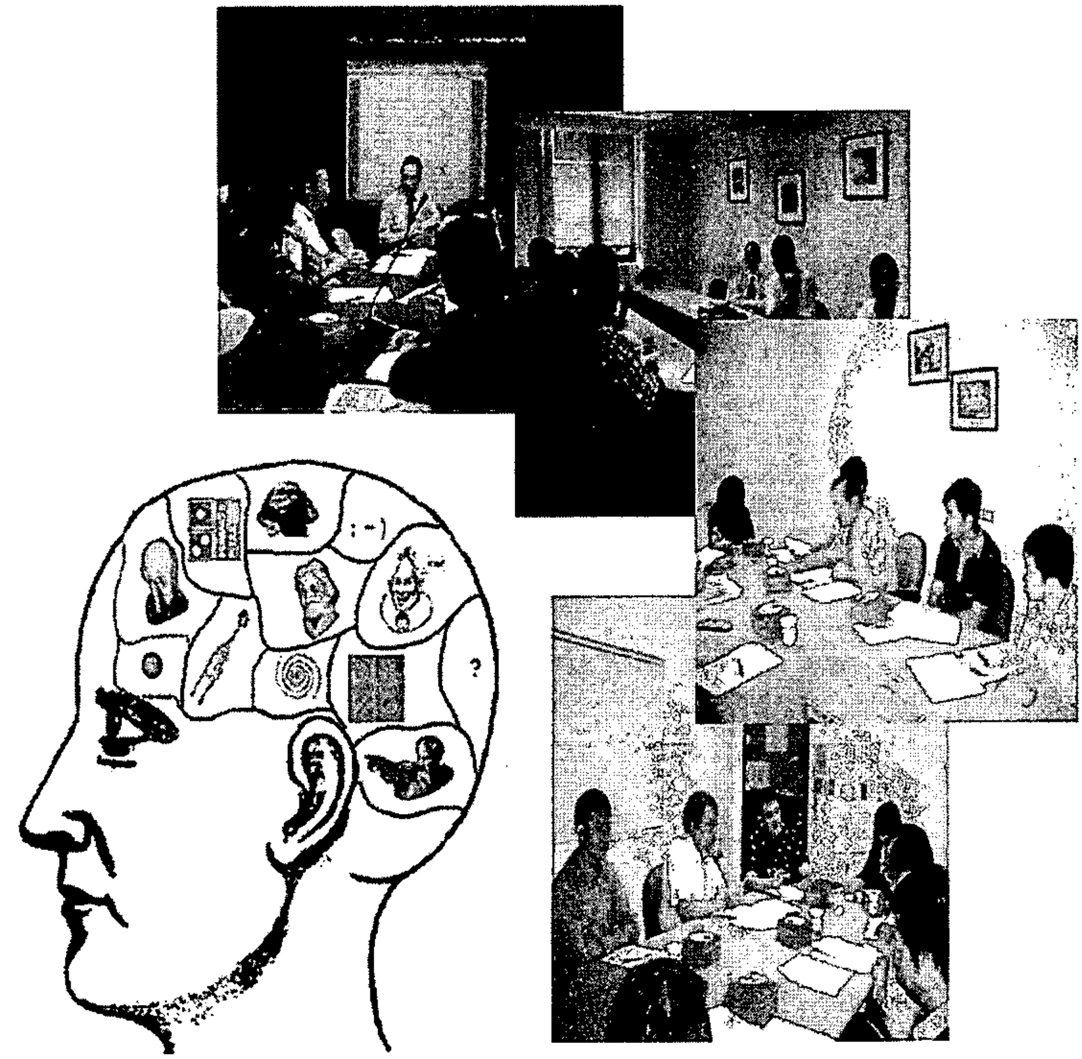
附錄九

台灣版---嚴重頭部外傷治療共識研討會



日期:95年9月23日
時間:上午10:00am~12:00am
地點:台北市立萬芳醫院五樓第三會議室

研 討 會 議 程 表

座長：邱文達/ 黃勝堅　　萬芳醫院 / 台大醫院

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- 急診處置 (Management in ER)　　評論者:張丞圭 / 紀煥庭

  Dr. 徐文星 (8 minutes)，林口長庚醫院

- 顱內壓監測 (ICP Monitor)　　評論者:蔡明達 / 龔瑞琛

  Dr. 于國藩 (8 minutes)，光田綜合醫院

- 腦灌流壓與輸液之原則

  (CPP and Fluid Management)　　評論者:徐文星

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- 鎮定劑之使用 (Sedation)　　評論者:邱文達 / 蔡行瀚

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  Dr. 陳婉琳 (8 minutes)，台北市立聯合醫院仁愛院區

- 顱內壓上升之處置

  (Management of Intracranial Hypertension)　　評論者:于國藩

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- 癲癇之預防治療 (Seizure Prophylaxis)　　評論者:黃勝堅 / 周啟文

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- 二線療法 (Second Tier Therapy)　　評論者:鍾文裕 / 邱正迪

  Dr. 張宏昌 (8 minutes)，馬偕醫院台東分院

- 結語 (Conclusion)

  Dr. 黃勝堅 (5 minutes)，台大醫院

台灣版--嚴重頭部外傷治療共識

邱文達 黃勝堅

前言

意外事故在台灣仍然是重要的死因，頭部外傷雖然在安全帽法實施後大量減少，然而嚴重頭部外傷發生後之死亡率仍然高達35%，如何使嚴重頭部外傷發生後得到最好的照顧實為當務之急。嚴重頭部外傷治療之進步，實有賴於國內神經外科專家學者共同努力建立台灣本土嚴重頭部外傷的治療共識。除了急診救護體系的進步與配合，加護照顧在治療嚴重頭部外傷的角色日趨重要，縱使已接受手術治療的頭部外傷病人仍需要嚴密的加護病房照顧。有關的理論最近二、三十年來有相當大的改變。1970 年代以來，如何控制顱內壓一直被認為是神經加護照顧治療嚴重頭部外傷的重點。近年來，由於對顱內壓升高的病理生理機制及腦部循環動力學的了解，相關的治療已有相當大的改變。以往將治療的目標專注在處理顱內壓升高，例如: 限水(fluid restriction)、高張利尿劑(mannitol、glycerol)、過度通氣(hyperventilation)及類固醇等使用均被重新再評估。主要的改變是因腦部監測(cerebral monitoring)技術的進步以及預防腦部缺血為(ischemia)概念的發展。目前腦部重症加護照顧的中心目標已經由顱內壓的控制轉為缺血的預防。因此，除了降低顱內壓之外，如何提升腦部的灌流(cerebral perfusion)及降低腦部代謝以避免缺血，已成為另一注意的焦點。

在嚴重頭部外傷的神經加護照顧中，主要面對的問題是二度傷害(secondary injury)其中包括全身性的二度傷害，如低血壓(hypotension)、缺氧(hypoxia)及 感染發燒等。尤其是頭部外傷常發生合併其他部位外傷。其中又以低血壓對不良的預後影響最大。腦部的二度傷害，如、腦部缺血、顱內壓升高(intracranial hypertention)、

腦水腫(brain edema)、血管痙攣(vasospasm)及癲癇的發作(seizure)等。所有的二度傷害都直接或間接造成腦部缺血，因此如何監測及預防二度傷害的發生，以避免腦部缺血便成神經加護照顧中最主要的工作。

美國神經外科醫學會(American Association of Neurological surgeons)與腦外傷基金會，於 1995 及 2000 年發表了嚴重頭部外傷處理之指引(Guidelines for the management of severe head injury)，我們將參考國外學者及台灣專家學者之意見，特別針對有關嚴重頭部外傷神經加護照顧當中重要的觀念，其包括急診之處理原則、顱內壓監測、顱內壓升高的處理原則、腦灌流、過度通氣、癲癇大發作之預防、營養及二線療法等加以討論說明。

本研究獲國家衛生研究院研究計畫 **(NHRI-EX95-9106PN)**之支助，並感謝來自台灣北、中、南、東區醫學中心、區域醫院等之神經外科訓練中心之專家學者。熱心的參與者共有：洪慶章、蔡行瀚、林天仁、蔣明富、張丞圭、張坤權、陳子勇、林子淦、蔡明達、鄭澄懋、鐘文裕、邱正迪、許育弘、廖國興、蕭勝煌、陳琬琳、陳怡龍、王有智、楊大羽、周啟文、于國藩、紀煥庭、龔瑞琛、洪國盛、黃旭霖、李明陽、王國瑋、許書雄、張宏昌、林家瑋、林乾閔、黃勝堅及邱文達等。這些專家學者放棄休假，在百忙中參與無數次的整合共識及修訂會議，終於完成台灣版輕度及嚴重頭部外傷的治療準則（共識)。他們對台灣神經外科界及國家社會的貢獻是無可限量的。同時也祈望各界先進，能給予批評與指正。

拾壹、本年度之著作抽印本或手稿

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Trauma

Head injuries in adolescents in Taiwan: a comparison between urban and rural groups

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Abstract

Background: Data pertaining to head injuries in adolescents in Taiwan are scarce. The purpose of this study was to investigate the trend and pattern of head injuries in adolescents in both urban and rural areas in Taiwan.

Methods: We collected data from major hospitals in the urban (20) and in the rural (4) areas of Taiwan for a period of 3 years. Data were obtained from the Head Injury Registry, a 10-year electronic database of head injury in Taiwan. The inpatient medical records of adolescents with head injury were thoroughly reviewed. Severity of head injury was classified by the GCS score, and patient outcome at discharge from hospital was measured by the Glasgow Outcome Scale. Differences and correlation between study groups (13-15 and 16-18 years old) in the urban and rural areas were examined using 2-tailed t and χ^2 tests.

Results: A total of 469 head injury cases in the urban area and 131 in the rural area were identified. Traffic accidents were the major cause of head injury, and motorcycles were the most predominant vehicles causing traffic accidents in both urban and rural areas. Intracranial hemorrhages were the most prevalent injury pattern in the study population. In both urban and rural areas, the severities of injury were not significantly different (P = .184), but the outcomes at discharge were significantly better in urban areas (P = .032). The correlation between the initial GCS and outcomes in both areas was significant (P < .001). Craniotomy was performed more frequently in the rural area than in the urban area (15.3% vs 7.2%). The mean hospital stay was shorter in the latter than in the former (P < .001). Education on helmet use, input of neurosurgical staff, and facility and emergency medical transportation service of head-injured patients following guidelines proposed by the WFNS are crucial for head injury and better control in rural areas.

Conclusions: The causes, patterns, and outcomes of head injury were statistically different between the 2 age groups of adolescents in urban and rural areas. Further studies on adolescent head injury are necessary.

Keywords: Adolescent; Glasgow Coma Scale; Glasgow Outcome Scale; Head injury; Helmet use law; Intracranial hemorrhage; Motorcycle

Abbreviations: EDH, epidural hematoma; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; ICHs, intracranial hemorrhages; JHS, junior high school; SAH, subarachnoid hemorrhage; SDH, subdural hematoma; SHS, senior high school; TBI, traumatic brain injury; WFNS, World Federation of Neurosurgical Societies.

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1. Introduction

Since 1989, patients with head injury have had a 10-fold higher mortality than those bluntly traumatized without head injury [15]. Head injury is the leading cause of death in accidents, and motorcycle-related traffic accidents compose the majority (71%) of accidents in Taiwan [3,5,9,12,13,20]. In the analysis of age groups with accident mortality, the 10- to 19-year age group had the highest mortality rate, especially in the 15- to 19-year age group [3,14,18,21,22]. As most victims of motorcycle-related head injuries were young, the resulting cognitive, psychological, and neurologic sequelae were overwhelmingly damaging to society [3]. How to prevent and control the mortality and morbidity of head injury in adolescents is therefore a challenging problem in Taiwan.

A long-term trend (1989-2000) showed that fatal head injuries in the age group from 15 to 20 years were decreasing [18]. On June 1, 1997, the helmet use law was implemented in Taiwan. Thereafter, the number of motorcycle-related head injuries and the severity of injury decreased, and better outcomes were obtained [3]. However, data regarding current status of head injuries in adolescents, especially the differences between urban and rural areas are lacking in Taiwan. Therefore, we conducted this study to investigate the distributions and patterns of head injuries in adolescents in both the urban and rural areas in Taiwan.

2. Materials and methods

2.1. Data collection

The data of patients with TBI in Taipei and Hualien were extracted from the Head Injury Registry. In the setting of the study, Taipei is defined as the urban area and Hualien County is defined as the rural area. These 2 areas differ in population density, the density and distribution of neurosurgical centers, manpower personnel, and facilities.

Taipei City is the capital of Taiwan. It covers an area of 271.8 km^2 and has a population of 2630000, with a population density of 9737/km^2. There are 20 major neurosurgical centers equally distributed throughout the whole city district. A board-certified neurosurgeon serves about 17533 people. It takes an average of 15 minutes to transport a patient with TBI by ambulance to a neurosurgical center.

Hualien County, located at the eastern part of Taiwan, is a mountainous area. The area of the county is 4638.6 km^2 (the largest county in Taiwan) and population is 400000; the population density is 133/km^2. There are only 4 neurosurgical centers in Hualien, all located downtown. A board-certified neurosurgeon serves about 26667 people in Hualien. However, the geographic limitations in Hualien make transportation of patients with TBI time-consuming. It takes, on average, more than 1 hour to transport patients with TBI from the periphery or hills to each center.

In this collaborative case-series study, data on adolescents (aged between 13 and 18 years) with head injuries were collected from July 1, 2001, to June 30, 2004. We divided the adolescents into 2 age groups, the 13- to 15-year group (JHS) and the 16- to 18-year group (SHS). Data were collected from 20 major hospitals in an urban area and 4 major hospitals in a rural area.

Data were also obtained from the Head Injury Registry, a 10-year electronic database with more than 100000 cases of head injury in Taiwan. The inpatient medical records of adolescents with head injury were thoroughly reviewed. Information pertaining to head injury including sex, age, GCS, cause and pattern of injury, presence of multiple systemic injuries, length of hospital stay, and GOS at discharge was analyzed. Diagnosis was made by brain computed tomography scans and skull x-rays to show various patterns of head injury: skull fracture, brain swelling/edema, and ICHs (epidural hematoma, subdural hematoma, ICH, subarachnoid hemorrhage).

2.2. Severity and outcomes

The severity of head injury was classified by the GCS score [11,19] as follows: (1) severe, score of 8 or below; (2)

Table 1
Demography of study adolescents in urban and rural areas

	Urban	Rural	P
No. of cases	469	131	
M:F	306:163 = 1.9	78:53 = 1.5	
JHS	127 (27.1)	46 (35.1)	
SHS	342 (72.9)	85 (64.9)	
Causes			<.001
Traffic	264 (56.3)	100 (76.3)	
Fall	81 (17.3)	8 (6.1)	
Assault	72 (15.4)	9 (6.9)	
Sports	26 (5.5)	3 (2.3)	
Traffic			.002
Motorcycle	163 (34.8)	78 (59.5)	
Bicycle	19 (4.1)	10 (7.6)	
Walking	32 (6.8)	32 (6.8)	
Rider	129 (27.5)	55 (42)	.025
Patterns			.011
Skull fracture	75 (16)	18 (13.7)	
Swelling	67 (14.3)	7 (5.3)	
ICHs	118 (25.2)	29 (22.1)	
Craniotomy	34 (7.2)	20 (15.3)	.011
GCS (JHS/SHS)			.184
3-8	30 (6.4) (8/22)	13 (9.9 (3/10)	
9-12	25 (5.3) (6/19)	12 (9.2) (6/6)	
13-15	414 (88.3) (113/301)	106 (80.9) (37/69)	
Outcomes and GCS score (severe/moderate/mild)			<.001
Dead	13 (2.8) (11/2/0)	7 (5.3) (6/1/0)	
Vegetative	3 (0.6) (2/1/0)	3 (2.3) (2/1/0)	
Dependent	7 (1.5) (4/2/1)	7 (5.3) (2/2/3)	
Independent	25 (5.3) (4/3/18)	8 (6.1) (1/3/4)	
Good	421 (89.8) (9/17/395)	106 (80.9) (2/5/99)	

Values are presented as n (%).

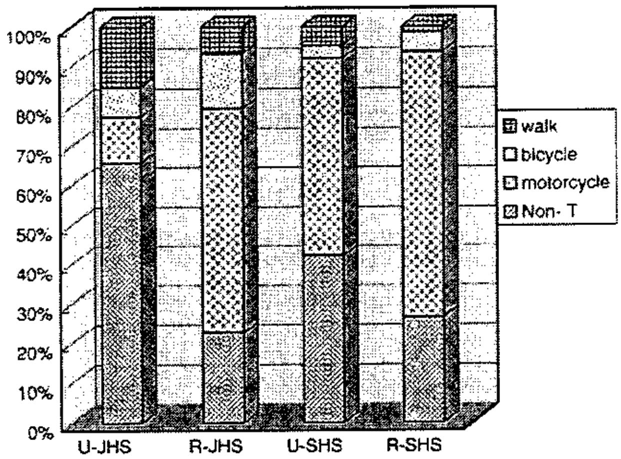

Fig. 1. Causes of head injury in groups (JHS, SHS) of adolescents in urban (U) and rural (R) areas. There were more motorcycle injuries in rural areas and nontraffic injuries in JHS groups of urban areas. Non-T indicates nontraffic.

moderate, score of 9 to 12, and the patient received neurosurgical intervention or had abnormal computed tomography scan findings; (3) mild, score of 13 to 15 or conditions not meeting any of the above criteria [3,9]. The GOS [10] was used to categorize the outcome of patients with head injury at the time of discharge from the hospital as follows: (1) death; (2) persistent vegetative state; (3) severe disability, conscious but dependent; (4) moderate disability, disabled but independent; (5) good recovery.

2.3. Statistical analysis

The incidence rates for head-injured adolescents were not calculated because the official statistics of the study population in both areas were not available. Differences and correlations between study groups and areas were examined by using 2-tailed t and χ^2 tests. A P value less than .05 was considered significant, and a P value between .05 and .10 was considered marginally significant.

3. Results

During the survey period, 469 adolescents (127 in JHS, 342 in SHS) with head injuries in the urban area and 131 (46 in JHS, 85 in SHS) in the rural area were identified. In the urban area, there were 306 (65%) teenaged boys and 163 (35%) girls with a male to female ratio of 1.9. In the rural area, there were 78 (60%) boys and 53 (40%) girls with a ratio of 1.5.

3.1. Causes of injury

In the urban area, the causes of injury included traffic accidents in 264 cases, falls in 81, assaults in 72, sports injuries in 26, falling objects in 3, and other causes in 23. In the rural area, the recorded accidents consisted of 100 traffic accidents, 11 hits by falling objects, 9 assaults, 8 falls, and 3 sports injuries. The differences in causes of head injury between the 2 areas were significantly different (P < .001). In the causes of traffic accidents, there were 163 (34.8%) cases caused by motorcycles, 32 (6.8%) while walking, and 19 (4.1%) caused by bicycles in the urban area. In the rural area, there were 78 (59.5%) by motorcycles, 10 (7.6%) by bicycles, and 4 (3.1%) by walking (Table 1). The difference in causes of traffic accidents between the 2 areas was also significant (P = .002). In the JHS and SHS groups of the urban area, causes of traffic accidents were 18 (14.2%) and 14 (4.1%) by walking, 14 (11%) and 149 (43.6%) by motorcycles, and 9 (7.1%) and 10 (2.9%) by bicycles, respectively (P < .001). In the rural area, the causes were 25 (54.3%) and 53 (62.4%) by motorcycles, 6 (13%) and 4 (4.7%) by bicycles, and 3 (6.5%) and 1 (1.2%) by walking for the JHS and SHS groups, respectively (P = .063) (Fig. 1 and Table 2). The causes of traffic accidents between the urban and rural areas in the groups were significantly different (P < .001) (Table 2). In the motorcycle-related traffic accidents, 129 (73%) and 55 (65%) cases were riders of motorcycles in the urban and rural areas, respectively (P = .025). There were 205 (43.7%) nontraffic injuries in the urban area and 31 (23.7%) in the rural area (P = .004) (Table 1).

3.2. Pattern of injury

The patterns of head injury were available in 55.5% of cases in the urban area, including 75 (16%) cases with skull fracture, 67 (14.3%) with brain swelling, and 118 (25.2%) with ICHs. In the rural area, 41% of cases had disclosed injury pattern, consisting of 18 (13.7%) skull fractures, 7 (5.3%) brain swellings, and 29 (22.1%) ICHs (Table 1 and

Table 2
Data in groups of adolescents

	JHS (age, 13-15 y)	SHS (age, 16-18 y)	P
Urban, n (%)	127 (27.1)	342 (72.9)	
Rural, n (%)	46 (35.1)	85 (64.9)	
Causes U/R			<.001
Motorcycle	14/25	149/53	
Bicycle	9/6	10/4	
Walk	18/3	14/1	
Patterns, U/R			.057
Skull fracture	20/6	55/12	
Swelling	22/5	45/2	
ICHs	23/10	95/19	
Severity, U/R			.111
GCS 3-8	8/3	22/10	
GCS 9-12	6/6	19/6	
GCS 13-15	113/37	301/69	
Outcome U/R			.170
Dead	4/2	9/5	
Vegetative	1/1	2/2	
Dependent	3/2	4/5	
Independent	8/5	17/3	
Good	115/38	306/68	
Craniotomy, U/R	16/7	18/13	<.001
Length of stay, U/R (d)	5.19/9.82	7.62/7.78	<.001

U indicates urban; R, rural.

Fig. 2). The difference in patterns of injury between both areas was statistically significant ($P = .011$). In the JHS and SHS groups in the urban area, the patterns of injury were as follows: 20 (15.7%) and 55 (16.1%) with skull fracture, 22 (17.3%) and 45 (13.2%) with brain swelling, and 23 (18.1%) and 95 (27.7%) with ICHs, respectively. In the rural area, the patterns in the JHS and SHS groups were as follows: 6 (13%) and 12 (14.1%) with skull fracture, 5 (10.9%) and 2 (2.4%) with brain swelling, and 10 (21.7%) and 19 (22.4%) with ICHs, respectively. The differences of injury patterns between the urban and rural areas in the groups were marginally significant ($P = .057$) (Table 2).

3.3. Associated injuries

There were 59 (46.5%) cases in the JHS and 198 (57.9%) cases in the SHS group in the urban area, and 19 (41.3%) cases in the JHS and 45 (52.9%) cases in the SHS group in the rural area sustaining associated injuries ($P = .437$). Cervical spine injuries were found in 1 case in the JHS and 2 cases in the SHS group in the urban area (0.6%), as well as in 2 cases in the JHS group in the rural area (1.5%).

3.4. Severity of injury (GCS) and outcomes (GOS)

During the study period, there were 30 severe, 25 moderate, and 414 mild head injuries reported in the urban area, and 13 severe, 12 moderate, and 106 mild head injuries in the rural area ($P = .184$) (Table 1). The outcomes at discharge were as follows: dead, 13 cases; vegetative, 3; dependent, 7; independent, 25; and good recovery, 421 in the urban area, and dead, 7 cases; vegetative, 3; dependent, 7; independent, 8; and good recovery, 106 in the rural area. The outcomes in the urban and rural areas were significantly different ($P = .032$) (Table 1). The initial GCS scores and outcomes in both areas had a significant correlation (higher GCS scores had better outcomes) ($P < .001$) (Table 1 and Fig. 3).

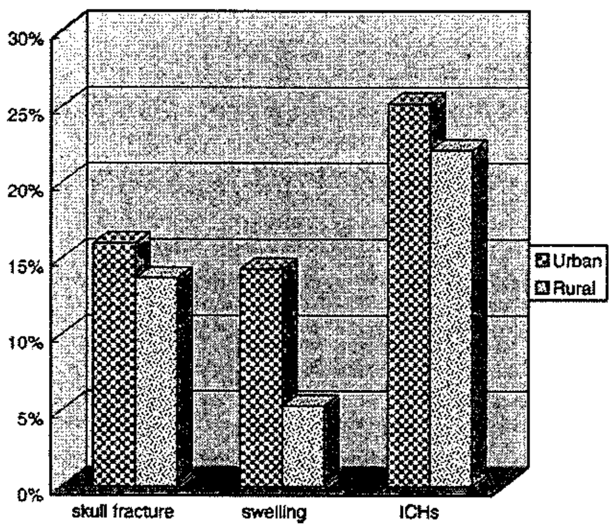

Fig. 2. Patterns of head injury in urban and rural areas. Lesions were more in urban areas and ICHs were the most prevalent lesions.

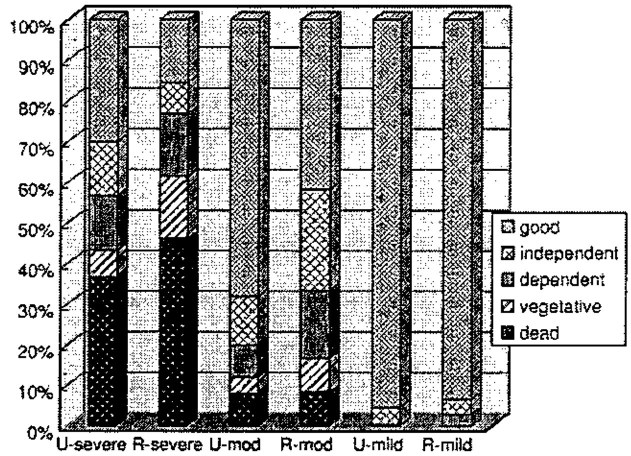

Fig. 3. Severity of head injury classified by GCS (severe, moderate, mild) and outcomes measured by GOS in urban (U) and rural (R) areas. The outcome was significantly affected by the severity of injury.

3.5. Age and GCS/GOS

In the urban area, there were 8 (6.3%) severe, 6 (4.7%) moderate, and 113 (89%) mild head injuries in the JHS group, and 22 (6.5%) severe, 19 (5.5%) moderate, and 301 (88.%) mild head injuries in the SHS group. In the rural area, 3 (6.5%) severe, 6 (13%) moderate, and 37 (80.4%) mild head injuries were found in the JHS group, and 10 (11.8%) severe, 6 (7.1%) moderate, and 69 (81.2%) mild head injuries in the SHS group. The severities in the groups of urban and rural areas were not statistically different ($P = .111$) (Table 2).

In the urban area, the outcomes were as follows: dead, 4 cases; vegetative, 1; dependent, 3; independent, 8; and good recovery, 115 in the JHS group, and dead, 9 cases; vegetative, 2; dependent, 4; independent, 17; and good recovery, 306 in the SHS group. In the rural area, the outcomes were as follows: dead, 2 cases; vegetative, 1; dependent, 2; independent, 5; and good recovery, 38 in the JHS group, and dead, 5 cases; vegetative, 2; dependent, 5; independent, 3; and good recovery, 68 in the SHS group. The outcomes of the groups in both areas were not statistically different ($P = .170$) (Table 2).

3.6. Craniotomy and hospital stay

There were 34 cases (7.2%; 16 cases in JHS and 18 in SHS) in the urban area and 20 cases (15.3%, 7 cases in JHS and 13 in SHS) in the rural area who underwent craniotomy during the study period ($P < .011$) (Tables 1 and 2). The mean length of hospital stay in the urban area was 5.19 days in the JHS group and 7.62 days in the SHS group. In the rural area, the mean length was 9.82 days in the JHS group and 7.78 days in the SHS group ($P < .001$) (Table 2).

4. Discussion

The head injury rate in Taiwan is still very high [9,12,20]. It was reported that the incidence rate was near

2-fold higher in the rural area than in the urban area [3,9,12,20]. After the enactment of preventive policies, the incidence rate and mortality from head injury decreased in various countries [3,15,21]. Therefore, we conducted this study to examine the head injury rate of adolescents in both urban and rural areas in Taiwan after the helmet use law was enforced. The accurate incidence rates of head injuries in this study could not be calculated because a suitable denominator (the size of the study population) was not available during the study period. However, by a rough estimation, the adolescents in the rural area had a higher incidence rate than those in the urban area (data not shown). This estimation is consistent with the report of Woodward et al [21]. We also found that males had more head injuries than females, a finding similar to the results of other studies [2,3,6,9,12,13,22].

4.1. Cause and pattern of injury

Traffic accidents are the leading cause of head injury [2,4,6,9,22], and motorcycle-related injury is the major etiology [5,7,9,12,13]. In this study, motorcycle-related injury was the principal etiology for head injury in both groups of the rural area and in the SHS group of the urban area. In the JHS group of the urban area, nontraffic injury was the major cause of head injury.

Lesions were found more frequently in the urban (55.5%) than in the rural (44%) area. Skull fracture and impaired consciousness were important indices in determining the risk of developing surgically significant intracranial hematomas [1,8]. ICHs were the major pattern of injury in both areas (Table 1 and Fig. 2). In the urban area, the SHS group had more ICHs than the JHS group (Table 2). More injuries with ICHs indicated that the higher severity of injury was caused by motorcycles in the SHS group.

4.2. Associated injuries

There were more associated injuries among the SHS than in the JHS groups in both areas, although not statistically significant. It could be due to more motorcycle-related injuries in the SHS group. According to the results of Chiu et al [3], the incidence rate of associated injuries decreased dramatically after the helmet use law was enforced (from 64.2%-72.2% to 41.3%-57.9%) [3]. In this study, cervical spine injury was found in only a few cases of the JHS groups in both areas. The incidence of cervical spine injury was also found to decrease in adolescents after the implementation of the helmet use law (from 2.6%-3.6% to 0.6%-1.5%) [3].

4.3. Severity (GCS) and outcomes (GOS)

There were more mild head injuries than severe ones in both urban and rural areas, although not statistically significant (Tables 1 and 2). The SHS groups in both areas had more cases with severe head injuries (Table 2) [22]. The distributions of injury severity in the urban and rural areas were similar to those of other studies [9,12,13,18].

The outcomes at discharge were significantly different between the urban and rural areas (P = .032) (Table 1). The initial GCS scores and outcomes in both areas were also different (Table 1 and Fig. 3). The outcome was significantly affected by the injury severity. Education on helmet use, input of neurosurgical staff, and facility and emergency medical transportation service of patients with head injury were crucial for head injury and control in rural areas [2,9,12,20].

4.4. Operation and hospital stay

It is reported that the incidence of neurosurgical intervention in head injury ranges between 2.5% and 23.7% [2,3,14,22]. In this study, craniotomy in the rural group was more than 2-fold higher than that in the urban group (15.3% vs 7.2%). The length of hospital stay was longer in the rural group (7.78-9.82 days) than in the urban group (5.19-7.62 days) [21]. The mean length of hospital stay was 10.2 days before the enforcement of helmet use law in Taiwan and 8.7 days thereafter [3].

In both urban and rural areas, the referral pattern was the same and basically followed the criteria of neurosurgical consultation and admission proposed previously. However, because of the shortage of neurosurgeons in rural areas and longer distance of transportation, the outcomes may not be related to the referral pattern.

4.5. Study limitations

The exact incidence rates of head injuries in the study populations could not be derived. We used the tertiary hospital–based data, which might not reflect the overall head injury distributions in the study areas. Tertiary hospitals usually receive more seriously head injured patients referred from surrounding subsidiary hospitals [16].

Craniotomy was done more frequently in the rural group (urban, 7.2%; rural, 15.3%); even more severity was found in the urban group. The different numbers of subtypes of intracranial hemorrhages (acute EDH, SDH, contusion ICH) will result in different incidence of craniotomy between the 2 groups. In the urban group, quality of intensive care, medical and nursing staff, and the distribution of facilities may be the major factors resulting in fewer borderline craniotomies, on which lie difficulties in decision making.

4.6. Preventive strategies

The enactment of compulsory helmet and seat belt use laws has led to a decrease in head injuries and change in injury patterns worldwide [3,17,18]. The preventive strategies should be tailored to different age groups with diverse causes. The helmet use law for motorcyclists should be strongly enforced in the SHS age group in both the urban and rural areas. Regulations for bicycle helmet use and pedestrian traffic rules should be enacted, especially for the JHS groups in both areas. Adolescents are at increased risk especially for nontraffic injuries in the urban area. Urban factors associated with elevated injury rate include high traffic volume, frequency of walking, and paucity of off-street areas [6]. Community interventions, such as creation of safe playgrounds, traffic engineering improvement, traffic safety education, and supervision of activities for off-school time, may be effective in preventing traffic injuries in adolescents [6].

5. Conclusions

The difference in causes, patterns, and outcomes of head injury between the 2 age groups of adolescents disclosed the clinical significance of subdivision in adolescents into JHS and SHS groups. Continuing studies, enhanced community interventions, and additional preventive strategies are clearly needed.

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Trauma

Current experiences in the use of the severe head-injury guidelines in Taiwan

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Abstract

Background: Head injury is the leading cause of death and disability for patients who experienced a major accident. It has been suggested that a well-planned neurointensive care management can effectively reduce the secondary brain insults. The BTF and the AANS proposed the Guidelines for the Management of Severe Head Injury in 1995. The purpose of this study was to obtain a consensus on whether the guidelines are suitable for treating patients with severe head injury in Taiwan.

Methods: Data from patients with severe head injury were collected from 6 different medical centers in Taiwan. The methods for controlling ICP, CPP, and hyperventilation, and the medical treatment with vasopressors and sedatives have been analyzed.

Results: Ninety-four patients with severe head injury (GCS $\leqq 8$) were included in the study. The male-to-female ratio was 2.9:1. Mean age was 43.9 $\pm$ 21.8 years. The GOS score for those patients with ICP higher than 20 mm Hg that resulted in poor outcome was approximately 2.91 times ($P <$ .05) higher than that of patients with ICP lower than 20 mm Hg.

Conclusions: The most beneficial feature of the guidelines was the close control of ICP with an ICP monitor. Patients who received prophylactic sedatives had a favorable outcome (odds ratio, 2.8; CI, 1.0-7.5). There were no significant statistical differences between patients with and those without application of hyperventilation for maintenance of CPP.

Keywords: Severe head injury; Outcome; Guideline; Cerebral perfusion pressure; Intracranial pressure; Sedative; Hyperventilation

1. Background

Traumatic brain injury is the leading cause of death and disabilities among all trauma patients in Taiwan [7]. The mortality rate of head injury, however, dropped significantly with a 26.8% decrease from 1995 to 2001 [2,8,20]. One of the most important reasons for the sharp decline in the incidence of head injury was the implementation of the

Abbreviations: AANS, American Association of Neurological Surgeons; BTF, brain trauma foundation; CBF, cerebral blood flow; CI, confidence interval; CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; EVD, extraventricular drainage; GCS, glasgow coma scale; GOS, glasgow outcome scale; ICP, intracranial pressure; $PaCO_2$, arterial pressure of carbon dioxide; TBI, traumatic brain injury.

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Helmet Law in 1997. In addition, improvement in acute management of head-injury patients, as is the case also in other countries, undoubtedly played a crucial role.

In 1995, the BTF and AANS developed the Guidelines for the Management of Severe Head Injury [20]. These evidence-based guidelines give physicians and trauma centers effective protocols to improve the outcome of all brain-injury patients especially those with severe head injury. The guidelines are also expected to reduce the high economic costs, and much effort has been done to provide healthcare professionals, nationwide, with the guidelines for treating individuals with severe head injuries.

However, a survey performed by the Taiwan Neurosurgical Society showed that 90% of neurosurgeons have heard of the guidelines, but the compliance was only 40% in routine neurosurgical practice. Additionally, there has been a lack of studies concerning the management and evaluation of its outcome in severe head injury. In the present study, we reviewed the guidelines in view of the practicability of the original guidelines and the possibility of developing some evidence-based guidelines to suit Taiwan's situation with the aid of our databank.

2. Materials and methods

2.1. Inclusion and exclusion criteria

Eligible patients included were those aged 18 years or older, who had sustained a closed or penetrating head injury with a postresuscitation GCS score of 3 to 8 and who required mechanical ventilation and ICP monitoring. Patients were excluded from the study if they had been lost to follow-up at 6 months after the injury.

2.2. Patient management

All patients were admitted to the neurointensive care unit after initial stabilization or emergent operation for evacuation of intracranial hematoma. Patient management was in accordance with the Guidelines for the Management of Severe Head Injury and included a stepwise algorithm for ICP and CPP control. For agitated patients, sedation was achieved by optionally using 1% propofol 5 to 15 mL/h, fentanyl (0.5 mg/10 mL per 1 amp), lorazepam (2 mg/1 mL per 1 amp), and midazolam (5 mg/1 mL per 1 amp) prn. Intracranial pressure monitoring was performed, and attempts were made to keep ICP lower than 20 mm Hg using various measures such as the following (schedule outlined in Table 1): (1) muscle paralysis with pancuronium and sedation; (2) drainage of CSF; (3) administration of osmotic diuretics; (4) hyperventilation to keep Pa_{CO_2} lower than 20 mm Hg. Cerebral perfusion pressure was maintained with the use of an intravascular volume expander and vasopressors. We divided the CPP value on the first day of admission into 2 groups—CPP less than 70 mm Hg and CCP higher than 70 mm Hg—and compared the outcomes between the 2 groups.

2.3. Data collection and statistical analysis

Data of the patients included basic demographic characteristics, use of ICP monitoring, ICP value, CPP value, partial pressure of CO_2 in arterial blood (Pa_{CO_2}), and sedative use. Outcome was evaluated with the 5-point GOS. Outcome analysis was performed by using the GOS score at the 6-month follow-up and was modified with special reference to favorable (score defined as 4-5) and unfavorable outcome (score defined as 1-3). Basic data were given as frequency and percentage. Hemodynamic and biologic parameters were compared using unpaired Student t test for between-groups comparison. We compared the differences between categorical variables and patients' outcomes using the χ^2 test. Logistic regression was used for analysis of correlation. A P value < .05 was considered statistically significant.

Table 1
Analysis of sex, age, severity, and treatment methods vs outcome of patients

	Good outcome	Poor outcome	*P*
Sex			.074
Male	23 (33.3%)	46 (66.7%)	
Female	13 (52.0%)	12 (48.0%)	
Age			.010
<40	24 (51.1%)	23 (48.9%)	
>40	12 (25.5%)	35 (74.5%)	
GCS			.004
4-5 points	4 (18.2%)	18 (81.8%)	
6-7 points	21 (55.3%)	17 (44.7%)	
ICP monitor			.124
Yes	21 (44.7%)	26 (55.3%)	
No	15 (30.4%)	32 (69.6%)	
ICP value 1st day			.047
<20 mm Hg	15 (55.5%)	12 (44.5%)	
≥20 mm Hg	6 (30.0%)	14 (70.0%)	
ICP average value of the initial 3 d			.025
<20 mm Hg	16 (55.1%)	13 (44.9%)	
≥20 mm Hg	5 (27.7%)	13 (72.3%)	
CPP			.036
Yes	21 (50.0%)	21 (50.0%)	
No	15 (28.8%)	37 (71.2%)	
CPP value 1st day			.547
>70 mm Hg	10 (50.0%)	10 (50.0%)	
≤70 mm Hg	3 (37.5%)	5 (62.5%)	
CPP average value of the initial 3 d			.267
>70 mm Hg	2 (28.6%)	5 (71.4%)	
≤70 mm Hg	11 (52.4%)	10 (47.6%)	
Sedation*			.014
Yes	23 (50.0%)	23 (50.0%)	
No	12 (25.5%)	35 (74.5%)	
Pa_{CO_2} 1st day			.307
25 ± 2 mm Hg	3 (23.1%)	10 (76.9%)	
35 ± 2 mm Hg	8 (40.0%)	12 (60.0%)	

* ICP-oriented sedation schedule. One percent Propofol 5-15 mL/h; Fentanyl 1 amp/5 mL N/S (optional); Lorazepam (2 mg/1 mL per 1 ample) (optional); Midazolam (5 mg/1 mL per 1 ample) (optional).

3. Results

A total of 135 patients were recruited between January 1, 2003, and June 31, 2003, from 6 large hospitals, each with a qualified neurosurgical training center (National Taiwan University Hospital, Taipei Medical University Wan Fang Hospital, Mackay Memorial Hospital, Chang-Hua Christian Hospital, National Cheng-Kung University Hospital, and Chi-Mei Hospital). Forty-one patients were excluded from this study because they showed no vital signs at the time of arrival in the emergency room or after cardiopulmonary resuscitation for more than 30 minutes. Therefore, only 94 patients with severe head injury were included in this study.

The male-to-female sex ratio of the patients was 2.9:1. The mean age of the patients was 43.9 ± 21.8 years with the majority being 20 to 29 years old (23.4%). Emergency craniotomy and evacuation of hemorrhagic mass lesions were performed in 65 patients (69.1%). The main mass lesion consisted of 30 subdural hematomas (46.2%), 15 epidural hematomas (23.1%), and 20 intracranial hematomas (30.7%). The mean time from the onset of injury to emergency craniotomy and evacuation was 8.4 ± 11.2 hours. Primary craniectomy (ie, leaving the cranium off at the end of the operation) was performed in 13 operated patients (20%). Five patients (7%) underwent delayed hemicraniectomy for intractable intracranial hypertension. The mean time from the onset of injury to delayed hemicraniectomy was 27.2 ± 15.3 hours. Forty-seven patients (51.0%) received an ICP monitoring procedure. Cerebral perfusion pressure values were recorded in 42 patients (44.7%). $PaCO_2$ values were recorded in 87 patients (93.5%), and 46 patients (49.5%) received sedation during their ICU stay. The data on the patients and methods of treatment are summarized in Tables 1 and 2.

Patients older than 40 years had a poorer outcome than those younger than 40 (P = .010). The outcome of patients with initial GCS scores of 6 to 7 was significantly better than that of patients with lower GCS scores (P = .004). Patients with ICP higher than 20 mm Hg on the first day of admission had a poorer outcome. Further analysis was performed by averaging the ICP on the first 3 days. The patients with ICP higher than 20 mm Hg had a poorer outcome than those with a lower ICP (P = .025). The outcomes of these 2 groups were not statistically different. The correlation between the average value for 3 days of CPP and the patients' outcome was not statistically significant. The study showed that patients receiving sedatives tended to have a better outcome. The difference in outcome between patients with $PaCO_2$ data of 35 ± 2 mm Hg and those with $PaCO_2$ data of 25 ± 2 mm Hg was not significant.

We used a logistic regression model and found that patients with ICP of 20 mm Hg or higher had a 2.91-fold poorer outcome (95% CI, 0.8-9.9). After modifying the age variable, the risk ratio decreased to 3.02-fold (95% CI, 0.8-11). Patients not receiving prophylactic sedatives were 2.9 times more likely to have a poorer outcome than those who received sedatives. When adjusted to the ICP variable, the risk ratio rose to 7.6 (95% CI, 1.1-54.7) (Table 2).

Table 2
Logistic regression analysis of patients' ICP value vs outcome

		Odds ratio[a]	95% CI	Odds ratio	95% CI
ICP Value	≤20 mm Hg	1		1	
	>20 mm Hg	2.91	0.8-9.9	3.02[b]	0.8-11.0
Sedatives	Used	1		1	
	Not used	2.9	1.2-7.0	7.6[c]	1.1-54.7

[a] Crude odds ratio.
[b] Odds ratio postadjusted age.
[c] Odds ratio postadjusted ICP.

4. Discussion

Traumatic brain injury is a major public health concern in Taiwan. The implementation of the Helmet Law in 1997 led to a significant reduction in mortality from 53% to 38% [7]. The benefits for patients who received care according to the BTF guidelines remained unclear in many countries. This is the first report in Taiwan to evaluate the significance and contribution of the BTF's guidelines with collaborative study at multiple centers.

4.1. Intracranial pressure

Intracranial pressure should usually be controlled between 15 and 20 mm Hg [4,5,28]. The guidelines recommend that ICP treatment should be initiated at an upper threshold of 20 to 25 mm Hg. In the present study, we found that patients with ICP lower than 20 mm Hg had a much better outcome than those with ICP higher than 20 mm Hg. The finding was comparable with those in most other large series. Monitoring of ICP is a valuable procedure in the treatment of patients, although this procedure has an infection risk rate of 4.7% to 10.3% [9,15,24,25]. Concerning the cost of ICP monitoring, only the Taiwan National Health Insurance reimburses the expenses for EVD.

The clinical course, score of GCS, and outcome expectation are key factors in determining whether to have surgical treatment such as craniectomy, removal of ICH, ventriculostomy, and insertion of ICP monitor. All the patients should also accept medical treatment for ICP control for the possibility of delayed brain edema.

4.2. Cerebral perfusion pressure

Cerebral ischemia is one of the most important secondary insults affecting outcome after severe TBI. In the study of Changaris et al [6], all severe head-injury patients died when the reading of the CPP was lower than 60 mm Hg, and patients usually had a better outcome when their CPP reading was higher than 80 mm Hg [12]. In their study, the CPP values were the patients' original values, which were obtained without the use of vasopressors. However, in this study, the CPP values were obtained after vasopressor use. Systemic complications were found when vasopressors were used to maintain CPP of greater than 70 mm Hg. Vasopressor use offsets the benefits of decreasing secondary damage to the brain tissues. In most cases, CPP is amenable to clinical manipulation. A randomized prospective trial is needed to elucidate the effects of CPP enhancement on avoiding global and focal ischemia. Data collections on systemic complications were not carried out in this study. The CPP value on patients' outcome has yet to be determined.

4.3. Sedation

Marshall et al [16] demonstrated that when traditional treatments (including osmotic diuretics use and hyperventilation) failed to lower ICP, there would still be about three fourths of patients who would be suitable for receiving high doses of barbiturates to lower ICP and would have a good outcome [3]. They also believed that barbiturates might be beneficial in treating malignant intracranial hypertension. In contrast, Ward et al [29] found that barbiturates were ineffective in reducing ICP and might cause complications [1,13,29]. It is not recommended to use sedatives routinely for patients with severe head injury. Barbiturates are reserved for second-tier treatment in patients with malignant intracranial hypertension [23]. The present study found that prophylactic use of sedatives in patients with severe head injury resulted in better outcome ($P < .001$). We used propofol in the sedation regimen and a number of studies suggested that long-term use of propofol would improve patients' outcome [14,21]. The mechanism of propofol in the human body is unclear, but many studies have demonstrated that propofol has a neuroprotective effect [17]. Although a barbiturate can reduce both the basic metabolic rate and oxygen consumption of the brain, it does not have any pronounced effects in removing free radicals and in inhibiting fatty peroxidation. In our laboratory, there is a prospective randomized controlled study going in progress which intends to compare the benefits of different regimens of sedation in severe head-injury patients. The preliminary results favor the effective use of Propofol in improving patients' outcome.

4.4. Hyperventilation

Aggressive hyperventilation has been a cornerstone in the management of severe TBI, but previous results clearly demonstrated that chronic prolonged hyperventilation resulted in vasoconstriction, which reduced CBF [10,11,18,19]. The guidelines therefore recommend that prolonged hyperventilation should be avoided after severe TBI [22,26,27]. In this study, hyperventilation ($Pa{CO_2}$- 25 ± 2 mm Hg) did not affect the patients' initial outcome. Even when $Pa{CO_2}$ in arterial blood was "controlled" at 35 ± 2 mm Hg, the patients did not show any signs of improvement. Hyperventilation may affect the carbon dioxide value within the arterial blood and would affect ICP and CBF, and, thus, is an important reference value for treating patients with severe head injury.

5. Conclusions

The findings in our study demonstrated that ICP monitoring contributed to a better patient outcome. However, CPP adjustment and use of vasopressors did not significantly improve the patients' outcome. The differences in hyperventilation threshold in ICP were not statistically significant. Prophylactic use of sedation resulted in a better outcome.

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Use of the WHOQOL-BREF for Evaluating Persons with Traumatic Brain Injury

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ABSTRACT

This study examined psychometric properties of a brief version of the World Health Organization Quality of Life questionnaire (WHOQOL-BREF) among persons with traumatic brain injury (TBI) and the relations of the WHOQOL-BREF domains, including physical capacity, psychological well-being, social relationships, and environment, to different indicators of TBI severity. Of the 354 eligible and available subjects from 22 hospitals in northern Taiwan over a 6-month period, 199 completed telephone interviews during data collection. Three indicators of TBI severity were used: the Glasgow Coma Scale, the presence of post-traumatic amnesia, and the abbreviated injury scale to the head. All domain scores of the WHOQOL-BREF had nearly symmetrical distributions: low percentages of ceiling and floor values (0 ~ 3%), low missing rates (0 ~ 0.5%) for all but one item (43.2%), and very good internal consistency (0.75 ~ 0.89) and test-retest reliability (0.74 ~ 0.95). The WHOQOL-BREF also exhibited excellent known-groups validity, as well as very good responsiveness and convergent validity with regard to employment, independence in daily life activities, social support, and depression. After adjustment for potential confounders, almost none of the domain scores of the WHOQOL-BREF significantly differed in the severity levels of the three severity indicators. In conclusion, the WHOQOL-BREF is an appropriate health-related quality of life (HRQL) instrument for persons with TBI. Furthermore, the initial severity of the TBI might not be suitable for predicting levels of HRQL in persons with TBI.

Key words: health-related quality of life; injury severity; reliability; traumatic brain injury; validity

INTRODUCTION

TRAUMATIC BRAIN INJURY (TBI) is a leading cause of death in both developed and developing countries (Frankowski, 1996; Lee, et al., 1990), and the economic impacts of TBIs are enormous; for instance, their costs in the United States were estimated to be $37.8 billion in 1985 (Max et al., 1991). More importantly, those people

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who survive TBI often sustain lifelong disabilities and face negative consequences in a variety of aspects of their health (O hanick, 1986). Accordingly, health-related quality of life (HRQL) measures, based on a person subjective appraisal of his/her own physical functioning, psychological functioning, and social interactions (Guyatt et al., 1993; Schipper et al., 1996), are appropriate for characterizing the impacts of these multiple consequences among persons with TBI. Furthermore, since clinicians and other health workers often underestimate the impacts of psychological aspects and emphasize the importance of the physical symptoms and signs among patients (Rothwell et al., 1997; Tennstedt et al., 1992), information on the HRQL can help identify the long-term needs for health care, as well as determine the success of healthcare programs among persons with TBI (van Baalen et al., 2003).

HRQL measures such as the Sickness Impact Profile (SIP) (Klonoff et al., 1986b; McLean et al., 1984; Temkin et al., 1988), the Short Form 36 (SF-36) (Findler et al., 2001; Mackenzie et al., 2002), and the Life Satisfaction Index-A (LSI-A) (Webb et al., 1995) have been applied to persons with TBI. More recently, the World Health Organization (WHO) cross culturally developed a short form of the WHO Quality of Life questionnaire (i.e., the WHOQOL-BREF), and defined HRQL as ndividuals□ perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns? (The WHOQOL Group, 1998). The use of this instrument for people with TBI seems to be promising in terms of its excellent validity and reliability among a variety of populations across many countries (WHO, 1996). However, its validation for persons with TBI has not yet been reported.

On the other hand, results for the relationship of the HRQL to TBI severity are inconsistent. Some studies reported that people with serious TBIs had lower HRQL scores than those with mild TBIs (Klonoff et al., 1986a; Kreuter et al., 1998); however, some reports recorded a reverse finding (Brown et al., 2000; Findler et al., 2001). There are several possible reasons to which these inconsistencies can be attributed. First, these studies used different indicators, including the Glasgow Coma Scale (GCS) (Teasdale and Jennet, 1974), the presence of post-traumatic amnesia, and the Abbreviated Injury Scale to the head (AIS-H) (AAAM, 1990), to evaluate the severity of TBI. However, the sensitivities of these indicators may differ considerably for HRQL scores. Furthermore, strong confounders, such as education level, alcohol consumption prior to the injury, and other variables in the relationship of TBI severity and HRQL scores, were not controlled in previous studies. Finally, the relationship of the severity of TBI and HRQL scores also depends on characteristics of the study sample; for example, scores for the HRQL tend to be more homogenous if persons with serious TBIs who have difficulty with verbal communication are not included (Johnston & Miklos, 2002).

This study examined psychometric properties of the WHOQOL-BREF in persons with TBI and determined the relations of severity indicators of TBI to four WHOQOL-BREF domain scores, with adjustment for potential confounders.

METHODS

Study Subjects and Procedures

Twenty-two hospitals in northern Taiwan, considered by the Head and Spinal Cord Research Group in Taiwan to have the ability to manage traumatic head injuries (Hung et al., 1992), were selected to recruit eligible subjects during a 6-month period from January 1 to June 30, 2002. Newly diagnosed traumatic brain injuries were identified by the presence among the discharge diagnoses of any of the following codes of the International Classification of Diseases, 9 rev. (ICD-9: 800 ~ 801.9, 803 ~ 804.9, and 850 ~ 854.9). In order to avoid double counting, patients transferred from other hospitals were excluded. In the 6-month period, 675 eligible subjects, including 173 with GCS scores at admission of 3? , 155 with scores of 9? 3, and 347 with scores of 14 or 15, were identified. The GCS scores were originally computed as the sum of coded values for three behavioral responses: eye opening, best verbal response, and best motor responses, with scores of 3 ~ 8, 9 ~ 12, and 13 ~ 15 indicating severe, moderate, and mild injuries, respectively (Teasdale and Jennet, 1974). However, it has recently been suggested to include patients with a GCS of 13 in the moderate head injury group, as their risk of complications is similar to that of patients with a GCS score of 9? 2 (WHO, 1980).

All patient information hone number, age, gender, education, time and cause of injury, alcohol consumption prior to injury (yes/no), post-traumatic amnesia (yes/no), GCS score at admission, and GOS score at discharge□ was extracted from hospital records. The phone number was used to conduct subsequent telephone interviews. The GOS is a 5-point scale: death, vegetative state, severe disability, moderate disability, and good recovery (Jennet and Bond, 1975). Additionally, by reviewing medical charts, an attending neurosurgeon computed AIS-H scores for these subjects. The AIS-H is a list of possible head injuries, with each patient assigned a severity value from 1 (minor) to 6 (fatal), based on a combination of anatomic lesions (location, size, and multiplicity) and impairment of consciousness (length of unconsciousness and nontransient neurological deficits) (AAAM, 1990).

Telephone interviews were also conducted with 354 subjects (when phone numbers were available) to collect information on marital status, employment, cognition, independence in activities of daily living (ADL), social support, depression, and the HRQL. Interview procedures and interviewer attitudes on the telephone were standardized through participation in a training course of 4 h duration. Among these subjects, 199 were interviewed, 85 had died, 17 survived in a vegetative state, and 53 declined to be interviewed. For the 321 subjects who could not be reached by existing phone numbers, their national identification numbers and names were used to search national mortality data from 2002 to 2003 in the Department of Health, Executive Yuan, ROC; 39 subjects were matched. Of the remaining subjects, 42 had incorrect phone numbers, 55 had no or disconnected phones, 4 were hospitalized, 79 had moved out of their original house, and 102 had no information available. For each of the subjects without information, five attempts were made to reach them, three at night and two during the day. A flow diagram of the study population is shown in Figure 1.

Compared to nonparticipants, the participants had higher GCS scores (13.3 vs. 12.0 points) and fewer associated injuries (45 vs. 55% being positive); however, no significant differences were detected respectively in other characteristics such as age at injury (47.2 vs. 43.2 years), gender (66 vs. 65% males), time since injury (1.1 vs. 1.0 years), and injury cause (55 vs. 58% motor vehicle crashes). This research was approved by the Institutional Review Board of Taipei Medical University, Taipei, Taiwan.

WHOQOL-BREF

As shown in the Appendix, the standard WHOQOL-BREF contains 26 items, 2 items from the overall quality of life and general health facet (Q1 and Q2) and 1 item from each of the remaining 24 health-related facets (The WHOQOL Group, 1998). The WHOQOL group defines a facet as a behavior (e.g., walking), a state of being (e.g., vitality), a capacity or potential (e.g., the ability to move around), or a subjective perception or experience (e.g., feeling pain). Specific facet definitions are specified in other WHOQOL publications (WHO, 1995). The 24 facets or items are further categorized into four domains: physical capacity (7 items), psychological well-being (6 items), social relationships (3 items), and environment (8 items). Specifically, Q3, Q4, Q10, and Q15 ~ Q18 are grouped into the physical domain; Q5 ~ Q7, Q11, Q19, and Q26 are grouped into the psychological domain; Q20 ~ Q22 are grouped into the social do-

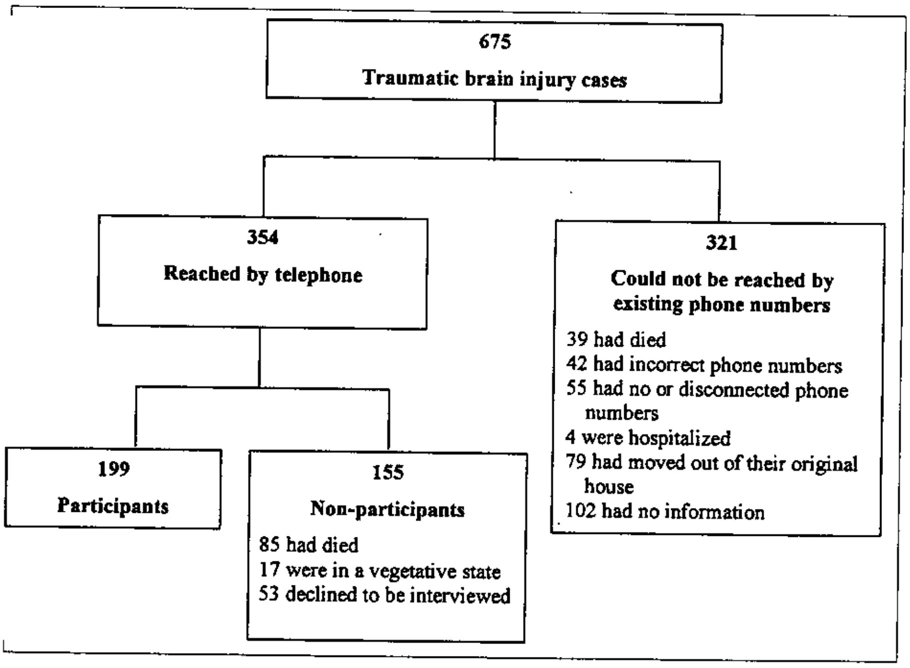

FIG. 1. Flow diagram of traumatic brain injury patients in this study.

main; and Q8, Q9, Q12 ~ Q14, and Q23 ~ Q25 are grouped into the environmental domain. Each item uses a scale from 1 to 5, with a higher score indicating a higher quality of life. Domain scores are calculated by multiplying the mean of all facet scores included in each domain by a factor of 4, and potential scores for each domain vary from 4 to 20 (e.g., score of social relationships = ((Q20 + Q21 + Q22)/3) × 4). The Taiwan version of the WHOQOL-BREF was developed in compliance with WHO guidelines on procedures of translation, as well as design and selection of appropriate items (WHO, 1994). The Taiwan version includes 26 items translated from the standard WHOQOL-BREF and two additional items of local importance (i.e., being respected and food availability); it showed very good reliabilities (including internal consistencies of 0.70 ~ 0.77 and test-retest reliabilities of 0.76 ~ 0.80) and validities (including content, criterion, discriminant, predictive, and construct validities) (Yao et al., 2002). In this study, the two local items were excluded from the analysis to facilitate potential future international comparisons; responses from the two items of the overall quality of life and general health facet were calculated as a single score with a range from 4 to 20, as each domain score.

Instruments for Cognition, ADL, Social Support, and Depression

To evaluate subjects? cognitive status over the telephone, the Telephone Interview of Cognitive Status (TICS) (Brandt et al., 1988; Breitner et al., 1990), a modified version of the traditional Mini-Mental State Examination items, was administered. This 13-item instrument includes the four domains of orientation, registration, calculation, and comprehension. TICS scores range from 0 to 50, with scores of 38 or lower indicating impaired cognition (de Jager et al., 2003).

The Barthel Index [Mahoney and Barthel, 1965] was used to assess functional independence in ADLs. The 10-item instrument includes self-feeding, getting in/out of bed, grooming, performing one toileting, bathing, walking, climbing stairs, self-dressing, and controlling the bowels and bladder. Items have different weights with two items rated on a 2-point scale (0 and 5), six items on a 3-point scale (0, 5, and 10), and two items on a 4-point scale (0, 5, 10, and 15). Scores of the instrument range from 0 to 100, with scores of 0 ~ 60, 61 ~ 90, and 91 ~ 100 indicating severe, moderate, and slight or no dependency, respectively (Shah et al., 1989).

The Social Support Survey (Sherbourne and Stewart, 1991), including the six domains of social network, tangible support, affection, positive social interaction, informational support, and emotional support, was used to evaluate social support. The open-ended item for social networks is not included in the calculation of the scale score, while the other 19 items are scored on 5-point scales. Scores of the instrument were rescaled to a 0? 00 range, with scores of 0 ~ 80 indicating a lack of social support.

The Center for Epidemiologic Studies Depression Scale (CES-D) consists of 20 items, emphasizing six affective components of a depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, psychomotor retardation, loss of appetite, and sleep disorders (Radolff, 1977). All items refer to the frequency of symptoms during the past week and are scored on 4-point scales. CES-D scores range from 0 to 60, with scores of 16 or more indicating depression (Weissman et al., 1977).

Score Distribution

The mean scores of the 26 items in the WHOQOL-BREF were calculated. The percentage of participants with missing values for each item and the distributions of minimum and maximum possible domain or facet scores (i.e., floor and ceiling values) were used to evaluate the difficulty of completion and the problematic score distribution, respectively.

Internal Consistency and Test-retest Reliability

Cronbach alpha (Cronbach, 1951) was used to examine the internal consistency of the four WHOQOL-BREF domains. Furthermore, a randomly stratified sample of 30 subjects by a 3-level severity of GCS (i.e., scores of 3 ~ 8, 9 ~ 13, and 14 ~ 15) was selected from the participants to assess the test-retest reliability over approximately 2 weeks. Intraclass correlation coefficients (Shrout and Fleiss, 1979) were calculated for the four domains.

Convergent Validity

To examine the convergence, correlations of certain WHOQOL-BREF domains with the GOS, Barthel Index, CES-D, and Social Support Survey were tested using Spearman correlation coefficient. It was assumed that those domains that are conceptually related would be relatively strongly correlated, whereas those domains with less in common would show weaker correlations. Accordingly, we hypothesized positive and moderate or high correlations ($r \geq 0.4$) between the following items: the WHOQOL-BREF physical capacity with the GOS and Barthel Index; the WHOQOL-BREF psychological well-being with the CES-D; and the WHOQOL-BREF psychological well-being and social relationships with the Social Support Survey.

Table 1. Sociodemographic and Injury Characteristics Among the 199 Subjects

Characteristic	*Mean ± SD*	*Percent (%)*
Age (y)	45.4 ± 20.3	
Time since injury (y)	1.0 ± 0.7	
Gender		
Male		64.3
Female		35.7
Education		
Elementary or below		26.8
High school		39.9
College or above		33.3
Marital status		
Single		40.2
Spouse present		42.8
Widowed/divorced		17.0
Employment status		
No		42.9
Yes		57.1
Cause of injury		
Motor vehicle crashes		58.1
Falls		26.3
Violence		7.1
Others		8.6
Alcohol consumption prior to injury		
No		70.7
Yes		19.3
Glasgow Coma Scale (GCS)		
3?		7.5
9? 3		22.6
14? 5		69.9
Abbreviated Injury Scale to the Head (AIS-H)		
1?		52.0
3?		35.7
5		12.2
Glasgow Outcome Scale (GOS) at discharge		
Severe disability		5.4
Moderate disability		9.7
Good recovery		84.9
TICS score[a]		
0? 8		25.6
39? 0		74.4
Barthel Index score		
0? 0		40.6
91? 00		59.5
Social Support Survey score		
0? 0		39.2
81? 00		60.8
CES-D score[b]		
0? 6		76.1
17? 0		23.9

[a]Telephone interview of cognitive status.
[b]Center for Epidemiologic Studies Despression Scale.

Known-groups Validity

The known-groups validity of the WHOQOL-BREF was also tested using Student *t* test or one-way analysis of variance (ANOVA) based on four characteristics, including employment, independence in ADLs, social support, and level of depression, known to influence health profiles among people with TBI (Johnston and Miklos, 2002; Webb et al., 1995; Zasler, 1997). For these characteristics, effect sizes were also calculated by the difference in each domain score between subgroups divided by the standard deviation of scores among all persons with TBI. Using Cohen criteria (Cohen, 1998), a clinically meaningful effect size of 0.2 ~ 0.5 was considered to be small, 0.5 ~ 0.8 moderate, and ≥0.8 large.

Responsiveness

Six months after the initial assessment, the WHOQOL-BREF was readministered to a random sample of 52 subjects selected from those who reported no employment at the time of the initial assessment. During the 6-month period, 10 out of these subjects had become employed. The responsive statistics for the four domains and the overall quality of life and general health facet were calculated by the difference in the mean change in scores for that domain from the initial to the follow-up assessment between subjects who had become employed and those who remained unemployed during the 6-month period divided by the standard deviation of score changes for the latter group (Guyatt et al., 1989). A similar clinically meaningful level of responsiveness was considered as with the criteria for discriminant validity.

Relation Between TBI Severity and the WHOQOL-BREF

A linear regression model was applied to determine the relations between each indicator of TBI severity and domain scores of the WHOQOL-BREF, with and without adjustment for confounders. There were three indicators of TBI severity in the study: the GCS, AIS-H, and posttraumatic amnesia. Domain or facet scores were also calculated and compared within levels for each of the TBI severity indicators.

Statistical Analysis Software, version 8.02 (SAS) was used to perform all statistical analyses.

RESULTS

The distributions of sociodemographic and injury characteristics are shown in Table 1. Of the 199 subjects, the means of age at injury and time since the injury were 45 and 1 year, respectively; 64.3% were male; and 19.3% had consumed alcohol consumption prior to being injured. For severity of TBI, 7.5% of these subjects had GCS scores of ≤8, 22.6% had scores of 9 ~ 13, and 69.6% had scores of 14 or 15. Approximately, 48.0% of subjects had AIS-H scores of 3 ~ 5, and 15.3% had GOS results indicating moderate-to-severe disability. Moreover, 25.6% of these subjects were cognitively impaired, 40.6% were dependent in ADLs, and 23.9% indicated depression. T1

As shown in Figure 2, scores of the 26 items of the WHOOL-BREF varied from 3.19 points for Q5 to 4.3 points for Q4. F2

As shown in Table 2, for each domain score in the WHOQOL-BREF, the median was close to the mean, in- T2

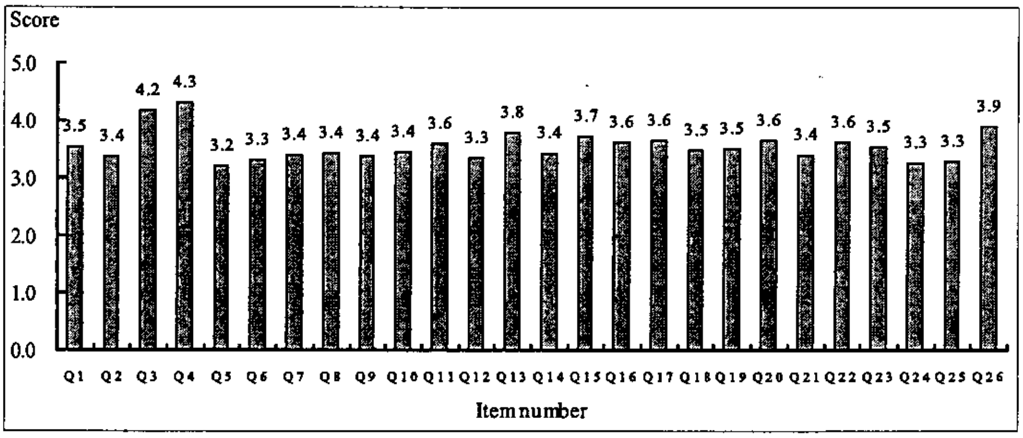

FIG. 2. Item scores of the WHOQOL-BREF.

TABLE 2. SCORE DISTRIBUTIONS, INTERNAL CONSISTENCY, AND TEST-RETEST RELIABILITIES OF THE WHOQOL-BREF DOMAINS

Domain/facet	*No. of items*	*Mean ± SD*	*Median*	*Min. (%)*	*Max. (%)*	*Missing range (%)*	*Cronbach α*	*Intraclass correlation*
OQL	2	13.8 ± 2.8	14.0	0.5	2.0	0.0? .0	0.75	0.87
PC	7	15.1 ± 2.7	15.4	0.0	2.5	0.0? .5	0.88	0.86
PW	6	13.9 ± 2.5	14.0	0.0	0.0	0.0? .5	0.89	0.95
SR	3	14.2 ± 2.5	14.7	0.5	3.0	0.0? 3.2	0.79	0.74
EN	8	13.7 ± 2.1	13.5	0.0	0.0	0.0? .5	0.82	0.90

OQL, overall quality of life and general health; PC, physical capacity; PW, psychological well-being; SR, social relationships; EN, environment.

dicating that the distributions of these domain scores were nearly symmetrical. Percentages of ceiling and floor values for each domain score were very low and varied from 0 to 3.0%. While the missing percentage for most items was 0, it was 43.2% for the sexual activity facet (Q21). Cronbach alpha coefficients varied from 0.75 to 0.89, and the intraclass correlation coefficients varied from 0.74 to 0.95.

For convergent validity, Spearman correlation coefficients were 0.53 and 0.31 between physical capacity and the GOS and the Barthel Index, respectively, −0.64 between psychological well-being and the CES-D, 0.52 between psychological well-being and the Social Support Survey, and 0.37 between social relationships and the Social Support Survey.

T3

Table 3 shows the results of the known-groups validity. Scores in all four domains and the overall quality of life and general health facet among subjects who were unemployed were dependent for daily activities, had weak social support, and indicated having depression were lower than those of their contrasting counterparts. Results other than those of the environmental domain of the Barthel Index were statistically significant. All effect sizes for discriminant ability were >0.2, and most of them were >0.5.

T4

As shown in Table 4, the effect size of the responsiveness in reference to employment status in the over-

TABLE 3. DISCRIMINANT ABILITY ANALYSIS FOR THE WHOQOL-BREF DOMAINS

Characteristic	*Statistic*	*OQL*	*PC*	*PW*	*SR*	*EN*
Employment status						
No	Mean	13.0	14.1	13.0	13.6	13.2
Yes	Mean	14.5	15.8	14.6	14.6	14.1
	p value	<0.001	<0.001	<0.001	<0.001	0.006
	Effect size	−0.53	−0.65	−0.62	−0.40	−0.70
Barthel Index						
0? 0	Mean	12.9	13.9	13.1	13.5	13.4
91? 00	Mean	14.5	15.8	14.4	14.6	13.9
	p value	<0.001	<0.001	<0.001	0.003	0.090
	Effect size	−0.57	−0.70	−0.52	−0.44	−0.24
Social Support Survey						
0? 0	Mean	13.3	14.7	13.5	13.8	13.2
81? 00	Mean	15.4	16.1	15.4	15.4	15.1
	p value	<0.001	<0.001	<0.001	<0.001	<0.001
	Effect size	−0.75	−0.52	−0.76	−0.64	−0.90
CES-D						
0? 6	Mean	14.2	15.7	14.4	14.3	14.0
17? 0	Mean	11.9	12.5	11.5	13.3	12.0
	p value	<0.001	<0.001	<0.001	0.034	<0.001
	Effect size	0.81	1.17	1.20	0.42	0.95

OQL, overall quality of life and general health; PC, physical capacity; PW, psychological well-being; SR, social relationships; EN, environment.

TABLE 4. RESPONSIVENESS OF EACH DOMAIN OF THE WHOQOL-BREF WITH RESPECT TO EMPLOYMENT STATUS

Domain/facet	Employed score change ± SD	Unemployed score change ± SD	Effect size
OQL[a]	1.60 ± 2.87	0.12 ± 3.00	0.49
PC	1.03 ± 2.61	0.38 ± 2.98	0.22
PW	0.27 ± 2.27	−0.93 ± 2.71	0.44
SR	0.07 ± 2.78	−0.30 ± 2.64	0.14
EN	1.00 ± 2.48	−0.55 ± 2.35	0.66

OQL, overall quality of life and general health; PC, physical capacity; PW, psychological well-being; SR, social relationships; EN, environment.

all quality of life and general health facet was 0.49. The effect sizes of physical capacity, psychological well-being, social relationships, and environment were 0.22, 0.44, 0.14, and 0.66, respectively.

T5 As shown in Table 5, the unadjusted scores of the overall quality of life and general health facet and each domain of the WHOQOL-BREF did not significantly differ in severity levels as indicated by the GCS, AIS-H, and post-traumatic amnesia. After adjustment for confounders, although the mean scores of the WHOQOL-BREF domains with regard to each indicator changed to some extent, the relationships between the three severity indicators and the four domains and the overall quality of life and general health facet of the WHOQOL-BREF remained similar.

DISCUSSION

Results of this study indicate that the WHOQOL-BREF is an appropriate HRQL instrument for persons with TBI, considering the nearly symmetrical score distribution, low proportions of floor and ceiling values, excellent known-groups validity, very good internal consistency and test-retest reliabilities, and good convergent validity and responsiveness. Minor modification of the

TABLE 5. RESULTS OF LINEAR REGRESSION MODELS FOR THE RELATION BETWEEN TBI SEVERITY AND THE WHOQOL-BREF WITH AND WITHOUT ADJUSTMENT FOR OTHER VARIABLES

Severity of TBI	Statistic	Unadjusted OQL	Unadjusted PC	Unadjusted PW	Unadjusted SR	Unadjusted EN	Adjusted OQL[a]	Adjusted PC[b]	Adjusted PW[c]	Adjusted SR[d]	Adjusted EN[e]
GCS											
3?	Mean	12.9	14.1	13.1	13.1	13.8	12.9	14.3	13.3	12.9	13.8
9? 3	Mean	14.0	15.3	14.1	14.1	13.8	14.3	16.0	14.7	14.2	13.9
14? 5	Mean	13.9	15.0	13.9	14.3	13.6	13.7	15.6	14.3	14.2	13.5
	p value	0.445	0.282	0.365	0.214	0.904	0.423	0.208	0.344	0.210	0.909
AIS-H											
1?	Mean	13.8	15.2	14.0	14.5	13.7	13.5	15.7	14.4	14.3	13.6
3?	Mean	14.0	15.0	13.9	14.1	13.8	14.1	15.7	14.4	14.2	13.9
5	Mean	13.4	14.9	13.8	13.1	13.5	13.6	15.2	14.2	13.1	13.6
	p value	0.713	0.829	0.901	0.051	0.855	0.676	0.844	0.923	0.050	0.849
Post-traumatic amnesia											
No	Mean	14.2	15.2	14.1	14.2	13.8	14.2	15.7	14.5	14.2	13.8
Yes	Mean	13.5	15.0	13.8	14.2	13.6	13.3	15.5	14.1	14.0	13.5
	p value	0.113	0.678	0.383	0.862	0.391	0.065	0.576	0.329	0.774	0.395

[a]Adjusted for education level.
[b]Adjusted for age, gender, education level, and alcohol consumption prior to injury.
[c]Adjusted for education and alcohol consumption prior to injury.
[d]Adjusted for education level.
[e]Adjusted for education level.

statement in Q21 might make it more appropriate for this patient population.

The high missing rates for Q21 reflects its sensitive nature, as well as problems related to sexual activities among persons with TBI; thus, statements for the item (ow satisfied are you with your sex life?? may need to be modified in order to improve the applicability of the WHOQOL-BREF for persons with TBI. To avoid a misunderstanding or an incorrect perception by subjects, the statement for Q21 could be revised to explicitly reflect its definition concerning a person urges and desires for sex. For instance, ow satisfied are you with your sex life, including intimate behavior other than sexual intercourse?? However, a substantial proportion of cancer patients in the United Kingdom (19%) and patients with chronic liver disease in The Netherlands (12 ~ 21.9%) did not answer questions about sexuality as well, while the missing value rates in the remaining items were <5% (Curran et al., 1998; 鉉 al et al., 2001). Hence, due to its sensitive nature, Q21 could possibly be replaced by another item in the social relationships domain of the full version of the 100-item WHOQOL questionnaire.

Spearman correlation coefficients of ≤0.4 between physical capacity and the Barthel Index and between social relationship and the Social Support Survey indicate that more-vigorous studies are needed to validate the convergent validity of the WHOQOL-BREF. The Barthel Index originally developed for severely ill patients may be insensitive for persons with TBI because of its limitation in scope and its inability to detect low levels of disability (McDowell and Newell, 1996), given that 54.8% of the subjects had maximum possible (100) points for the measure. The convergence of the three-item social relationships domain with the Social Support Survey may have been reduced by the high missing rates for Q21.

Only a few existing generic quality-of-life measures explicitly include the environment as an HRQL domain. However, the importance of the environment where people live has become recognized as relevant to a variety of health outcomes (Jackson, 2003). More recently, transportation, the surroundings, government policies, attitudes, and natural environments have been identified as environmental barriers, with the greatest impact on persons with TBI (Whiteneck et al., 2004). Nevertheless, addressing interactions among critical environmental variables and areas of deficits, such as cognitive impairment, can enhance adequate environmental modifications for maximizing the HRQL and reducing levels of handicap in persons with TBI.

AU2

Several investigators have considered adding a cognitive domain or related items to the existing HRQL measures such as the SIP and SF-36 to reflect neuropsychological impairment often evident in persons with TBI, which would improve the known-groups or discriminant validity and responsiveness of the generic HRQL (Berger et al., 1999; Mackenzie et al., 2002; Temkin et al., 1988). However, a modified version of the SIP, produced by adding 118 new items, did not show significant improvement in discrimination (Temkin et al., 1988), and the modification of the SF-36, by the addition of four new items relevant to cognitive functioning, remained poorly discriminative in the two summary scores for physical and mental health, despite the cognitive domain exhibiting very good discriminant ability (Mackenzie et al., 2002). Since the HRQL aspires to evaluate a person subjective feelings about different aspects of health associated with TBI and its sequelae, such as cognitive impairment impact, an independent cognitive domain for persons with TBI might not be necessary for a generic HRQL measure.

Some comments are required about the relationship of the HRQL with TBI severity. First, it should be noted that relations between the HRQL and TBI severity can be influenced by such factors as the nature of the severity indicator of TBI, sensitivity of the HRQL instruments, and the study sample. The nature of the severity indicators of TBI somewhat differs and may evaluate different aspects of TBI severity (e.g., the GCS assesses a subject level of consciousness, while the AIS-H characterizes anatomic damage). Differences in sensitivity (e.g., discrimination and responsiveness) among HRQL measures, such as the SIP, SF-36, LSI-A, and WHOQOL-BREF, may also affect the relationship between TBI severity and HRQL scores. A more-sensitive HRQL measure often has a stronger association with TBI severity. Also, the relation can be reduced because of lack of the full spectrum of TBI severity from the study sample (e.g., people who cannot communicate over the telephone are rarely included in HRQL studies). Second, the initial severity of TBI, often assessed at hospital admission, might not be appropriate for predicting levels of HRQL among persons with TBI, partly because the assessment can be confounded by some personal attributes such as alcohol consumption (Waller, 1988). Finally, the effect of the magnitude of these factors in the relation of the HRQL with TBI severity may differ in different domains of the HRQL.

Three limitations to this study need to be highlighted. First, it may be less valid to generalize these results to all people with TBI. Fewer people with severe TBI were available or willing to give information for the WHOQOL-BREF over the telephone, and their domain scores may have differed (e.g., people with severe disabilities are usually more dependent on environmental compensation and may be more sensitive to environmental barriers). Nevertheless, the internal consistency, test-retest reliability, and convergent and discriminant validities did not significantly differ between subjects who had GCS scores of ≤13 and those with GCS scores of ≥14 (data not shown). Second, differences in the domain scores of the WHOQOL-BREF regarding injury severity, employment status, independence in ADLs, social support, and so on can be confounded by one preinjury psychosocial status. In other words, people who are unemployed, dependent on others for ADLs, lacking social support, and depressed might tend to have more-severe TBI and vice versa. Finally, for the WHOQOL-BREF, the impact of the telephone-administered mode has not been validated by other modes of administration, even though the telephone interviews for other HRQL measures were reported to be comparable to personal interviews and self-administration (Leidy et al., 1999; Revicki et al., 1997).

Based on subjective evaluations of one position in life, the WHOQOL-BREF is one of the very few well-constructed generic HRQL instruments, and it can enhance our ability to examine the multiple consequences of TBI, monitor short- and long-term alterations in multiple dimensions of perceived health (particularly in environmental well-being), and prioritize interventions according to their impacts on the health dimensions of these patients. Furthermore, the cross-cultural WHOQOL-BREF may facilitate international comparisons of the HRQL in persons with TBI.

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APPENDIX. WHOQOL-BREF

Q1. How would you rate your quality of life?
Q2. How satisfied are you with your health?
Q3. To what extent do you feel that physical pain prevents you from doing what you need to do?
Q4. How much do you need any medical treatment to function in your daily life?
Q5. How much do you enjoy life?
Q6. To what extent do you feel your life to be meaningful?
Q7. How well are you able to concentrate?
Q8. How safe do you feel in your daily life?
Q9. How healthy is your physical environment?
Q10. Do you have enough energy for everyday life?
Q11. Are you able to accept your bodily appearance?
Q12. Have you enough money to meet your needs?
Q13. How available to you is the information that you need in your day-to-day life?
Q14. To what extent do you have the opportunity for leisure activities?
Q15. How well are you able to get around?
Q16. How satisfied are you with your sleep?
Q17. How satisfied are you with your ability to perform your daily living activities?
Q18. How satisfied are you with your capacity for work?
Q19. How satisfied are you with yourself?
Q20. How satisfied are you with your personal relationships?
Q21. How satisfied are you with your sex life?
Q22. How satisfied are you with the support you get from your friends?
Q23. How satisfied are you with the conditions of your living place?
Q24. How satisfied are you with your access to health services?
Q25. How satisfied are you with your transport?
Q26. How often do you have negative feelings such as blue mood, despair, anxiety, depression?

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WEN-TA CHIN

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Title: Clinical correlation between CT numbers and Nakaguchi classifications of chronic subdural hematoma

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Running title: Correlation of CT numbers and CSDHs

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Abstract

Background

Chronic subdural hematomas (CSDHs) were classified into homogenous, laminar, separated, and trabecular types based on their internal architecture and stage in the natural history of CSDH. The recurrence rate of CSDH ranges from 9 to 20 %. The purpose of this study is to establish a quantitative analysis of correlation between the CT number and recurrence rate of CSDH.

Methods

From Jun 2003 to Feb 2005, there were 28 consecutive patients with CSDH were treated. The CSDHs were classified into four groups: group 1- homogenous type, group 2 ? laminar type, group 3- separated type and group 4- trabecular type. The average CT number of CSDH was measured with an image analyzing software program (PACS, AGFA, Web-1000). In unilateral CSDH, the definitive CT number of hematoma was defined as an average of each slice. In bilateral CSDH, the CT number of each slice was defined as an average of both sides and the definitive CT number of bilateral CSDH was an average of the value of each respective slice. One-Way ANOVA with Scheff test was used for statistical analysis.

Results

The mean age of patients was 75.5 years. (Range: 53-91). The mean CT number of each group was: Homogenous type: 23.41 $\pm$ 4.85 HU, laminar type: 42.93 $\pm$1.26 HU, separated type: 61.04 $\pm$ 2.16 HU, trabecular type: 31.03 $\pm$ 4.32 HU. The homogenous type had the lowest CT number: (16.50-30.56 HU) among the four groups. The variance between each pair of groups was statistically significant (group 1 versus 2: $P < 0.001$) (group 1 versus 3: $P< 0.001$) (group 1 versus 4: < 0.001) (group 2 versus 3: $P< 0.001$) (group 3 versus 4: $P < 0.001$).

Conclusion

The separated type of CSDH showed highest CT number, which according to Nakaguchi, indicates the greatest tendency for recurrence.

Word count of abstract: 302

Key words: chronic subdural hematoma (CSDH), CT numbers, correlation, recurrence rate

Abbreviation list

ANOVA: ANalysis Of VAriance between groups

CSDH: Chronic subdural hematoma

PACS: Picture Archiving and Communication System

HU: Hounsfield unit

FDP: Fibrin degradation products

CI: Confidence interval

1. Background

Ever since Wepfer reported a case of chronic subdural hematoma (CSDH) in 1656 [18], there have been considerable advances in pathophysiology, diagnostic methods, and managements of CSDH. Many authors have dealt with the etiology of CSDH. However, controversies still exist even now with regard to the mechanism of recurrence of CSDH [4,7,9]. The factors which influence the recurrence are extremely valuable because CSDHs have a high recurrence rate ranging from 3 to 20%, even after burr-hole surgery [1,2,10-12]. Nakaguchi classified CSDHs into four types -homogenous, laminar, separated, and trabecular type according to their characteristics of the manifestations [14]. In the study of Nomura, the separated type showed the highest tendency to rebleed with considerable hyperfibrinolytic activity among four types [15]. Different types of CSDHs may be related to recurrence differently. In this study, we attempt to show that CT numbers are a useful diagnostic procedure as well as a useful parameter for the evaluation of the recurrence of CSDHs.

2.Methods

Patients

From Jun 2003 to Feb 2005, 28 consecutive patients with CSDHs were treated in this institution. Patients were collected using the system of PACS, AGFA, Web-1000. The patients with bilateral CSDHs consisting of different Nakaguchi types were excluded. Out of these 28 patients, 17 with marked neurological deficits underwent surgery (7: bilateral, 10: unilateral).

The operative methods included craniotomy and burr hole drainage on one side (for a unilateral CSDH) or both sides (for a bilateral CSDH). Only one burr hole was made on each symptomatic side.

Classifications of CSDH

For all the 28 cases, cranial CT studies were performed with parameters from the foramen to the vertex (3 mm slice thickness at the skull base region and 7 mm slice thickness at the convexity region). CSDHs were classified into four Nakaguchi types according to their morphological findings (Fig 1), namely, group 1- homogenous type: (7 cases), group 2- laminar type:(7 cases), group 3- separated type: (7 cases) and group 4- trabecular type: (7 cases).

Data processing

The average CT number [5] of CSDHs was measured with an image analyzing software program (PACS, AGFA, Web-1000). At each level of the axial view, the area of hematoma on the brain CT was encircled. The average CT number of the selected area was then calculated (Fig 2).

Definition for definitive CT number calculation

In cases of unilateral CSDHs, the definitive CT number of hematoma was defined as an average of each slice (each axial view). In cases of bilateral CSDHs, the CT number of each slice was an average of both sides and the definitive CT number of hematoma was an average

of the value of each respective slice. The algorithm was simplified as follows:

Unilateral CSDH: definitive CT number = average CT number of each slice

Bilateral CSDH: CT numbers of each slice (A) = average of both side

Definitive CT number = average of each A

Statistical methods

For statistical analysis, the brain CT image was used to measure the difference in the hematoma intensity by measuring the CT number. The CT numbers of the four groups of CSDHs in the 28 cases were examined by means of Oneway ANOVA. Statistical significance was taken as P < 0.001. If a significant overall difference was present, multiple comparisons were performed with Scheff test. Each average value was presented as mean 峠D.

3. Results

The ages of 28 patients ranged between 53 and 91 years (mean = 75.5). There were 22 males and 6 females. It is likely that the definitive CT numbers of the 28 patients, either unilateral or bilateral CSDHs, could be calculated by our designed algorithm. The basic data and the CT numbers of the 28 patients are listed in Table 1.

Analysis of CT numbers of CSDHs

The mean values of the CT numbers of the homogenous type (group 1), the laminar type (group 2), the separated type (group 3), and the trabecular type (group 4) are showed in Table 2. The separated type had the significantly highest average CT numbers (CT numbers: 57.81 ? 64.20 HU), followed by the laminar type (CT numbers: 41.18 - 44.16 HU). The trabecular type was the third (CT numbers: 25.67-37.11 HU). The homogenous type was the lowest among the four types. When the 95 % CI for the means of the four types were compared, the homogenous type had the widest range (18.92 to 27.91). The difference between each pair of groups was statistically significant (Table 2, P <0.001).

4. Discussion

According to the theory of Nakaguchi, the four types of CSDHs in his classification represent respective stages of the pathogenesis [14]. The four stages of CSDHs represent the initial formation (homogenous), development (laminar), mature (separated), and absorption (trabecular), respectively. The tendency for rebleeding of CSDHs depends on the balance between coagulative and fibrinolytic activity [6,15], which is the most active in the separated stage and most inactive in the trabecular stage. In the present study we evaluated the extent of the balance of coagulative and fibrinolytic activity using CT numbers, which represent the intensity of hematoma and indirectly evaluate the possibility for recurrence. The extent of the fibrinolytic and coagulative activity is proportional to the tendency for recurrence in different stages. Radiologically, the four types present different neuroradiological patterns with regard to intensity. It is likely that the extent of vascularity, fibrinolytic, and coagulative activity of subdural hematoma can be detected by means of the intensity of hematoma on a CT scan.

In our study, we quantified the intensity of a certain selected region by means of the CT number. In the homogenous stage, 95% CI for the mean was the widest of the four types (95% CI = 18.92 ? 27.91). In the development of CSDHs, the establishment of the outer and inner membranes around the subdural space was defined as the homogenous stage [16,19,20]. In the homogenous type, brain CT revealed low to high density [14]. The intensity (CT number) of the homogenous type ranged from low to high level. The laminar type had greater vascularity than the homogenous stage [3,4,14,16,17] and the brain CT revealed high density along the inner membrane [14]. The intensity of the laminar type was higher than the low-dense homogenous type because of greater vascular congestion [5, 21,22]. In general, as the subdural hematoma matures, the natural process moves to the separated stage. The separated stage is characterized with hyperfibrinolytic activity and is reactive in the activity of fibrin degradation products

(FDP) and plasminogen activators [14,17]. The brain CT in the separated stage reveals two components of different densities [14]. The intensity in the separated stage is the highest because of the highest cellularity and vigorous activity for fibrinolysis. The trabecular stage represents the resolution stage of CSDHs [5]. The brain CT reveals a high density septum running between the outer and inner membranes [14]. The intensity of the trabecular stage is the lowest because this stage is most steady.

In the present study, the intensity of hematoma ranged from hypodense to hyperdense in the homogenous stage. The wide distribution in CT numbers was unique of the homogenous stage. On the contrary, the CI in each of the other three stages was narrower than that of he homogenous stage. The mean CT number of the homogenous stage tended to be low because of wide distribution. In fact, mean CT number of the homogenous stage was the lowest among the four stages in our study (mean: 23.41 $\pm$ 4.85 HU). According to the result of Nakaguchi, the rebleeding tendency in the homogenous stage was moderate, not the lowest, among the four stages [13,14,19]. It is an exception to the ule? that the intensity in the homogenous stage is proportional to the rebleeding tendency.

In this study, the average CT number of the separated stage was the highest (mean = 61.04 $\pm$ 2.16 HU). The second was that of the laminar stage (mean = 42.93 $\pm$1.26 HU). If the homogenous type was disregarded, the trabecular stage was the lowest (mean = 31.03 ± 4.32 HU). It is then evident that the difference between the four types was statistically significant. (P<0.001). According to Nakaguchi study, the separated stage had the highest recurrence rate and the trabecular type had the lowest [14]. The laminar stage produced greater vascularity than homogenous type, producing a higher recurrence rate than the homogenous type [14,20]. In the study of Kurokawa et al, mixed high and low intensity in T2WI or low intensity in T1WI is the most predictable factor to show rapid aggravation for bilateral CSDH [6]. The correlation between CT numbers for the four stages and recurrence tendency in our study showed good agreement with the results of Nakaguchi study. It is therefore likely that the CT number can be used as a diagnostic tool to predict the tendency for recurrence.

In conclusion, our study established quantitative evidence by means of the CT number (intensity) for the evaluation of the natural pathogenetic process of CSDH. Patients with high average CT numbers, such as those of the separated type or high-dense homogenous type, should be watched more carefully both at admission and after operation because of the high recurrence rate reported in these patients.

5. Acknowledgements

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Trauma

Emergency air medical services for patients with head injury

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Abstract

Background: Patients suffering head injury in remote islands of Taiwan, which have a shortage of manpower and facilities, depend on EAMS for prompt and definitive treatment. Emergency air medical services are becoming an increasingly important issue in improving the quality of primary care and avoiding medicolegal problems. The purpose of this study was to investigate the characteristics of patients with head injury and use of EAMS.

Methods: We reviewed all patients, especially head injury victims transported by air ambulance from a remote island, Kinmen (400 km from Taiwan Main Island), from January 2001 to December 2003. Data were collected with regard to demographics, disease classification, mechanism of injury, severity of head injury, ventilator use, and mortality rate.

Results: A total of 215 patients were transferred, of whom 57 (27%) had head injury. The mean age of patients was 48.6 ± 23.8 years. Males accounted for 72% of the cases (male/female ratio, 2.6:1). Motor-vehicle accidents were the most common mechanism of injury (68%). There were 21 (37%), 20 (35%), and 16 (28%) patients in the minor, moderate, and severe head-injury groups, respectively. Nineteen patients (33%) received mechanical ventilation. The overall mortality rate was 14 % (8/57). In the severe head-injury group, the mortality rate was 44% (7/16).

Conclusions: The higher incidence of head injury (26.5%) in EAMS than in ground transportation (19.8%) suggests that preflight assessment and in-flight management of patients conducted by an experienced escort team following guidelines for head injury in EAMS are a very important issue.

Keywords: Head injury; Emergency air medical services; Ventilator; Remote island

1. Introduction

Traumatic brain injury is the leading cause of death and disability among all traumas in Taiwan [6,7]. Annually there are 200 cases of head injury per 100000 persons in the United States. The mortality rate of head injury in various countries ranges from 16.9% to 44% [4]. The mortality of head injury in Taiwan accounts for approximately 28% of all accidents [7]. As regards the incidence rate of head injury, Taiwan has a much higher rate than most other

Abbreviations: EAMS, emergency air medical service; EMS, emergency medical service; EMT-P, emergency medical technician-paramedic; GCS, glasgow coma scale; NTD, new Taiwan dollar; SOP, standard operating procedure.

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countries. One of the major reasons is that the motorcycle is the most popular transportation vehicle in Taiwan.

According to previous studies by this institute, the incidence rate of head injury in the offshore islands of Taiwan is much higher than that in most developed countries [8,15]. Management of patients with head injury in the offshore islands of Taiwan depends on EAMS because of geographic limitations. The area of this study focuses on Kinmen, an island 400 km away from Taiwan Main Island (Fig. 1). Kinmen is seperated by the Taiwan Strait and has a population of 58933 [3]. Medical facilities and manpower are inadequate as compared with Taiwan Main Island. However, Kinmen has been developing rapidly because of tourism between China and Taiwan since the implementation of the "mini three links" in 2001. According to the statistics from the Tourism Bureau of Kinmen County at the time, the monthly number of domestic tourists was estimated to be more than 3000. It reached more than 420000 including tourists from both China and Taiwan in 2002 [2]. Unfortunately, there is a lack of neurosurgeons, emergency and critical care physicians, and facilities for management of patients with head injury. Patients who have either a major illness or trauma have to be transferred to Taiwan Main Island for further evaluation and management [21].

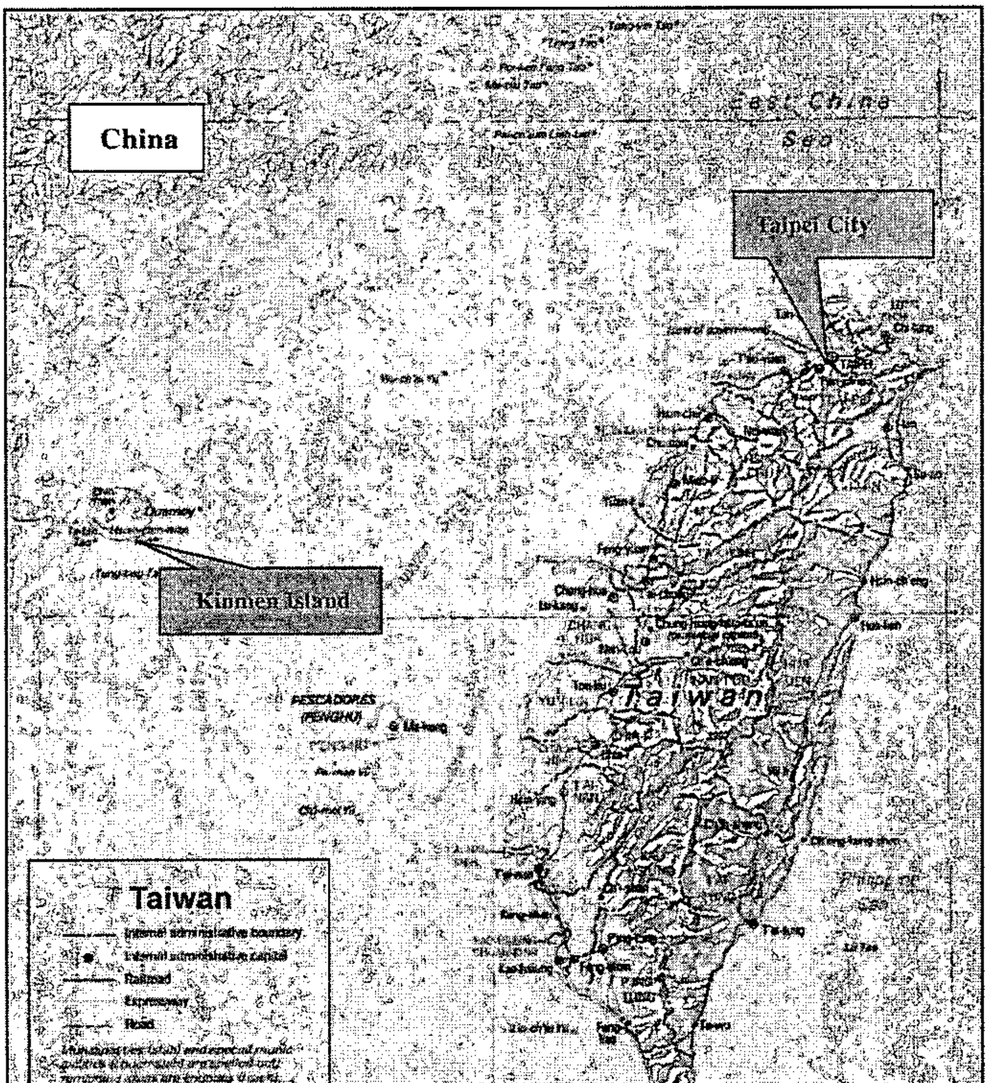

Fig. 1. Geographic location of Kinmen (circled on the left) and its relationship with Taiwan Main Island.

Table 1
Demographic data of all EAMS

		N = 215 (%)
Sex	Male	146 (67.9)
	Female	69 (32.1)
Mean age (y)	48.6 ± 23.8	
Age distribution (y)	0-15	16 (7.4)
	16-30	38 (17.7)
	31-45	35 (16.3)
	46-60	45 (20.9)
	61-75	54 (25.1)
	75-90	24 (11.2)
	>90	3 (1.4)
Disease category	Major illness	141 (65.6)
	Trauma	74 (34.4)

Investigations on EAMS of patients with head injury from a remote district, such as an offshore island, are scarce in this country as well as in other countries. The purpose of this study was to investigate the characteristics of patients with head injury in EAMS.

2. Methods

This is a retrospective study conducted from January 2001 to December 2003 analyzing all patients, especially patients with head injury, transferred by a fixed-wing aircraft (Fokker 50). The SOPs of transport are described as follows. (1) The medical flight crew consists of a physician, a flight nurse, and an EMT-P. All of them have good experience in critical care and emergency medicine. (2) Emergency air medical services requested by a local physician are based on the mechanism and severity of the injury (3) The management of the patient during ground and air transport follows the guidelines of the American College of Critical Care Medicine [13] and the Brain Trauma Foundation [19]. (4) The time en route to arrival at the trauma center is approximately 2 hours, and all flight missions are completed within 6 to 8 hours upon request.

The patients' demographics, causes of injury, disease classification, and GCS scores were collected. The severity of head injury was defined as follows: minor GCS: 14 to 15; moderate GCS: 9 to 13; and severe GCS, less than 8.

Further analysis was made on oxygen use, ventilator use, interventions performed, and the mortality rate. Data were analyzed using summary descriptive statistics with SPSS 11.5 (SPSS, Chicago, Ill).

Table 2
Demographic data of patients with head injury

		n (%)
Sex	Male	41 (71.9)
	Female	16 (28.1)
Mean age (y)	46.7 ± 21.3	
Age distribution (y)	0-15	3 (5.3)
	16-30	10 (17.5)
	31-45	11 (19.3)
	46-60	15 (26.3)
	61-75	13 (22.8)
	76-90	5 (8.8)
Total		N = 57 (100)

Table 3
Mechanism of injury and distribution of neurosurgical severity

	GCS	
	n	%
Mechanism		
Motor-vehicle accident	39	68.4
Fall	15	26.3
Attempted suicide	2	3.5
Gunshot	1	1.8
Total	57	100
GCS		
14-15	21	36.8
9-12	20	35.1
≤8	16	28.1
Total	57	100

3. Results

A total of 215 EAMS missions were performed from January 2001 to December 2003 on a fixed-wing aircraft (Fokker 50) from Kinmen. Among these 215 patients, 141 (65.6%) had a major illness and 74 (34.4%) had trauma (Table 1); of the 74 trauma patients, 57 (77%) had head injury. Therefore, head injury accounted for 74% (57/74) of trauma cases and 26.5% (57/215) of all EAMS cases.

In the head-injury group, the mean age of patients was 48.6 ± 23.8 years. Males accounted for 72% (41/57) of the cases (male/female ratio, 2.6:1). The patients' demographic data are summarized in Table 2. Motor-vehicle accidents were the most common mechanism of injury (68%). There were 21 (37%), 20 (35%), and 16 (28%) patients in the minor, moderate, and severe head-injury groups, respectively. The mechanism of injury and severity of head injury are listed in Table 3. Eighty-six percent (49/57) of patients used oxygen either because of a lack of cabin pressure in aviation (5000 ft) or for treatment for hypoxia. There were 19 patients (33%) who received mechanical ventilation (Uni-Vent Eagle Model 754, Impact Instrumentation Inc) and

Table 4
Interventions performed by flight medical crew

	n	Valid (%)
Standard monitoring		
Electrocardiogram	29	50.9
Pulse oximetry	53	93.0
Oxygen	49	86.0
Urinary catheter	23	40.4
Nasogastric tube	20	35.1
Fluid administration	56	98.2
Advanced intervention		
Blood transfusion	15	26.3
Inotropics	13	22.8
Resuscitation	2	3.5
Intubation	1	1.7
Extra intravenous lines	6	10.5

89% (51/57) of patients received osmotic diuretics, sedative, and anti-epileptic agent treatments. The types of intervention performed by the flight medical crew are summarized in Table 4.

Three patients with bilateral pupillary dilatation and loss of spontaneous respiration were not considered for air transport, since their families decided against heroic measures. One patient expired within 24 hours of admission to the receiving hospital and seven patients expired within 24 hours of admission. The mortality rate in the mild, moderate, and severe head-injury groups was 0% (0/21), 5% (1/20), and 44% (7/16), respectively. The overall mortality rate was 14% (8/57). There were no aviation incidents or medicolegal problems.

4. Discussion

With ground transport, the regular trauma-to-major illness incidence ratio in the emergency room ranges from 1:6.7 to 1:2.0. Head injury comprises about 60% of all trauma cases [11,12]. In the present study of EAMS, the incidence ratio of trauma-to-major illness was 1.9:1, and head injury accounted for 77% of cases of trauma in EAMS. However, in ground transportation, patients with head injury comprise only 59% of all cases. The higher incidence ratio of disease category (trauma-to-major illness) in EAMS demonstrates the major difference between EAMS and ground transportation. The higher incidence of head injury (26.5%) in EAMS than in ground transportation (19.8%) [11,12] suggests that the appropriate management of patients conducted by an experienced escort team following the guidelines for head injury in EAMS is a very important issue.

The age distribution of patients with head injury in the present study of EAMS was mainly in the middle-age group (Table 2). There were 33 (58%) patients older than 45 years. However, in Taiwan Main Island, the most prevalent age for head injury is in the young-age group (20-29 years old) [7]. The reason is that most of the young people in remote islands would like to go to cities for their career. People who are older than 65 years represent 12.8% of the Kinmen population, as compared with 9.2% in Taiwan Main Island. As for the sex ratio, there was a male predominance (male/female ratio, 2.6:1) in our study group, which is similar to that in ground transportation in major cities.

The most common mechanism of head injury in the present study was motorcycle accidents (68.4%). This is different from that in most Western countries, where falls or car accidents represent the most common mechanism of traumatic brain injury [16]. The major reason is that the motorcycle is the most popular transportation vehicle in both Taiwan Main Island and Kinmen.

The overall mortality rate of patients in this study (14.0%) was lower than that in most other reports with ground ambulance transport (13%-43%) [1,10,22]. The percentage of ventilator use is higher in this study (33%) compared with the ground transport group of critical patients (31%) [1,5,10,22]. It is related to the ability of the escort team to manage patients more easily in the air. In a review of the literature, overall mortality is highest in patients transported by helicopter (35.7%), especially in trauma scene flight (prehospital transport) [17,20,23]. The lower overall mortality rate in our series compared with ground and helicopter transport may be attributed to the composition of the medical flight crew, in-flight monitoring, treatment given during evacuation, and type of aircraft. However, the mortality rate in the severe head-injury group (44%) in the present study is slightly higher than that in the ground transport group (38%-43%) [1,5,10,22]. Older age and the high percentage of severe injury in the present study may be related to higher mortality in the severe head-injury group.

Composition of the medical flight crew is an important part of EAMS. There have been cumulative reports suggesting that the experiences and capabilities of the medical flight crew were associated with patient outcome [9,14,17,18,22]. In the present study, all flights were staffed by a well-trained physician, nurse, and EMT-P to monitor the patient's condition and to perform interventions, especially in the air and in interhospital transportation of critically ill patients. The patient's condition is to be maintained or improved during the transfer. The escorting doctor should be aware of the differences between working in an airborne environment and in a static ground-based facility.

The mode of transport depends on clinical requirements, vehicle availability, and the conditions at the receiving sites. Helicopters are better used for emergency scene flight, with flight distance of less than 100 km. It is suggested that a flight range longer than 100 km is better transported by a fixed-wing aircraft. Several studies have questioned the safety of helicopter use by drawing attention to the limitations placed on flight crews, noise, vibration, and confined space limits [10,18,22]. For an adequate airborne medical care environment, the pressurized cabin provides controlled ambient pressure at high altitudes. This enables a high-speed, long-range, low-noise, and comfortable flight. The Fokker 50 aircraft belongs to Mandarin Airlines Company and is normally used for commercial domestic flight, especially between remote islands and Taiwan Main Island. It was used for EAMS as a chartered air ambulance with a stretcher fixed on the back of 10 seats. The cost of each flight including the fee for the escort team is NTD 450000 (US$13500).

The limitation of this study is due to the fact that it was not possible to obtain an appropriate comparison population, and we could not compare the mortality of our patients with similar patients ground-transported and treated by EMS units. To the best of our knowledge, a similar series has not yet been reported in the literature.

5. Conclusions

Head injury is responsible for significant morbidity and mortality nationwide. The higher percentage of patients with moderate and severe head injury and ventilator use indicates that a 24-hour alarm center and experienced physicians are necessary for EAMS of critically ill patients in remote islands. This study demonstrates the characteristics of patients with head injury in EAMS transported by a fixed-wing aircraft. This experience in transporting patients with head injury from a remote island to a major city may prove to be a good model for EAMS in other countries. Further efforts should be made to manage patients with head injury in EAMS.

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Clinical Article

Multiparametric analysis of cerebral substrates and nitric oxide delivery in cerebrospinal fluid in patients with intracerebral haemorrhage: correlation with hemodynamics and outcome

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Summary

Background. There is no information regarding the possible role of cerebral substrates in the pathogenesis of neuronal injury in intracerebral haemorrhages (ICHs). Purposes of this prospective study were to clarify whether changes in substrates are the consequence of the initial brain damage in ICH and to elucidate the relationship among the biochemical mechanisms and clinical course of patients with ICH.

Method. During a period of two years, patients (GCS $\leq$8) who had ICH secondary to an aneurysm (SAH), stroke (sICH), or trauma (tICH) and underwent ventriculostomy with ICP monitoring and/or underwent cranial surgery were randomly enrolled in this study. Extracellular concentrations of glutamate, aspartate, glycine, GABA, lactate, lactate/pyruvate ratio, and glucose in the CSF were measured by use of high-performance liquid chromatography (HPLC). The nitric oxide (NO) concentration in the CSF was analyzed by chemiluminescence.

Findings. There were 75 patients (38 women and 37 men) with ICH included in this study. Twenty-one patients had SAH, 28 sICH, and 26 tICH. In tICH patients, there was a 30-fold increase in glutamate and a 10-fold in aspartate over reference values. The levels of glutamate, aspirate, GABA, lactate, glucose, and NO differed significantly among the three groups ($p<0.001$). There were no significant differences in glycine and L/P ratio among the groups. The initial GCS, the mean CPP and outcome six months after the insult were all significantly correlated with the concentration of substrates ($p<0.01$), both within groups and among the total sample. The CSF levels of glutamate, lactate, NO and glucose correlated significantly with outcome ($p<0.005$).

Conclusions. This study confirms the correlation between the level of EAAs and the outcome of ICHs, suggesting that neurochemical monitoring of these substances may have a role in caring for patients.

Keywords: Cerebral substrates; excitatory amino acid (EAA); intracerebral haemorrhage (ICH); microdialysis; nitric oxide (NO); subarachnoid haemorrhage (SAH).

Introduction

Although the role of excitotoxic amino acids (EAAs), particularly glutamate, has been described in ischemic stroke and head trauma, there is no information regarding their possible contribution to the pathogenesis of neuronal injury in intracerebral haemorrhage (ICH) [1–3, 15, 29, 30]. Both experimentally and in clinical studies, cerebral ischemia and traumatic brain injury are associated with excess liberation of EAA, enhancement of anaerobic metabolism, and release of nitric oxide (NO) byproducts [1–3, 8, 22, 26–30].

The three most frequent types of intracerebral haemorrhage (ICH) are subarachnoid haemorrhage (SAH), spontaneous intracerebral haemorrhage (sICH), and traumatic intracerebral contusion haemorrhage (tICH). Secondary brain damage after these acute cerebral insults is of increasing interest because it may be as important to the outcome as is the initial lesion [24]. Secondary brain damage after ICH has been attributed to vasospasm following SAH, ischemia following sICH or SAH, and diffuse brain swelling following tICH. The search for early indicators of secondary deterioration has been enhanced by several new invasive and noninvasive techniques for monitoring patients with ICH [24].

This study was performed to measure the extracellular concentrations of various cerebral substrates and nitric oxide in the acute period after ICH. We sought to clarify whether changes in these substrates vary depending on the type of ICH, whether the levels are predictors of subsequent neurological damage, and to assess the biochemical mechanisms and clinical course of patients with different types of ICH.

Materials and methods

Consent

This study was approved by the medical ethics committee of the hospital. Written informed consent was obtained from the patients or their next of kin.

Patient characteristics

From January 2003 to December 2004, patients admitted to the Department of Neurosurgery at Mackay Memorial Hospital with a diagnosis of SAH, sICH, or tICH and whose initial Glasgow Coma Scale (GCS) on arrival at the emergency repartment was ≤8 were considered for enrolment in this prospective study. Of those, only patients who underwent ventriculostomy with monitoring of intracranial pressure (ICP) and/or cranial surgery were selected. The insertion of an external ventricular drain was determined by conventional clinical indications unrelated to the purpose of the study. Patient outcome was graded on the Glasgow Outcome Scale (GOS) at 6 months after injury. This assessment was made by an independent neurologist (P. T.) who was unaware of the study data.

The ICP monitoring was measured hourly through the ventriculostomy, along while simultaneous measurement of mean arterial pressure (MAP) and cerebral perfusion pressure (CPP). CSF samples (2 to 3 ml) were collected at daily intervals as long as the external ventricular drain remained in place and patent.

Amino acid analysis by HPLC

The CSF samples were immediately frozen at −80 °C in liquid nitrogen until analysis. Analysis of the concentrations of glutamate, aspartate, glycine, GABA, lactate, and glucose, and the lactate/pyruvate ratio, were performed by high-performance liquid chromatography (HPLC) (HPLC9, BAS, U.S.A.). The amino acids were derivitized by o-phthalaldehyde (OPA; Sigma, Saint Louis, U.S.A.) before automatic injection into the HPLC column. Fluorometric detection for quantitation of amino acids was performed as previously described [5, 10, 15, 23].

NO assay by chemiluminescence

The NO concentration in the CSF specimens was analyzed by chemiluminescence using a Sievers 280 NO analyzer (Sievers Inc., Boulder, CO) according to the manufacturer's instructions. We chose to integrate NO release over 4 minutes because this period accounted for >90% of the NO peak. The protocols for NO measurement were adapted from published procedures [6, 13].

Statistical analysis

All data are presented as the mean ± standard deviation (SD). We compared the substrate levels we measured with the reference values in the literature [2, 9, 13, 23, 24, 25]. Statistical analysis was performed on a personal computer using Statistical Package for Social Science software (SPSS Inc. Chicago, U.S.A.), version 10.0. Analysis of variance (ANOVA) was used to compare the means among three groups and a post hoc Tukey's honestly significant difference (HSD) test was used to test for differences in the means of two groups. The initial GCS on admission, the GOS six months after insult, the mean CPP during the period of substrates measurement were examined for correlation with the mean substrate concentrations by using Pearson correlation coefficients. Differences were considered statistically significant at a p of <0.05.

Results

Patient profiles (Table 1)

A total of 75 patients (38 women and 37 men) with ICH were included in this study. Their ages ranged from 21 to 79 years, with a mean of 46 years. Twenty-one patients had SAH, 28 sICH, and 26 tICH. The GCS, CPP and GOS were all lower in the tICH group than in the other two. However, the difference among the three groups was not significant (p > 0.05).

CSF collection

CSF was collected on a daily basis over a period ranging from 3 to 14 days (mean, 8.6 ± 3.0 d).

Concentration of substrates (Table 2)

Excitatory amino acids (EAA)

Glutamate/aspartate. The glutamate concentration was 30-fold higher than the reference value in patients with

Table 1. *Demographic and clinical data of 75 patients with ICH*

	SAH	sICH	tICH	P value
Number	N = 21	N = 28	N = 26	
Gender	M = 9	M = 14	M = 14	
	F = 12	F = 14	F = 12	
Age (years)	47 ± 6	56 ± 7	34 ± 5	0.176
GCS	5.9	6	5.4	0.827
CPP (mmHg)	84.6 ± 8.9	86.4 ± 7.6	82.3 ± 10.5	0.659
GOS	3.6	3.8	3.4	0.277

Table 2. *Mean concentration of CSF substrates in patients with ICH*

	Ref. values#	sICH (n = 28)	SAH (n = 21)	tICH (n = 26)
Glutamate*	3.2 ± 0.4	78.6 ± 5.3†,‡	71.1 ± 4.0†,§	95.7 ± 6.3‡,§
Aspartate*	1.7 ± 0.2	13.7 ± 0.7†,‡	13.1 ± 0.6†,§	15.8 ± 1.2‡,§
Glycine	16.8 ± 3.5	57.1 ± 3.1†,‡	62.9 ± 3.3†	65.0 ± 3.9‡
GABA*	9.1 ± 1.7	38.6 ± 2.1†,‡	30.4 ± 1.4†,§	26.6 ± 1.5‡,§
Lactate*	100–200	1330.5 ± 74.3†,‡	1411.8 ± 72.4†,§	1572.9 ± 116.1‡,§
L/P	23 ± 4	22.7 ± 1.8†	21.6 ± 1.6‡	49.4 ± 2.9†,‡
Glucose*	50	80.0 ± 4.8†,‡	86.5 ± 4.8†,§	94.7 ± 5.9‡,§
NO*	2.6–5.2	21.4 ± 1.1†,‡	26.2 ± 1.3†,§	28.2 ± 1.2‡,§

* $p < 0.001$; difference among all three groups by ANOVA.
†,‡,§ $p < 0.05$; difference between two groups by post hoc Tukey HSD test Mean ± SD (μmol/L), # reference values [2, 13, 20, 23, 24, 25].

tICH. The difference in glutamate values among three groups was statistically significant ($p < 0.001$); it was highest in the tICH group, followed by sICH and then SAH. A significant difference existed also between the SAH and the sICH groups and between the SAH and tICH groups ($p < 0.05$). Aspartate was also highest in patients with tICH, nearly 10 times higher than the reference value. It was significantly higher in the tICH group compared with SAH ($p < 0.05$) and sICH ($p < 0.05$), and between the SAH and the sICH groups ($p < 0.05$).

Inhibitory amino acids (IAA)

Glycine/GABA. The glycine concentration in patients with tICH was 4 times higher than the reference value, and it was highest in the tICH group, followed by SAH and then sICH. A significant difference also existed between the tICH and the sICH groups and between the SAH and sICH groups ($p < 0.05$). The concentration of γ-aminobutyric acid (GABA) in the sICH group was 4 times higher than the reference level, and the levels in the three groups differ significantly.

Energy-related substrates

Lactate, lactate/pyruvate ratio (L/P ratio), glucose. The concentration of lactate in the tICH group was 10 times higher than the reference level. The difference of lactate value among three groups was statistically significant ($p < 0.001$), and the level in the tICH group was significantly higher than in the sICH group ($p < 0.05$). The L/P ratio was 2-fold higher than the reference value in patients with tICH. The ratios were significantly higher in the tICH group compared with the SAH ($p < 0.05$) and the sICH ($p < 0.05$), and between the SAH and the sICH groups ($p < 0.05$). The glucose level was higher in patients with tICH. The glucose values differed significantly among all three groups ($p < 0.001$).

Nitric oxide

The NO concentration was 26.2 ± 1.3 μmol/L in patients with SAH, 21.4 ± 1.1 μmol/L in the sICH group, and 28.2 ± 1.2 μmol/L in the tICH group. It was highest in patients with tICH, a 10-fold increase over the reference value. The difference among the three groups was statistically significant.

Substrates, GCS, and GOS

In the tICH group (n = 26), the GCS gradually improved over 10 days, simultaneously with decreases in the average levels of substrates (Fig. 1). In each group, the initial GCS, mean CPP, and the GOS six months after the insult all correlated significantly with the mean concentration of substrates except for GABA and L/P (Table 3). The tICH group had higher levels of glutamate, asparate, lactate and L/P ratio, all of which correlated to a lower GCS, CPP, and GOS (Tables 2

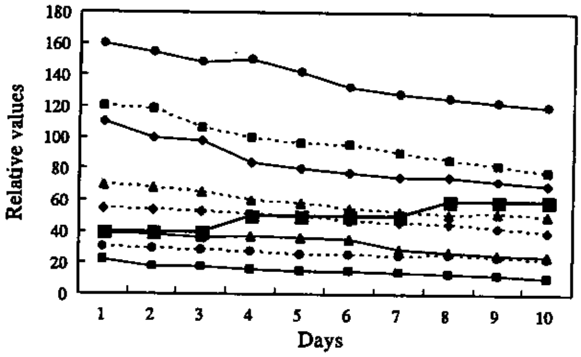

Fig. 1. Changes in the average substrate levels and the mean GCS over 10 days in the tICH group (n = 26). For clarity, the mean GCS was multiplied by 10 and the mean lactate level by 0.1. —■— GCS (×10), --■-- Glutamate, —●— Lactate (×0.1), —▲— NO, —◆— Glucose, —■— Asparate, --▲-- Glycine, --●-- GABA, --◆-- L/P

Table 3. *Correlation of outcome, initial GCS, and mean CPP with CSF substrates in patients with ICH (n = 75)*

Pearson correlation	GOS	GCS	CPP
Glutamate	−0.442**	−0.432**	−0.443**
Lactate	−0.441**	−0.461**	−0.446**
NO	−0.374**	−0.356**	−0.388**
Glucose	−0.304**	−0.264*	−0.368**
Asparate	−0.282*	−0.293*	−0.332**
Glycine	−0.279*	−0.289*	−0.315**
GABA	−0.222	−0.232*	−0.204
LP ratio	−0.161	−0.165	−0.176

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

and 3). On linear regression analysis, the GOS correlated most significantly to CSF levels of glutamate, lactate, NO and glucose (Table 3 and Fig. 2).

Discussion

Spontaneous intracerebral haemorrhage accounts for 10% to 15% of all cases of stroke and is associated with high mortality and morbidity [15, 16]. Vasospasm and ischemia continue to be the major causes of neurological complications after SAH [9]. In traumatic brain injury, EAA have a pivotal role in neuronal death [11, 15, 20,

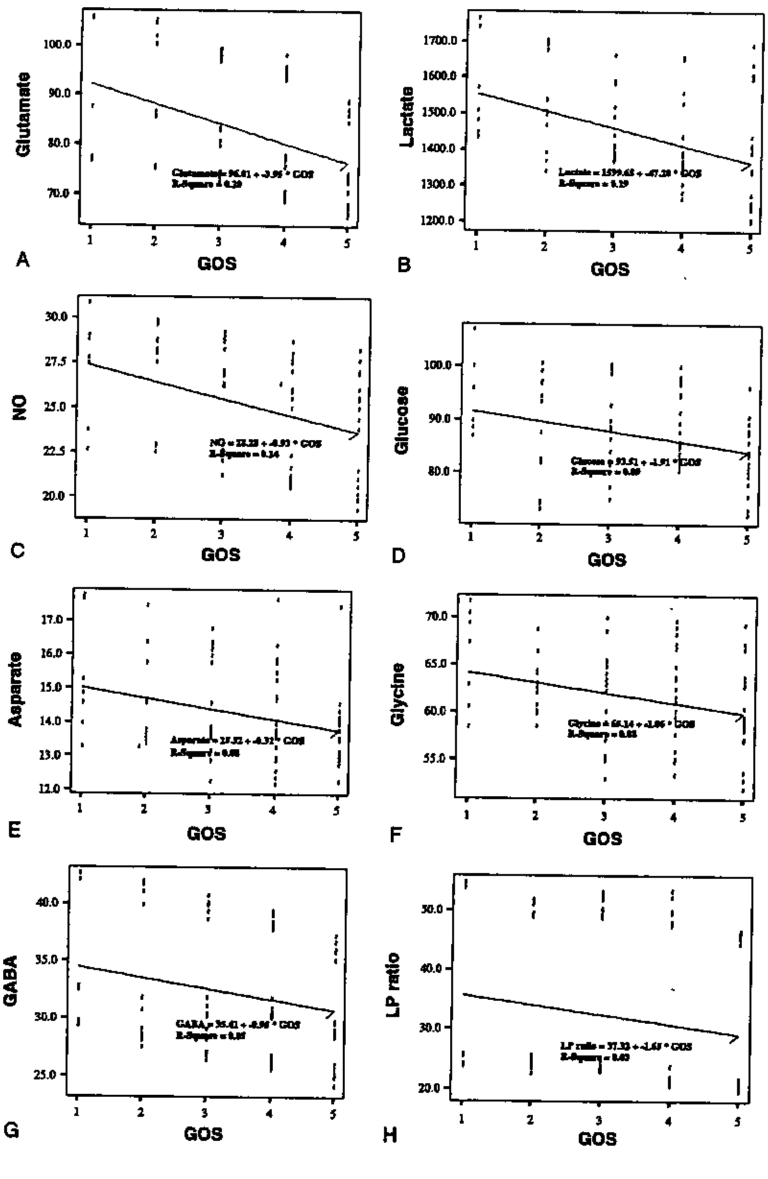

Fig. 2. Linear regression analysis of Glasgow Outcome Scale (*GOS*) and substrates levels. Glutamate, lactate, NO, and glucose correlated most significantly with GOS. (A) Glutamate, (B) lactate, (C) NO, (D) glucose, (E) aspartate, (F) glycine, (G) GABA, (H) L/P

30]. In addition to mass effect, the presence of a hematoma induces three early pathophysiological changes in the surrounding parenchyma: neuronal and glial cell death, vasogenic edema, and breakdown of the blood–brain barrier [15, 16]. Doppenberg *et al.* reported the devastating effects of space-occupying traumatic intracranial hematomas on substrate delivery [4]. Qureshi *et al.* showed that glutamate and other amino acids accumulate in extracellular fluids in the perihematoma region [15]. Our study showed significant elevation of the levels of cerebral substrates in the CSF of patients after ICH.

Each neuron contains approximately 10 mmol/L glutamate [11, 15]. Mechanical injury from pressure by a hematoma on the surrounding tissue may lead to release of intracellular stores of glutamate into the extracellular space. In addition, injury to astrocytes actively involved in the removal of glutamate may potentiate the extracellular accumulation of glutamate. Excessive concentrations of glutamate lead to activation of both NMDA and non-NMDA receptors and cell death [1, 8]. In both our study and that of other investigators, there was 30-fold increase in CSF glutamate and a 10-fold increase in aspartate in patients with tICH [30], suggesting that glutamate and aspartate are markers of cellular degradation [1].

Glycine is an amino acid which induces a long-lasting inhibitory postsynaptic response. It is a neurotransmitter with cortical hypothalamic projection. It is also produced by glycinergic neurons in the spinal cord, accounting for its presence in CSF obtained by lumbar puncture [23]. We observed a 4-fold increase of glycine in CSF from ventriculostomy in patients with all types of ICH. This suggests glycinergic neuron activation at the brain level with hypothalamic involvement. GABA is the most important inhibitory amino acid in the brain. During and Spencer demonstrated concomitant rises in the level of glutamate, aspartate, and GABA during seizures [5]. We did not find any significant differences in glycine and GABA values in the different types of ICH.

We found increases in lactate up to 10 times and in glutamate level up to 30 times over the standard values. Glutamate clearly influences the release of lactate following traumatic brain injury. Glutamate may drive lactate production to provide lactate as an energy substrate to neurons [1]. In patients with ICH, a sudden increase in lactate, the L/P ratio, and glutamate may serve as a warning signal [9, 21]. The strong positive correlation between glutamate and glucose may indicate an effect of glutamate on glucose uptake by cells which differs according to the type of injury. We found that the CSF levels of lactate, and glucose and the L/P ratio differed significantly among the three groups. These substrates may be useful for monitoring patients for secondary damage after traumatic brain injury [12].

Nitride oxide is frequently called a double-edged sword in cerebral ischemia. It is a powerful dilator of cerebral vessels and has been reported to have both neuroprotective and cytotoxic effects [13, 17]. The elevated NO level after SAH may be caused by cerebral ischemia [9, 15, 18, 22, 24–26]. Overall, NO correlates with glucose, lactate, and glutamate [19]. The higher NO level in patients with a poorer clinical score at presentation may be a result of greater induction of NO synthase activity as a result of a greater cerebral insult [13]. In our study, the NO level was increased 10 times over the reference value in the tICH group, but the concentration did not differ significantly among the three groups.

Vespa *et al.* reported that the levels of glutamate, aspartate and glycine released into the extracellular fluid at a CCP of less than 70 mmHg were statistically significantly higher than at higher levels of CPP ($p < 0.001$) [28]. In our study, change in CPP also significantly affected the release of cerebral substrates after ICH ($p < 0.01$). Yamamoto *et al.* reported that glutamate concentration was not correlated with initial GCS score [29]. No significant correlation has been found for the concentration of NO metabolites with the patient's preoperative condition, the presence of symptomatic vasospasm, or prognosis [25]. In our study, cerebral substrate levels correlated significantly with the patient's initial GCS ($p < 0.01$). Concentrations of glutamate, aspartate and GABA have been found to correlate closely with outcomes of SAH ($P < 0.05$) [13, 14, 24, 29]. Brain lactate, pyruvate and the lactate/pyruvate ratio have also been recommended for use in estimating the severity of stroke and for predicting the outcome [3]. In a study of SAH, the NO level correlated with clinical severity but not with the neurological outcome [13]. Our study demonstrated a significant correlation between the concentration of CSF substrates in patients with ICHs and the outcome at 6 months, as assessed by the GOS ($p < 0.01$).

In this study, several methodological limitations must be noted. Because our study was limited to severely injured patients with ventriculostomies in place, our results are not necessarily generalizable to less severely injured patients. Laboratory analysis of microdialysis samples performed using HPLC is regarded as the gold standard [7]. However, this technique is time consuming and not practical for clinical application in the intensive care unit or operating theatre. An on-line bedside analyzer would be preferable for real-time monitoring. The reference values we used were extracted from the literature, so we could not control for any differences in laboratory techniques. Also, we analyzed the levels of cerebral substrates in ventriculostomy CSF without using microdialysis, a method which allows assessment of regional differences within the brain. It may be that there are local effects that do not correlate well with global physiological changes, such as CPP or outcome. Besides, our study could not define the role of the blood–brain and blood-colloid-CSF barriers in the transport of substrates from the blood to the CSF. Because glutamate, aspartate, glycine, and GABA are secreted directly by neurons in the brain itself; the cellular energy metabolites lactate, pyruvate, and glucose may come from neurons or from systemic metabolism; and NO is the product of NO synthases, enzymes which are expressed in the brain [1, 9, 15, 21, 24, 28].

The success of treatment for delayed cerebral ischemia after ICH is time-dependent, and neuronal monitoring methods which can detect early subclinical levels of cerebral ischemia may improve overall treatment results [13, 15]. The aim is to characterize patterns of neuronal injury (using glutamate and aspartate, glycine) and markers of energy metabolism (using glucose, pyruvate and lactate) in patients with ICH [21]. It is hoped that the development of neuroprotective therapy based on monitoring of these substrates may reduce the incidence of secondary brain damage [30]. For example, glutamate antagonists have been shown to reduce the extent of infarction in animal models. Several of these agents have been investigated in phase II or III clinical trials for efficacy in acute stroke [15].

Conclusion

This study confirms the correlation between EAAs and lactate in the outcome of ICH, suggesting that neurochemical monitoring of these substances may have a role in caring for patients. Monitoring of these substrates may also help expand our knowledge of pathophysiological processes in ICH. Knowledge of the mechanisms underlying these processes seems to be necessary for the development of specific treatment strategies.

Acknowledgements

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Comments

This is an excellent paper. This represents an extremely large body of work, with multiple neurochemical analytes being measured in 75 patients with intracerebral haematomas of different types. This is the only such study of its kind in the world to date, as far as I am aware, in such large numbers of patients and it certainly makes a useful contribution to the literature.

Ross Bullock
Richmond

The current study compares ventricular concentrations of several amino acids (glutamate, aspartate, etc.), lactate, glucose, and NO in patients with intracerebral haemorrhage with acute (GCS, CPP) and chronic (GOS) clinical evaluation parameters. The main finding of the study is that the concentration of the biochemical markers correlates well with the clinical situation of patients.

The basic design of the study and the methodology used by the authors is sound, the manuscript is well written, and the data are well discussed. It is also interesting to see that measurements in the CSF, which are easily performed, result in accurate values with such a small error and do not seem to be inferior to data obtained by microdialysis.

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Trauma

The risk of malpractice litigation in care to head-injury patients in comparison with other high-risk patient groups: an inpatient-based epidemiological study in Taiwan

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Abstract

Background: The purpose of this study was to assess the risk of being sued in district courts for care to head-injury patients from the perspective of epidemiology.
Methods: This research was designed to be a retrospective population-based cohort study. We researched the incidences of litigations arising from head-injury inpatients under neurosurgical care, all neurosurgical inpatients, and birth inpatients in Taiwan, and computed their relative risks. The study period was from 1998 to 2002.
Results: The average annual incidence rate of becoming a plaintiff for head-injury neurosurgical inpatients was 15 per million; for all neurosurgical inpatients 11.8 per million; and for birth patients 33.5 per million. The relative risk comparing head-injured neurosurgical inpatients against all neurosurgical inpatients was 1.27; whereas comparing head-injury neurosurgical inpatients against birth inpatients was 0.45, and comparing all neurosurgical inpatients against birth inpatients, 0.35.
Conclusions: The findings of our population-based study indicate that for the inpatient populations, whether head-injury patients or not, neurosurgeons in Taiwan are facing a relatively lower rate of litigation in comparison with those treating birth patients. Nonetheless, head-injury patients still pose a major challenge in the ED, and misdiagnosis remains the major complaint of plaintiffs in subsequent litigations.

Keywords: Head injury; Medical malpractice; Litigation; Cohort study; Incidence; Relative risk

1. Introduction

In January 2005, Little Chiu, then a 4-year-old girl, was slammed against a wall by her reckless father and became brain dead eventually. Two doctors were subsequently reprimanded by the Physician Disciplinary Committee of the DOH and indicted by the prosecutor for professional negligence. The public discontent was caused by the failure of the chief resident of neurosurgery and the on-call neurosurgeon to see the child in person during the midnight consultation by the emergency physicians [3,5,10]. This incident deeply troubled the neurosurgical specialists in Taiwan. They worried that all the punishments imposed an undue burden and would lead to chilling effects on neurosurgery.

In a joint study conducted by the Harvard School of Public Health and Columbia Law School [17], the key informants identified 6 specialties that are at high risk for litigation. Neurosurgery is one of the 6, accompanied by emergency medicine, general surgery, orthopedic surgery, obstetrics/gynecology, and radiology. The majority of professional liability carriers in the United States also designate neurosurgery in the high-risk group [16]. A Turkish study, which examined the opinions given by the courts and public

Abbreviations: DOH, Department of Health; ED, emergency department; NHI, National Health Insurance; CT, computed tomography; MRI, magnetic resonance imaging.

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defenders in Turkey, indicated that neurology and neurosurgery were involved in 10.53% of malpractice cases, next to obstetrics/gynecology (16.82%) and general surgery (10.69%) [2]. Relevant research in Taiwan is scarce and was mostly done in the 1990s by questionnaire surveys, which indicated that 44% of physicians had experienced medical disputes, and the high-risk group consisted of anesthesiology, obstetrics/gynecology, orthopedic surgery, and surgery [19], without specifying neurosurgery.

How risky is it for neurosurgeons to care for head-injury patients in terms of the possibility of facing litigation in the courts? According to a US government report, obstetrics/gynecology specialists were involved in 12.4% of the claims closed in 1984 and ranked number 1 among all specialties, whereas neurosurgeons were only involved in 2.6% of the claims and ranked 14th [8]. Childbirth negligence cases continue to be the area where physicians are losing the majority of cases that go to the jury in the United States; for instance, plaintiffs won 60% of these cases in 2002 [1]. However, as there are disproportionate numbers of obstetrics/gynecology patients and neurosurgery patients, the question then becomes how risky are the head-injury patients for neurosurgeons in comparison with other patient populations.

The purpose of this study was to assess the risk of being sued in court for caring for head-injury patients from the perspective of epidemiology. Giving birth has been considered the most risky practice in obstetrics in terms of professional liability which we compared with caring for giving birth to see, relatively speaking, how risky it is for neurosurgeons to care for head-injury patients. Most of the previous researches focus on physician-level analyses. Our research aimed at assessing the risks of encountering litigations in specified patient populations from an epidemiological perspective.

2. Materials and methods

This research was designed to be a retrospective cohort study. Our intent was to determine the incidences of lawsuits arising from head-injury inpatients under neurosurgical care, all neurosurgical inpatients, and birth inpatients. The number of inpatients for each category of occurrence that resulted as district court cases for each year was determined. The incidence rates were derived from dividing the number of specific lawsuits by the number of predefined categories of inpatients for each year. Whether there was a significant difference among the mean incidences of the 3 groups was tested by Student t test. The relative risks of looming litigation later on in each category of inpatients were computed by comparing the respective incidences.

The study period was set to be from 1998 to 2002 after taking data availability into account. The study materials included the inpatient reimbursement claim dataset of the NHI from 1998 to 2002. Because NHI is a mandatory health insurance, nearly 100% of all diseases, injuries, and births are treated by health care providers under contract with NHI. Therefore, we were able to ascertain the occurrences of all inpatient admissions of the desired parameters. The principal diagnoses with ICD-9-CM diagnosis codes 800-804, 850-854, and 873 were included in the head-injury inpatient population.

Whether the case progressed to court was ascertained by looking into the district court decision database of the Judicial Yuan from August 1999 to November 2005. The Judicial Yuan is the highest governmental office in charge of judiciary affairs, and it started publishing court decisions in August 1999. We traced back to the year of the occurrence in the court's decision. Only those decisions between 1998 and 2002 were included in our analyses.

According to Florida's experience on medical professional liability insurance claims, there is, on average, a 1.2-year gap between occurrence and reporting [9]. It took, on average, 75.16 days to close a criminal trial and 85.97 days to close a civil trial at the district court level in Taiwan in 2004 [11]. A 2- to 3-year time lag between the occurrence of an unsatisfactory medical event and the first court judgment is a reasonable expectation according to the initial database exploration. If the same occurrence gave rise to more than 1 litigation in this study, only 1 was counted.

3. Results

From 1998 to 2002, the annual number of inpatients in the whole nation averaged 2 700 000. Of this number, there were on average 251 894 births with an average cesarean section rate of 33.5%. On the other hand, neurosurgeons take care of an average of 69 275.6 inpatients annually. Of

Table 1
Descriptive statistics of target categories of inpatients by year

	1998	1999	2000	2001	2002	Average
Total inpatients nationwide	2455960	2590140	2690847	2814986	2945904	2699567.4
Total births	247220	258849	279024	240964	233413	251894
Natural birth	163900	172293	185423	160730	155259	167521
Cesarean section	83320	86556	93601	80234	78154	84373
Total head injury inpatients	98880	96557	89845	87262	82923	91093.4
Total neurosurgical inpatients	56840	66724	69827	74157	78830	69275.6
Head injury	21840	26442	26620	26592	27927	25884.2
Non–head injury	35000	40282	43207	47565	50903	43391.4

Table 2
Descriptive statistics of litigations arising from target categories of inpatients by year

	1998	1999	2000	2001	2002	Average
Litigation related births	11	11	7	4	9	8.4
Criminal litigation	7	7	4	2	3	4.6
Civil litigation	4	4	3	2	6	3.8
Total births	247220	258849	279024	240964	233413	251894
Incidence of litigation-related births	0.0000445	0.0000425	0.0000251	0.0000166	0.0000386	0.0000335
Litigation-related head injury neurosurgical inpatients	0	0	1	1	0	0.4
Criminal litigation	0	0	1	0	0	0.2
Civil litigation	0	0	0	1	0	0.2
Total neurosurgical head injury inpatients	21840	26442	26620	26592	27927	25884.2
Incidence of litigation-related head injury neurosurgical inpatients	0	0	0.0000376	0.0000376	0	0.000015
Litigation-related neurosurgical inpatients	1	0	1	2	0	0.8
Criminal litigation	1	0	1	1	0	0.6
Civil litigation	0	0	0	1	0	0.2
Total neurosurgical inpatients	56840	66724	69827	74157	78830	69275.6
Incidence of litigation-related neurosurgical inpatients	0.0000176	0	0.0000143	0.000027	0	0.0000118

this number, 25 884.2 were head-injury–related admissions, which accounts for 37.4% of total neurosurgical inpatient admissions. There were, on average, 91 093.4 head-injury inpatients annually, which indicates that more than two thirds of head-injury patients were cared for by physicians other than neurosurgeons. The descriptive statistics of the inpatient populations are summarized in Table 1.

After an extensive search of the Judicial Yuan database, we found that there were only 2 head-injury inpatients who later sued their neurosurgeons in the district courts in the entire study period. One was treatment related and the other diagnosis related. One sued for civil damages and the other sued for criminal convictions. Even if we look at the entire inpatient population of all neurosurgical departments, there were only 2 more inpatients who sued their neurosurgeons in criminal courts. Both cases had to do with operations on tumors. All 4 decisions at the district court level for both head injuries and non–head injuries, were for the defendant physicians. Therefore, the average annual incidence rate of becoming a plaintiff among neurosurgical head-injury inpatients was 15 of 1 million. And the average annual incidence rate of becoming a plaintiff for all neurosurgical inpatients was 11.8 of 1 million. There was no significant difference between the 2 categories (P = .76).

In contrast, there were a total of 42 birth-related litigations from 1998 to 2002. The average annual incidence rate of becoming a plaintiff among birth patients was 33.5 of 1 million. This incidence is significantly higher than that of all neurosurgical inpatients (P = .02), but not significantly higher than that of head-injury neurosurgical inpatients (P = .12). The detailed year-by-year breakdown is shown in Table 2.

Aside from respective incidences, the relative risk derived from comparing head-injury neurosurgical inpatients against all neurosurgical inpatients was 1.27, which means head-injury neurosurgical inpatients were 1.27 times as prone to litigation as neurosurgical inpatients considered as a whole. On the other hand, the relative risk derived from comparing head-injury neurosurgical inpatients against birth inpatients is 0.45, which means head-injury neurosurgical inpatients had 45% the risk of suing compared with birth inpatients. In addition, the relative risk derived from comparing all neurosurgical inpatients against birth inpatients was 0.35.

4. Discussion

Unlike physicians working with the American system, physicians in Taiwan are likely to face both civil liabilities and criminal convictions in malpractice lawsuits, and the situation is similar to that in Japan [13]. However, criminal action in Japan is usually reserved for serious cases involving obvious errors [13]. On the contrary, in Taiwan, although the patients and their families have the choice of either suing in the civil court directly or going to the prosecutor to seek an indictment, most plaintiffs opt for the latter for the sake of convenience and economy. If the physician is eventually convicted, he or she will face up to 5 years of imprisonment in the case of a death claim [6] and civil liability will be unavoidable.

Although we initially thought we would find a higher incidence of litigations, there were in fact only 2 head-injury–related litigations in our study period that sued neurosurgeons. One was treatment-related and the other diagnosis-related. Even when we researched the non–head-injury inpatients, we only found 2 more criminal litigations, of which both had to do with operations on tumors. If we simply look at the absolute number of litigations that made their way to Taiwan's court system, the results are not too bad. Most of the claims should have been either settled out

Table 3
Other head injury litigations recorded in the available judicial database but not included in this study

Year of occurrence	Type of judicial proceedings	Defendant	Plaintiff's assertion	Judgment
1996	Criminal	Emergency physician[a]	Diagnosis related	For defendant
1997	Criminal	Neurosurgeon	Diagnosis related	Against defendant
2001	Civil	Emergency physician	Diagnosis related	For defendant
2002	Civil	Hospital	Fall caused by care negligence	For defendant
2003	Civil	Emergency physician	Diagnosis related	For defendant
2003	Criminal	Neurosurgeon	Diagnosis related	For defendant
2003	Criminal	Oral surgeon	Diagnosis related	For defendant

[a] Emergency physician refers to the physician who sees the plaintiff in the emergency room with unspecified specialty.

of court or denied by the prosecution in Taiwan. The phenomenon of the low number of lawsuits was also observed in Japan, which has a similar court system and culture. The number of medical malpractice suits was around 0.2 per 100 Japanese physicians in the 1990s [13]. It has been argued that this might be attributed to different practice patterns and much fewer lawyers in Japan [7].

However, the occurrence of lawsuits only reflects the "tip of the iceberg." According to a physician survey funded by the DOH in 1991, 42% of medical malpractice disputes were settled out of court in Taiwan, only 10% were litigated, and the rest remained unresolved throughout [4]. There are several alternative medical dispute resolution mechanisms in Taiwan. Pursuant to the Medical Care Act, the disputing parties can go to the county or city government's DOH to apply for mediation, and the medical affairs review committee of the respective DOH is responsible for administering mediation [12]. For instance, according to the statistics of Taipei City Government, they received 138 medical dispute complaints in 2003; of this number, 30 filed for mediation and 50% were successfully resolved [18]. Various consumers' associations also provide disgruntled patients venues to settle their disputes with healthcare providers. All these alternative medical dispute resolution mechanisms make court appearances less necessary in Taiwan.

In searching the Judicial Yuan database, we incidentally found 7 other head-injury cases that were not included in our study either because they were outside the designated time frame or because the lawsuits were not against neurosurgeons. Interestingly, in the majority of these cases, the plaintiffs sued their emergency physicians and their assertions were diagnosis related (Table 3). Most head-injury patients will be rushed to the ED. Physicians who work in the ED regardless of specialties are likely to be the first physicians they encounter. Therefore, it appears that head-injury patients are a higher risk group of patients for the ED doctors than for the neurosurgeons, and the major complaint from the patients or their families is misdiagnosis.

Judging from the above, the first point of contact with head-injury patients will be in the ED. That being said, we recognized the major limitation and assumption of our research: whether we found the accurate head-injury patient population neurosurgeons face. Because emergency doctors take care of most of the head-injury cases in the ED, neurosurgeons will only see ED head-injury patients when consulted under normal channels. We assume that the cases for which neurosurgeons are consulted, and those subsequently giving rise to litigation against neurosurgeons, most likely become inpatients one way or another. Therefore, the number of head-injury contacts for neurosurgeons as estimated by use of inpatients, although a bit underestimated, should not be far from the real contact numbers.

The other characteristic of our study is that we used the district level judgments as the end point of our follow-up time. In most cases, the plaintiffs can still appeal to the appellate courts and to the Supreme Court. However, for the purpose of this study, the beginning of the neurosurgeons' ordeals will give us an approximation of the risk of this line of practice.

Undoubtedly, a good portion of the claims are either settled out of the judicial system or denied by the prosecution in Taiwan. However, the same phenomenon must have applied to obstetricians. Even if the absolute number of litigations did not give us the real picture of the number of malpractice disputes physicians are facing, the relative-risk approach can serve as a good positioning beacon. Neurosurgeons, although still having a high-risk job, obviously face a lower patient-risk population compared with obstetricians in terms of the propensity for suits, about 35% to 45% the level of birth patients.

Specialists at high risk of litigation tend to practice defensive medicine. There are possibly 2 types of behaviors in defensive medicine: assurance and avoidance. Among the various possible assurance behaviors, neurosurgeons are most likely to order more CTs, MRIs, or x-rays; in terms of avoidance behaviors, they are more likely to stop performing certain procedures [17]. If we look at the data shown in Table 3, it appears that the most important allegation against physicians in head-injury lawsuits is misdiagnosis. Therefore, it makes perfect sense to reason that neurosurgeons are also likely to order more CTs, MRIs, or x-rays as an assurance measure in facing head-injury patients.

Just like the trend in the United States [1,14], in Taiwan there are more medical malpractice litigations over time and the monetary awards are also increasing. According to a physician-level longitudinal study of whether obstetricians will change their threshold for cesarean delivery, the results indicated that obstetricians learned from the experience of suffering malpractice claims; however, it is only in the event of a large claim that obstetricians would increase cesarean rates [9]. By analogy, whether neurosurgeons will change their practice pattern because of the Little Chiu incident will depend on how much penalty the 2 physicians will ultimately receive in the end.

In addition to the concern of the increased practice of defensive medicine among specialists, we also wonder whether the Little Chiu incident will turn medical graduates away from choosing neurosurgery because of the extensive coverage of the media and the fact that one of the defendants was a neurosurgery resident. According to a longitudinal study conducted in the United States, medical students continued to choose high-risk specialties although they perceived problems in the climate of mounting litigations, and the reasons for their choice were enjoyment and that procedure-oriented specialty offers more effective treatment [15]. Whether this optimism holds true in Taiwan needs more observation.

5. Conclusions

Neurosurgery has generally been considered a high-risk specialty. The real risk might be exaggerated every time a high-publicity malpractice litigation happens. The findings of our population-based study indicate that in the inpatient populations, whether they are in the head-injury population or not, neurosurgeons in Taiwan are facing a relatively lower rate of litigation in comparison with physicians caring for birth patients (ie, 45% of the risk level for care to birth patients). However, head-injury patients still pose a major challenge in the ED, and misdiagnosis remains the major complaint of plaintiffs in subsequent litigations.

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Trauma

Multicenter evaluation of propofol for head-injured patients in Taiwan

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Abstract

Background: The present study was a multicenter, retrospective study which aimed to evaluate the efficacy of propofol, a new choice of pharmacotherapy in head-injured patients.

Methods: Head-injured patients admitted to 3 hospitals during the period from January 2003 to December 2004 were included in this clinical trial. Data on patients' demographics, laboratory data, GCS score, ICP, CPP, concurrent medications, and therapeutic outcomes were collected.

Results: Among the 104 patients included, only 44 were given propofol. The average age was 40.8 ± 22 years for all patients, with 41.91 ± 20.41 and 43.48 ± 23.19 years for the propofol group and nonpropofol group, respectively (P = .097). There was no significant difference in baseline GCS score between the 2 groups (5.86 ± 1.84 vs 5.66 ± 1.59, P = .729). Mean ICP for the first 3 days in the ICU was 17.23 ± 9.0 mm Hg in the propofol group and 33.19 ± 32.56 in the nonpropofol group, respectively (P = .017). Mean CPP for the first 5 days in the ICU was 71.10 ± 15.32 mm Hg in the propofol group and 43.20 ± 29.92 mm Hg in the nonpropofol group (P < .001). A higher survival rate was found in the propofol group (81.8% vs 46.7%, P < .001).

Conclusions: The present study demonstrated that propofol improved the outcome in recovery phase of head-injured patients.

Keywords: Propofol; Head injury; Head trauma; Intracranial pressure; Sedatives

1. Introduction

Evidences on the use of sedatives in the management of head-injured patients have increased in recent years. The Guidelines for the Management of Severe Head Injury have proposed new, evidence-based treatment recommendations to reduce the mortality and morbidity of head injury. Use of sedatives, as well as careful control of ICP, maintenance of CPP, and use of hyperventilation and vasopressors, has been proposed as mainstay therapies [8]. A paper from the Society of Critical Care Medicine [38] also provided valuable guidelines on the sustained use of sedatives and analgesic agents in critically ill adults. However, there have been few studies that directly compared the effectiveness and adverse effects of different agents in the head-injured population. Determining the drug of choice for sedation in this group of patients warrants new studies to provide evidence.

The idea that sedatives provide advantages to the head-injured patients is based on several reasons. The general purposes of using sedatives in the ICU are to provide amnesia, hypnosis, and pain-free condition, as well as to relieve agitation and anxiety [3,8,21,37]. These agents may additionally decrease cerebral metabolism and raise ICP in head-injured patients [21]. It is suggested that an ICP greater than 20 mm Hg is a serious threat to initiate the

Abbreviations: CBF, cerebral blood flow; $CMRO_2$, cerebral metabolic rate for oxygen; CPP, cerebral perfusion pressure; CSF, cerebral spinal fluid; CT, computed tomography; GCS, Glasgow Coma Scale; ICP, intracranial pressure; ICU, intensive care unit; MAP, mean arterial pressure; $PaCO_2$, arterial carbon dioxide partial pressure.

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therapy, including sedatives, mannitol, diuretics, or hyperventilation [12,24,31,33,35,37]. Sedation also further enables the manipulation of respiration, which is essential in the treatment of increased ICP [13,22]. The requirements for "ideal" sedatives are not only to put head-injured patients in a stable and peaceful phase, but also to improve the clinically important data. Thus, careful consideration is necessary to select the best regimen.

Sedation regimens for head-injured patients are quite variable [31]. Agents used in these patients include benzodiazepines, barbiturates, narcotics, and propofol. Among the above sedatives, barbiturates are recommended by the Guidelines for the Management of Severe Head Injury [8]. However, a recent meta-analysis [32] found no evidence that barbiturate therapy in head-injured patients could improve the ultimate outcome. Thus, it is important to compare the data from other agents to determine a more ideal sedative agent than barbiturates for head-injured patients.

Propofol, a short-acting sedative-anesthetic agent which is structurally a phenolic derivative with high lipophilicity, has recently been used in head-trauma patients with increasing frequency [30]. The drug is known to induce sleep and reduce brain metabolism and CBF [23]. Propofol is fitted into a 3-compartmental pharmacokinetic model [1,4]. Its relative short half-life allows inducing the patients into conscious sedation quickly and also arousing them quickly so that one can perform intermittent neurologic examination [3]. Because of its unique pharmacokinetic and pharmacodynamic characteristics, propofol is used in head-injured patients [15]. It also provides neuroprotection through GABA inhibition [16]. In noncomparative studies in patients with head injury, propofol has been shown to maintain a mean CPP higher than 60 mm Hg and to reduce or maintain mean ICP [3,14,30]. Use of propofol in head injury patients should be further evaluated to understand its efficacy and safety.

The objective of the present multicenter, retrospective study was to evaluate the efficacy of propofol on the survival rates in treating severe head-trauma patients in Taiwan.

2. Materials and methods

2.1. Patient population and data collection

From January 2003 to December 2004, patients who sustained traumatic head injury and were admitted to Taipei Municipal Wan Fang Hospital, National Taiwan University Hospital, and Tamshui Mackay Memorial Hospital were included in this clinical trial. Patients were selected according to the following criteria: age of more than 12 years and less than 79 years; traumatic brain injury with a post resuscitation GCS score of 3 to 13; and requirement for mechanical ventilation. Patients were excluded if treated with other sedative agents at the same time; had poor prognosis and thus aggressive treatment, except supportive care, was not begun within 48 hours of injury, or if propofol was not administered for a minimum of 12 hours; had spinal cord injury with paraplegia or quadriplegia, or fixed dilated pupils with a GCS score of less than 3 after initial resuscitation. The severity of head injury for the patients was classified by GCS score according to the following definitions: moderate severity, if the patients have a GCS score of between 9 and 13; severe, if GCS score is between 5 and 8; and critical, if GCS score is between 3 and 4 [33].

The collected variables included age, sex, body weight, clinical symptoms, surgical date, admission date, GCS score at admission, diagnosis, complications, date of surgery, ICU length of stay, therapeutic outcome (discharge or death), and date of discharge. Clinical data collected were mean daily ICP, mean daily CPP, mean daily $PaCO_2$, mean daily fluid balance. The required daily doses for mannitol, sedative agents, vasopressors, neuromuscular blockage agents, systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature were monitored and recorded. Intracranial pressure was continuously monitored and recorded every hour, and CPP was recorded every 4 hours in the ICU. Safety data were also collected. Any documented severe adverse drug reaction had been included into the data collection form.

2.2. Treatment protocol

The stepwise management protocol to control ICP and CPP included CSF drainage and administration of mannitol, vasopressors, and sedatives. Drainage of CSF can reduce the volume in the cranium and promote better blood flow. Use of sedatives, including propofol, was depended on the clinical evaluation of neurosurgeons according to the clinical condition of the critical patients. The dose of propofol was initiated at 5 μg/kg per minute for 5 minutes and slowly titrated up to 100 to 150 μg/kg per minute at a rate of 12.5 μg/kg per minute every 5 minutes. The dose was increased as needed for agitation or if ICP levels persisted above 20 mm Hg. The depth of sedation targeted Ramsey Sedation Scale of 4, allowing the patient with brisk response to light glabellar tap or loud noise. Propofol was temperately discontinued to exam the muscle strength to reach grade of 3 every day. Propofol was used for at least 3 days and discontinued once the patient was extubated. Mannitol 2.5 to 5.0 g/kg was administered every 2 to 3 hours as needed to maintain an ICP of less than 20 mm Hg in all the medical centers. To keep effective CPP higher than 60 mm Hg, vasopressors were given if systolic blood pressure dropped to less than 100 mm Hg or CPP to less than 60 mm Hg. Pentobarbital, the sedative of choice among barbiturates, as well as other barbiturates, was discouraged for use in all centers in this study.

2.3. Drug administration

The sedatives used in all the hospitals were propofol (Diprivan®, containing propofol, 200 mg/20 mL per amp; Astra Zeneca Co Ltd). The vasopressors used in the trial

Table 1
Demographics

	Propofol group (n = 44)	Nonpropofol group (n = 60)	P*
Sex			
Male, n (%)	31 (70.75)	40 (66.67)	.832
Female, n (%)	13 (29.55)	20 (33.33)	
Age	41.91 ± 20.41	43.48 ± 23.19	.097
12-19 y, n (%)	8 (18.18)	10 (16.67)	
20-39 y, n (%)	13 (29.55)	20 (33.33)	
40-64 y, n (%)	13 (29.55)	11 (18.33)	.811
65-79 y, n (%)	10 (22.72)	19 (31.67)	
Body weight (kg)	66.66 ± 15.47	64.64 ± 12.65	.963
Baseline GCS score*	5.86 ± 1.84	5.66 ± 1.59	.729

* Statistical test by χ^2 test ($P < .05$).

included dopamine (Dopmin®, containing dopamine HCl 200 mg/5 mL per amp; Synmosa Biopharma Co Ltd, Taiwan), norepinephrine (Levophed®, containing norepinephrine bitartrate 4 mg/4 mL per amp; Abbott Laboratories Services Corp, Taiwan Branch), and epinephrine (Bosmin®, containing epinephrine HCl 1 mg/1 mL per amp; Daiichi Pharmaceutical Taiwan Ltd). The neuromuscular blockage agents were atracurium (Tracrium®, containing atracurium besylate 25 mg/2.5 mL per amp; Glaxo Operations UK Ltd, Taiwan), pancuronium (Pavulon®, containing pancuronium bromide 8 mg/2 mL per amp; Organon-Taiwan), and vecuronium (Nocuron®, containing vecuronium 10 mg per amp; Organon-Taiwan).

2.4. Statistic analysis

All statistical analyses were performed using the SPSS software (version 10.0, SPSS Inc, Chicago, Ill). Statistical significance for all analyses was defined as a P value of less than .05. Quantitative variables were compared by using the independent t test, if they were normally distributed, or the Mann-Whitney U test, if they were not. Qualitative variables were compared by using the χ^2 test or Fisher exact test.

3. Results

3.1. Subjects

From January 1, 2004, to December 31, 2004, 151 head-injured patients were admitted to the 3 medical centers mentioned above. Of the 151 patients, 24 were excluded because their age was either less than 12 years (3 patients) or more than 79 years (21 patients). Of the remaining 127 patients, 23 patients were excluded from the present study according to the exclusion criteria. The data of the remaining 104 patients were therefore analyzed.

Baseline and interventional physiologic data are shown in Table 1. Of the 104 subjects, 71 were males and 33 were females. The mean age was 40.8 ± 22 years and the median GCS score was 6 (range, 3-10) on admission. Among the 104 patients who met the inclusion criteria, only 44 were given propofol. The mean age was 41.91 ± 20.41 years for the propofol group and 43.48 ± 23.19 years for the nonpropofol group ($P = .097$). The 2 groups did not differ significantly in age, body weight, and sex. The mean GCS scores for the 2 groups were not statistically different, and the median GCS scores at admission were 6 in both groups. The proportion of patients with a GCS score of 3 to 8 was 93.18% in the propofol group and 95% in the nonpropofol group ($P = .729$).

3.2. Outcome

A higher survival rate was found in the propofol group than in the nonpropofol group (81.82% vs 46.67%, $P < .001$) as shown in Table 2. There was a statistically significant difference in the mean ICP for the first 3 days in the ICU (propofol vs nonpropofol group: 17.23 ± 9.0 vs 33.19 ± 32.56 mm Hg, $P = .017$, respectively). Intracranial pressure was also significantly different between the 2 groups on day 1 ($P = .009$), day 2 ($P = .003$), and day 3 ($P = .043$) as shown in Table 3. Mean CPP for the first 5 days in the ICU was 71.10 ± 15.32 mm Hg in the propofol group and 43.20 ± 29.92 mm Hg in the nonpropofol group, respectively ($P < .001$). The mean daily $PaCO_2$ was similar between the propofol group (30.78 ± 4.07 mm Hg) and the nonpropofol group (32.00 ± 6.20 mm Hg) ($P = .288$). The mean GCS score within 5 days in the propofol group was significantly lower than that in the nonpropofol group (7.14 ± 2.62 vs 5.66 ± 2.76, $P = .007$), with smaller proportion of patients with a GCS score of 3 to 8 in the propofol group than in the nonpropofol group after 5 days of

Table 2
Outcomes of patients in the propofol and nonpropofol groups

	Propofol group (n = 44)	Nonpropofol group (n = 60)	P
Survival rate, n (%)	36 (81.82)	28 (46.67)	<.001[a]
Mean ICP for the first 3 d (mm Hg)	17.23 ± 9.0	33.19 ± 32.56	.017[b]
Day 1	15.71 ± 10.33	31.43 ± 26.60	.009[b]
Day 2	17.77 ± 9.06	43.38 ± 39.35	.003[b]
Day 3	19.67 ± 10.52	39.71 ± 42.91	.043[b]
Mean CPP for the first 5 d (mm Hg)	71.10 ± 15.32	43.20 ± 29.92	<.001[b]
Mean GCS in the first 5 d	7.1 ± 2.6	5.7 ± 2.8	.007[b]
Day 1	6.5 ± 1.7	5.7 ± 2.3	.041[b]
Day 2	7.1 ± 2.7	5.7 ± 2.6	.013[b]
Day 3	7.3 ± 3.4	5.9 ± 3.1	.026[b]
Day 4	7.9 ± 3.6	6.2 ± 3.5	.027[b]
Day 5	8.1 ± 3.7	6.1 ± 3.5	.027[b]
Mean $PaCO_2$ for the first 5 d (mm Hg)	23.15 ± 8.12	24.71 ± 8.34	.350

[a] Statistically significant by χ^2 test ($P < .05$).
[b] Statistically significant by independent t test ($P < .05$).

Table 3
Mortality rate for each injury category

Injury categories	Propofol group (n = 44)		Nonpropofol group (n = 60)		P
	n	Mortality (%)	n	Mortality (%)	
Critical	12	2 (16.67)	16	11 (68.75)	.022*
Severe	29	5 (17.24)	41	21 (51.22)	.005*
Moderate	3	1 (33.33)	3	0 (0)	.6*
Total	44	8 (18.18)	60	32 (53.33)	<.001*

* Statistically significant by χ^2 test ($P < .05$).

treatment (13.5% vs 18.5%). No significant adverse drug reaction has been collected from the medical charts.

3.3. Drug administration

The mean daily dose of propofol was 1430.48 mg/d in patients of the propofol group. Vasopressors were required in 45 patients, including 12 patients (26.67%) in the propofol group and 33 patients (73.33%) in the nonpropofol group ($P < .001$). The most commonly used vasopressors in the trial were dopamine and norepinephrine. Among the 45 patients using dopamine, mean dose of dopamine was statistically higher in the propofol group than in the nonpropofol group, which was 333.28 ± 318.25 mg/d and 666.40 ± 362.53 mg/d in the propofol and nonpropofol group, respectively ($P = .026$). Mean doses of norepinephrine were similar in the 2 groups (13.83 ± 22.41 mg/d in the propofol group vs 20.28 ± 14.79 mg/d in the nonpropofol group, $P = .508$). There were 101 patients given mannitol, including 44 (100%) in the propofol group and 57 (93.47%) in the nonpropofol group, respectively ($P = .138$).

3.4. Subgroup analysis—mortality rates in injury categories

Patients were further categorized into critical (baseline GCS score of 3-4; 28 patients), severe (baseline GCS score of 5-8; 70 patients), or moderate (baseline GCS score of 9 to 13; 6 patients) subgroups based on the baseline GCS score. The mortality rate was associated with the severity of the injury of the patients, with a value of 46.43% in the critical group, 37.14% in the severe group, and 16.67% in the moderate group (Fig. 1).

The mortality rates for patients with or without propofol in the 3 subgroups are shown in Table 3. Patients using

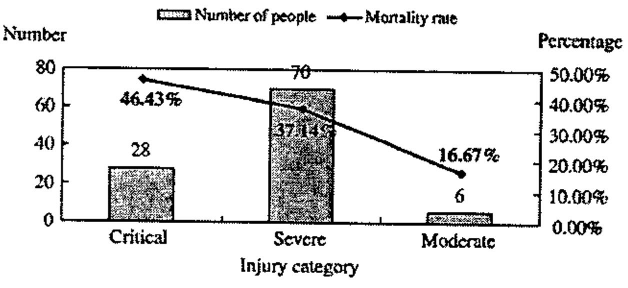

Fig. 1. The relationship between mortality rate and injury category. *Injury categories: critical, if GCS score was between 3 and 4; severe, if GCS score was between 5 and 8; and moderate, if GCS was between 9 and 13.

propofol had significantly lower mortality rates than patients not using propofol in the critical subgroup ($P = .022$) and severe subgroup ($P = .005$). There was no difference for patients with or without propofol treatment for the moderate subgroup.

4. Discussion

The data of the present study demonstrated that the head-injured patients in Taiwan treated with propofol had a higher survival rate, decreased ICP, higher CPP, and better GCS scores. The 2 groups with or without administration of propofol did not differ in the treatment of mannitol. The percentage of patients requiring vasopressors in the propofol group was lower than that in the nonpropofol group ($P < .001$). As vasopressors were administered to keep effective CPP above 60 mm Hg, the higher rate of administration indicated more unstable hemodynamics in the nonpropofol group than in the propofol group. The data showed that propofol has effectively decreased ICP to less than 20 mm Hg and maintained CPP above 70 mm Hg in the propofol group, which reached the suggested targets endorsed by current guidelines to improve the survival rate in head-injured patients.

A limitation of the present study is the nature of retrospective study. The baseline standard care might not be the same in all patients. As the criteria to give skeletal muscular blockade agents and vasopressors were the same for all surgeons in the 3 centers, the impact of the major confounding factors on the results was limited. Retrospective data collection reduced the reporting rate of adverse drug reactions, as minor adverse reactions might not have been documented. The study was also limited by the nature of retrospective review which was unable to give a standard interpretation of CT data and to collect the data of postinjury assessment at 6 months or 1 year. More outcome variables need to be measured in further studies.

The efficacy of different sedatives used in head-injured patient has been investigated in few studies. The effects of barbiturates in severe head injury are controversial. Some studies showed that the use of barbiturates improved ICP control and outcomes [24,25], but this effect was not significant in a recent meta-analysis [32]. Pentobarbital has an average half-life of 15.6 hours in head-injury patients [7] and often produces withdrawal symptoms, including delirium, convulsions, and possibly death, and tolerance, psychological, and physical dependence after continued use. It is also recommended to monitor blood pentobarbital concentrations frequently and regularly to adapt the dose to changes in clearance and thus increase the inconvenience of administration.

The efficacy of benzodiazepams in head-injured patients has been assessed by previous studies. Studies comparing propofol with midazolam showed that both agents equally reach the desired level of sedation and hemodynamics, but the propofol group woke up faster after discontinuation [34,36]. Although midazolam reliably reduces $CMRO_2$ and CBF, an increase in ICP was reported when control ICP was less than 18 mm Hg [29]. Midazolam is metabolized by the liver to its active α-hydroxy-midazolam (1-OH-midazolam [1-OH-M]), which may accumulate in patients with renal failure. It also interacts with many drugs undergoing CYP3A4 metabolism in clinically significant level [6]. For long-term sedation in the ICU, propofol has the same safety and effectiveness, but better cost-benefit ratio and quality of sedation than midazolam [5,9,10,34]. A study compared lorazepam, midazolam, and propofol in critically ill trauma patients, showed that the 3 agents provided equal efficacy on sedation. Lorazepam, although more cost-effective, caused oversedation more commonly than the 2 other agents [22].

Narcotics such as morphine, fentanyl, and sulfentanil have no effect on $CMRO_2$ or CBF but increased ICP in some patients [2,14,19]. The short-acting neuroprotectant etomidate is not suited for prolonged use due to its renal toxicity and adrenal suppression [20,39]. In a randomized, double-blind trial with moderately or severely head-injured patients, ICP and CPP were generally similar in groups treated with propofol or morphine [17]. Less intensive therapy for ICP control and similar long-term neurologic outcomes were obtained in the propofol group than in the morphine group.

Compared with other sedatives, several properties of propofol make it an attractive choice for head-injured patients. Propofol has no significant drug interactions or metabolites and does not require drug concentration monitoring. Its short onset of action and elimination of half-life permit frequent neurological assessments [1,4,24]. The effect of propofol on CBF, cerebral metabolism, and ICP reduction has been reliably proved in a number of studies [30].

The use of propofol is limited by some side effects in head-injured patients. The most common adverse effects associated with propofol include hypotension, hypertriglyceridemia, infusion syndrome, increased liver function tests, and even rhabdomyolysis [11,22,26,36,39]. Other adverse effects associated with propofol include respiratory acidosis during weaning from the ventilator, green discoloration of the urine, and rare occurrence of anaphylactic reactions [18,39]. Hypertriglyceridemia is due to the fat emulsion formulation of propofol and is actually counterbalanced by providing more energy source for patients under physical distress. In relatively high doses, infusion syndrome can occur and lead to mortality [18,26]. It has been discouraged to infuse propofol at rates higher than 5 mg/kg per hour in the ICU [11]. Dose-related side effects should be closely monitored and can be avoided by using appropriate titration method of administration.

Racial difference in the dose-response relationship of propofol has been discussed in the literature. Previous studies have found that there was a statistically significant difference between Caucasians and African Blacks in the arousal time from intravenous anesthesia with propofol [27]. The ratio recovery time based on the consumption of propofol was significantly lower in whites than in all the other groups [28]. The present study provides additional evidence on the use of propofol to treat head-injured patients in Taiwanese. With the profile of severe side effects, a distinct regimen of propofol use should be investigated in more detail in the future to avoid unwanted side effects in head-injured patients in Taiwan.

The data of the current study demonstrated that propofol improved the recovery phase in patients with head injury. Propofol decreased ICP to less than 20 mm Hg and maintained CPP above 70 mm Hg. The survival rate in the propofol group was significantly higher than that in the nonpropofol group. Propofol can be suggested for use in the treatment of head-injured patients because of the beneficial clinical outcomes and unique pharmacokinetic/pharmacodynamic characteristics. Further studies are needed to establish the best protocol for using propofol in head-injury patients.

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Trauma

Survey of traumatic intracranial hemorrhage in Taiwan

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Abstract

Background: Injury ranked third among the top 10 leading causes of death in Taiwan from 1964 to 1996 and is still among the top 10 presently. Among transportation accidents, motor vehicle–related injury had the highest incidence rate, often resulting in traumatic head injury.

Methods: This survey was conducted from July 1, 1994, to June 30, 2002, and was collected from 55 major hospitals in Taiwan. A total of 90 250 patients with TBI were enrolled, and 27 585 cases were identified to have TIH. In this study, SPSS 10.0 (SPSS, Chicago, Ill) was used to process the data. Regarding the rating model itself, reliability and correlation tests were conducted to calculate the coefficiency, and factor analysis was carried out to verify its validity.

Results: The incidence rate of male-to-female ratio was 2.65. Traffic injuries (67.6%) were the leading causes of TIH. Among the traffic injuries, motorcycle-related traumatic injuries had the highest incidence rate (69.6%). In the logistic regression analysis, older patients had the highest risk of developing TIH. Patients without a motorcycle helmet had a higher risk (odds ratio, 1.40) of developing TIH than those with a helmet. As regards the types of injuries, pedestrian injury (odds ratio, 1.61) had the highest risk of developing TIH.

Conclusions: Although traffic injuries, especially those caused by motorcycles, are the major cause of intracranial hemorrhage, we have to pay due attention to falling, pedestrian, and bicycle injuries, as these are all major causes of intracranial hemorrhage.

Keywords: Head injury; Traumatic intracranial hemorrhage; Traumatic brain injury

1. Introduction

Injury ranked third among the top 10 leading causes of death in Taiwan from 1964 to 1996. Since July 1997, the law regarding compulsory helmet wearing by all motorcycle riders has been in force, and this helmet law reduced the head trauma cases by one third and the number of cranial operations by 42%, which results in a drop in the ranking of injury to fifth place. However, the mortality of injury remains high in Taiwan especially among individuals aged younger than 34 years [1,2].

Among the transportation injuries in Taiwan, motor vehicle–related injury has the highest incidence rate and often results in traumatic head injury. Intracranial hemorrhage complicates the TBI occasionally, and this miserable situation occurs mainly in young males. Because of the high productivity and work ability of the young people, especially young males, such injuries will affect their welfare and that of their family, and even the whole society as well. Family income may be affected if a young man is disabled by accidental head injury. From the viewpoint of social economy, the huge medical expenses from long-term

Abbreviations: GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; ICD-9, international classification of diseases (ninth edition); TBI, traumatic brain injury; TIH, traumatic intracranial hemorrhage.

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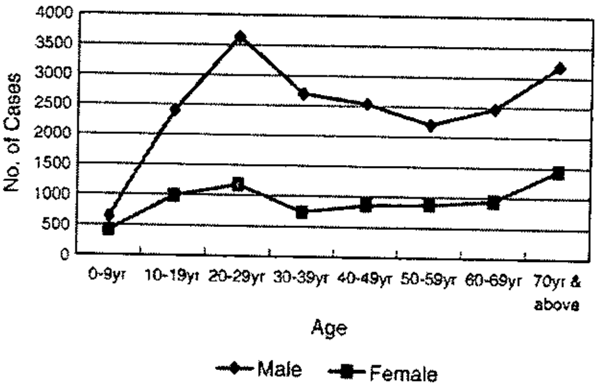

Fig. 1. Correlation of age and sex in intracranial hemorrhage.

treatment and rehabilitation will not only seriously consume medical resources but also affect the overall economic development and increase the burden of the whole country indirectly. Therefore, we should consider this as a key issue in determining the policy of national health care [3].

To determine the severity and prognosis of intracranial hemorrhage caused by head trauma in Taiwan, we carried out a study on 90 250 head trauma cases from 55 hospitals from July 1, 1994, to June 30, 2002. There were a total of 27 585 head trauma–related intracranial hemorrhage cases. By studying the causes, severity, and prognosis of these cases, we made an attempt to learn more details about traumatic intracranial bleeding and to discover the risk factors for future prevention of the complication.

2. Methods

2.1. Study subjects

Basing on ICD-9, trained personnel reviewed from July 1, 1994, to June 30, 2002, the head injury admission notes and diagnostic charts of 55 hospitals in Taiwan, and transcribed those head trauma medical records into a structured questionnaire. All collaborating hospitals had more than 100 beds and also had adequate facilities and experience for head trauma management. The questionnaire used for this study had been tested for both reliability and validity, and the basic information about head trauma such as the medical history, sex, age, head trauma condition and severity (GCS) were recorded. The questionnaire also addressed the date of hospital admission, the presence or absence of intracranial hemorrhage and the bleeding area, the injury condition, whether or not a helmet was worn, treatment status, and outcome (GOS). The study focused only on hospitalized cases, and outpatient or dead-on-arrival cases were excluded.

2.2. Head trauma definition

Head trauma was defined as obvious brain injury, concussion, or skull fracture. The definition of clinical manifestations included loss of consciousness, posttraumatic amnesia, and neurologic deficits. The presence of any one of the abovementioned signs or symptoms was diagnosed as head trauma [4-6].

2.2.1. Glasgow Coma Scale

The GCS is an index for assessing patient's consciousness. By grading an individual's eye opening, motor responses, and verbal responses, the level of consciousness can be assessed. The highest score for an adult is 15, whereas the lowest score is 3. Hung et al [7] classified the GCS into 3 levels: severe injury (3-8 points), moderate injury (9-12 points), and mild injury (13-15 points).

2.2.2. Glasgow Outcome Scale

The GOS was used to categorize the outcome of patients with TBI at the time of hospital discharge as follows: (1) death; (2) persistent vegetative state; (3) severe disability—conscious but dependent; (4) moderate disability—disabled but independent; and (5) good recovery [6,8].

2.2.3. Traumatic intracranial hemorrhage definition

Traumatic intracranial hemorrhage was based on computed tomography scan diagnosis and defined as head trauma–related injury. Traumatic intracranial hemorrhage included epidural hematoma, subdura hematoma, intracerebral hemorrhage, subarachnoid hemorrhage, and intraventricle hemorrhage. If there were more than 2 kinds of hemorrhage identified by the computed tomography scan, we registered this patient to each category of hemorrhage simultaneously.

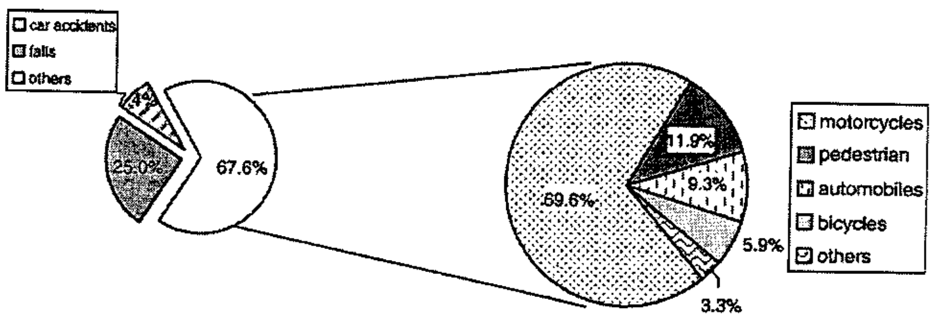

Fig. 2. Causes of intracranial hemorrhage.

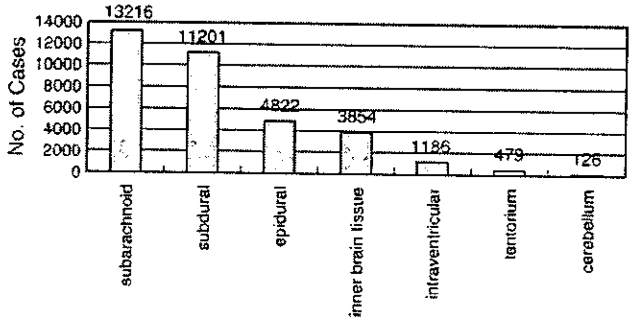

Fig. 3. Sites for intracranial hemorrhage.

2.3. Data processing and analysis

Researchers collected the questionnaires from each hospital regularly. After decoding the collected questionnaires, all data were saved in an Excel file followed by processing with SPSS 10.0 for statistical analysis (SPSS, Chicago, IL, USA). Frequency distribution and percentage were used as basic descriptive statistical data, followed by the χ^2 test. Logical regression analysis was then performed to those variables with a significant difference.

3. Results

There were 90250 head trauma cases from 55 hospitals in Taiwan. A total of 27585 patients were diagnosed to have intracranial hemorrhage, including 19865 males (72.6%) and 7514 females (27.4%). The male-to-female ratio was 2.7(Fig. 1). In the mortality rate of intracranial hemorrhage, male deaths occurred 3 times as often as female deaths (2369 [75.0%] vs 789 [25.0%]). Among all the age groups, those from 20 to 29 years carried the highest rate (4852 [17.7%]) (Fig. 1).

Among various causes of intracranial hemorrhage, the most common was traffic injuries (18573 [67.6%]), followed by falls (6873 [25.0%]) and assaults (945 [3.4%]). Further analysis of the types of vehicles causing injuries shows that motorcycle injuries were the first with

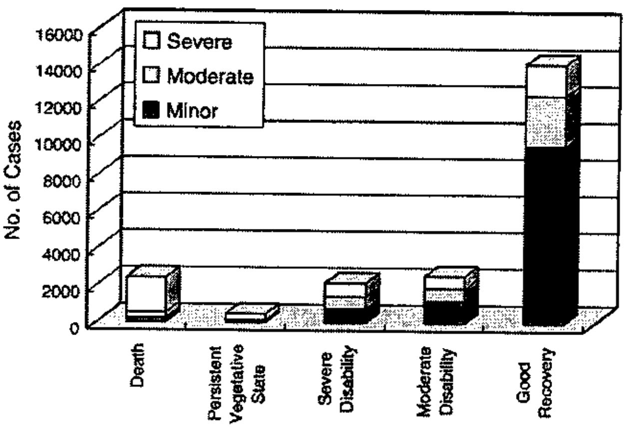

Fig. 4. Correlation of intracranial hematoma and severity (GCS) and prognosis (GOS).

12052 cases (69.6%); pedestrian accidents were the second with 2066 cases (11.9%). Car injuries were the cause in 1623 cases (9.3%), bicycles in 1030 cases (5.9%), and the other causes, such as train injuries, were rare (Fig. 2).

For the major location of the hemorrhage, we found that subarachnoid hemorrhage occurred in 13216 (47.9%), subdural in 11201 (40.6%), epidural in 4822 (17.5%), intracerebral in 3854 (14.0%), and intraventricular in 1186 (4.3%) (Fig. 3).

By using the GCS to assess the severity of head trauma with intracranial hemorrhage, we found 13242 (52.5%) mild cases, 5154 (20.4%) moderate cases, and 6849 (27.1%) severe cases. Based on the results of the GOS, we observed 3180 (13.5%) individuals who died from intracranial hemorrhage, 610 (2.6%) who became persistently vegetative, 2435 (10.3%) who remained severely disabled, 2767 (11.7%) who had moderate disability, and 14581 (61.9%) who had a good recovery (Fig. 4).

χ^2 Analysis was used to determine the correlation among variables of sex, age, cause of injury, and hemorrhage condition within the group of TIH. The analysis showed that males tended to have a higher chance of intracranial hemorrhage than females (33.3% vs 25.8%), and that the difference was statistically significant ($P < .001$).

Table 1
Correlation between variables of sex, age, cause of injury, and hemorrhage condition among intracranial trauma cases

Intracranial hemorrhage	Yes, n (%)	No, n (%)	Total	P
Sex				<.001
Male	19865 (33.3%)	39745 (66.7%)	59610	
Female	7514 (25.8%)	21606 (74.2%)	29120	
Age				<.001
0-9 y	1074 (24.8%)	3260 (75.2%)	4334	
10-19 y	3407 (27.3%)	9078 (72.7%)	12485	
20-29 y	4852 (24.1%)	15313 (75.9%)	20165	
30-39 y	3472 (25.7%)	10038 (74.3%)	13510	
40-49 y	3429 (28.9%)	8417 (71.1%)	11846	
50-59 y	3099 (35.3%)	5676 (64.7%)	8775	
60-69 y	3457 (42.8%)	4613 (57.2%)	8070	
≥70 y	4686 (47.3%)	5218 (52.7%)	9904	
Causes				<.001
Car injuries	18573 (31.6%)	40256 (68.4%)	58829	
Falls	6873 (36.2%)	12089 (63.8%)	18962	
Others	2035 (18.1%)	9202 (81.9%)	11237	
Types of injuries				<.001
Motorcycles	12052 (31.2%)	26556 (68.8%)	38608	
Bicycles	1030 (37.4%)	1724 (62.6%)	2754	
Pedestrian	2066 (39.0%)	3236 (61.0%)	5302	
Automobiles	1623 (27.1%)	4371 (72.9%)	5994	
Others	546 (32.3%)	1145 (67.7%)	1691	
Types of falls				<.001
High-height (>1 m)	1944 (41.6%)	2724 (58.4%)	4668	
Low-height (≤1 m)	1517 (33.7%)	2983 (66.3%)	4500	
Tripped/tumbled	2526 (33.8%)	4945 (66.2%)	7471	
Wearing helmets				<.001
Yes	1906 (25.2%)	5670 (74.8%)	7576	
No	7646 (32.9%)	15583 (67.1%)	23229	

Correlation between age stratification and intracranial hemorrhage showed a significantly higher incidence in older patients (>50 years old) with head trauma ($P < .001$). Among the causes of head trauma, we found that injury caused by falling had a higher incidence of intracranial hemorrhage (36.2%) than traffic injuries (31.6%), and this was also statistically significant ($P < .001$). Comparison of traffic-accident types showed that pedestrian injuries had the highest rate (39.0%) of intracranial hemorrhages; bicycle injuries came next (37.4%), followed by motorcycle (31.2%) and car accidents (27.1%) ($P < .001$). As to falling injuries, a fall from a high place (≥1 m) had a higher incidence for intracranial hemorrhage (41.6%) than a fall from a lower place (<1 m) (33.7%) and a fall on slippery floors (33.8%). Among motorcycle incidents, helmet wearing was the key factor affecting intracranial hemorrhage. People who did not wear a helmet had a higher rate of intracranial hemorrhage than those who did (32.9% vs 25.2%); the difference was statistically significant ($P < .001$) (Table 1).

The correlation between severity (GCS) and intracranial hemorrhage makes it obvious that severely injured patients had a far greater chance than patients with minor injuries to develop intracranial hemorrhage (27.1% vs 2.4%). Those who did not have intracranial hemorrhage mainly sustained mild injury (92.4%); yet among those who had intracranial hemorrhage, 52.5% had mild injury. This result showed a statistically significant difference ($P < .001$). When studying the correlation between prognosis (GOS) and intracranial hemorrhage, we found that deaths among cases with intracranial hemorrhage were much more frequent than among cases without intracranial hemorrhage (13.5% and 0.6%, respectively). In fact, 91.7% of all cases without intracranial hemorrhage had a good prognosis, yet only 61.9% of cases with intracranial hemorrhage had a good prognosis. The data also showed statistical significance ($P < .001$) (Table 2).

Finally, we added the variables such as injury causes, vehicle-accident types, falling, and wearing of a helmet or not at the time of the injury, and reanalyzed those variables

Table 2
Correlation between severity (GCS) and intracranial hemorrhage, and correlation between prognosis (GOS) and intracranial hemorrhage

Intracranial hemorrhage	Yes, n (%)	No, n (%)	Total	P
Severity (GCS)				<.001
Severe	6849 (27.1%)	1441 (2.4%)	8290	
Moderate	5154 (20.4%)	3219 (5.3%)	8373	
Minor	13242 (52.5%)	56265 (92.4%)	69507	
Total	25245	60925	86170	
Prognosis (GOS)				<.001
Death	3180 (13.5%)	370 (0.6%)	3550	
Persistent vegetative state	610 (2.6%)	98 (0.2%)	708	
Severe disability	2435 (10.3%)	1160 (2.0%)	3595	
Moderate disability	2762 (11.7%)	3160 (5.4%)	5922	
Good recovery	14581 (61.9%)	53206 (91.7%)	67787	
Total	23568	57994	81562	

Table 3
The most significant risk factors affecting intracranial hemorrhage

	OR[a]	95% CI	OR[b]	95% CI
Sex				
Male	1.44	1.40-1.48	1.48	1.43-1.53
Female	1	–	1	–
Age				
≥70 y	2.73	2.52-2.95	2.72	2.51-2.95
60-69 y	2.28	2.10-2.47	2.22	2.05-2.41
50-59 y	1.66	1.53-1.80	1.64	1.51-1.79
40-49 y	1.24	1.14-1.34	1.22	1.12-1.32
30-39 y	1.05	0.97-1.14	1.01	0.94-1.10
20-29 y	0.96	0.89-1.04	0.93	0.86-1.00
10-19 y	1.14	1.05-1.23	1.11	1.02-1.20
0-9 y	1	–	1	–
Causes				
Car injuries	2.09	1.98-2.20	2.18	2.07-2.29
Falls	2.57	2.43-2.72	2.34	2.21-2.48
Others	1	–	1	–
Types of car injuries				
Motorcycles	1.22	1.15-1.30	1.28	1.21-1.37
Bicycles	1.61	1.46-1.77	1.55	1.41-1.71
Pedestrian	1.72	1.59-1.86	1.61	1.48-1.75
Others	1.28	1.14-1.44	1.27	1.13-1.43
Automobiles	1	–	1	–
Types of falls				
High-height	1.40	1.30-1.51	1.64	1.52-1.78
Low-height	0.99	0.92-1.10	1.14	1.05-1.24
Falls	1	–	1	–
Wearing helmets				
No	1.44	1.36-1.52	1.40	1.32-1.48
Yes	1	–	1	–

[a] Crude odds ratio.
[b] Adjustment for age and sex.

with age and sex to obtain the most significant risk factors for intracranial hemorrhage (Table 3). We found that injury caused by falling carried a risk 2.34 times (95% confidence interval [CI], 2.21-2.48) higher than that of other variables, and the risk was 2.18 times higher for traffic injuries (95% CI, 2.07-2.29). As to the types of traffic injuries, pedestrian and bicycle injuries had the highest chances of developing intracranial hemorrhage, that is, 1.61 times (95% CI, 1.48-1.75) and 1.55 times (95% CI, 1.41-1.71), respectively. For the causes of falling injuries, falls from a higher place (>1 m) had a greater chance (1.64 times) than those on slippery floors (95% CI, 1.52-1.78) to be complicated with intracranial hemorrhage. In the motorcycle injuries, the chance of having intracranial hemorrhage among motorcyclists not wearing a helmet was 1.4 times higher than among those wearing a helmet (95% CI, 1.32-1.48) (Table 3).

4. Discussion

As far as our survey has revealed, Taiwan probably has the highest mortality rate of accidental injury in the world [9]. A review in 1983 showed that there were about 12.5% traumatic injuries with head trauma. Further analysis of the causes of mortality in these traumatic patients shows that

55% of the cases were directly related with head injuries. Among these patients with head-injury, about 30% had intracranial hemorrhage. Such a high incidence of TIH compelled us to face this issue seriously.

In our research on patients with intracranial hemorrhage, 19865 (72.6%) were males—much more numerous than females (7514 [27.4%]). Furthermore, the mortality rate of intracranial hemorrhage among male patients was 3 times higher than that among female patients. This result may be explained by the fact that males are most often in charge of high-risk jobs, and this gives them a higher chance of being exposed to danger. Besides, most males are more active than females and also tend to enjoy adventures or exciting activities [10].

An analysis of the head injury–related intracranial hemorrhages with age stratification shows that the age group from 20 to 29 years had the highest incidence, which was about 17.7% among all the patients with TIH. The age in this range coincides with the adolescence-adult period. People in this age group are usually very energetic, showing a lack of an adequate coping system. Sometimes they prefer to release the pressure by way of excessively speedy riding or driving of the vehicles. Therefore, it is understandable why so many injuries occurred and caused the highest incidence of TIH in this age group [11].

As to the cause of TIH, 67.6% of the cases were primary due to traffic injuries. Studies from other countries also show that traffic injuries are the most frequent cause, followed by falling [4,12-20]. In addition, the type of vehicles involved in the injuries was found to be primarily motorcycles (69.6%). The data on head injuries also showed that falling accidents caused intracranial hemorrhage more often than car injuries. However, among car injuries, pedestrian injuries had the highest chance, exceeding that of bicycle injuries with reference to intracranial hemorrhage. As motorcycles are the most popular transportation vehicles used in Taiwan, their number has increased dramatically in recent years. Because the incidence of traffic injuries is very high, and also because of the high proportion of motorcycles, motorcycle injuries are by far the most frequent cause of injury. These facts may divert our attention away from accidents caused by falling, pedestrian, and bicycles, and this will be another important issue requiring further evaluation.

As shown in Table 1, among all motorcycle injuries that caused intracranial hemorrhage, the number of those patients without helmet protection was 12% higher than that of those with a helmet. Therefore, in 1997, the Taiwanese government decreed that every motorcyclist wear a helmet for cranial protection, and this resulted in a dramatic decease in the number of head injuries, thus proving the great value of helmet wearing [21]. However, there are still some injuries caused by motorcyclists without a license or those under the legitimate age for qualification. These illegal motorcyclists are not mature enough to handle traffic situations adequately and, therefore, may endanger pedestrians, other motorcyclists, or car drivers on the road. The government should pay more attention to this serious problem.

5. Conclusion

It is true that in traffic injuries, motorcycle injuries are the primary cause of intracranial hemorrhage, but we should not forget to pay proper attention to falling, pedestrian, and bicycle injuries, as they are also major causes of intracranial hemorrhage. Policies and laws related to prevention of intracranial hemorrhage need to be enforced not only on falling, pedestrian, and bicycle injuries but also on how to reduce the severity of injury when injuries have taken place. We believe that an improvement in the traffic environment, for example, by installing safety equipment (railings or armrests), can reduce falling injuries, and rearranging sidewalks for pedestrians and bicycles and strictly prohibiting car entry can also help to reduce injuries. Furthermore, we may consider the helmet law for bicyclists. This bicycle helmet law has been enforced in some countries for more than 10 years. Australia was the first to enforce this law and reported a reduction in the incidence of head injuries by 39% [22]. The United States is also promoting helmet use for biking, which has also considerably reduced the medical expenses and mortality rate [23].

Many policies, such as compulsory helmet wearing and inspection of drunken drivers, have been implemented in recent years and have reduced the mortality rate of accidental injury. In 2002, 8489 people died from injuries in Taiwan; thus, injury dropped from third to fifth place among the 10 most common causes of death (Fig. 5). With this remarkable achievement, the government is still focusing its primary attention on motorcycle- and vehicle-injury prevention. We can be sure that if we make proper efforts in the prevention of falling, pedestrian, and bicycle injuries, the mortality rate from injuries will

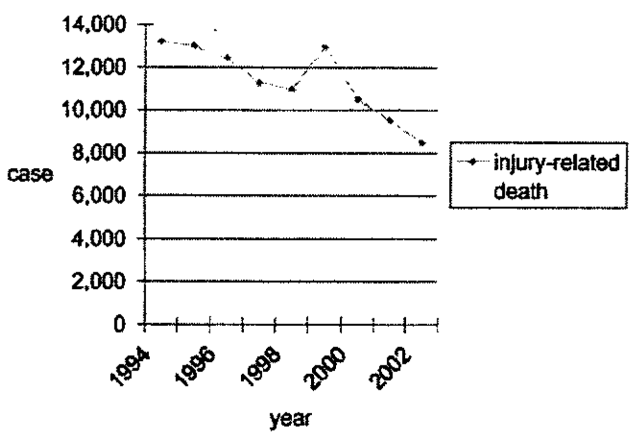

Fig. 5. Trend of Injury-related deaths in Taiwan, 1994-2002.

decrease even more, and this will help us build a better and safer living environment.

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Trauma

Clinical experience of hydroxyethyl starch (10% HES 200/0.5) in cerebral perfusion pressure protocol for severe head injury

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Abstract

Background: The present study was undertaken to evaluate 10% hydroxyethyl starch (HES 200/0.5) with regard to its clinical outcome and safety in the treatment of severe head injury.

Methods: Retrospective review of patient data from a prospectively designed standard treatment protocol for severe head injury. The standard protocol included (1) cerebral perfusion pressure higher than 60 mm Hg, (2) colloid solution (10% HES 200/0.5) 1000 mL/d in combination with crystalloid solution, (3) stepwise management of intracranial hypertension. Renal function, coagulation function, and electrolytes were evaluated every other day. The data of intracranial pressure, mean arterial pressure, cerebral perfusion pressure, intake, output, mannitol, complications, and outcome were recorded and analyzed.

Results: There were 78 patients, aged 45.61 ± 21.80 years, in this study. The initial Glasgow Coma Scale score was 6.35 ± 1.38. Seventy-three patients received operations with intracranial pressure monitoring. Blood transfusion was surgery related (days 1 and 2); otherwise, it was rarely used ($P < .05$). Prolonged prothrombin time was shown only 7 (2.65%) times of 234 of blood sampling. There was no anaphylactic reaction, pulmonary complications, or renal function deterioration in the course of our observation. The chart review of the patients at 6 months revealed the following: favorable outcome, 55.1%; unfavorable outcome, 33.3%; and mortality, 11.6%.

Conclusions: The 10% HES (200/0.5) can be used in the treatment protocol of severe head injury. There is no definite bleeding complications documented by current dosage of HES. Besides, balanced fluid management can be achieved without causing serious pulmonary complications. However, a further randomized, prospective study is needed to define the actual benefit of HES in fluid management and clinical outcome.

Keywords: Pentarstarch; Hydroxyethyl starch; Severe head injury; CPP-targeted therapy

1. Introduction

Adequate volume management is of major importance in critically ill patients [1,5,8,13,28] especially in severe head injury [15,33,23,44]. Clifton et al [9] reported that negative fluid balance was associated with poor prognosis. A large volume of fluid is needed to maintain adequate systemic blood pressure and cerebral perfusion pressure (CPP) [36,37]. Several infusion solutions are available for this purpose, including blood products, human albumin, crystalloids, and synthetic colloids [1,15,32,36]. Most of the studies have used albumin or fresh frozen plasma (FFP) as

Abbreviations: CPP, cerebral perfusion pressure; CVP, central venous pressure; EtCO2, end-tidal carbon dioxide pressure; FFP, Fresh frozen plasma; GCS, Glasgow coma scale; GOS, Glasgow outcome scale; HES, hydroxyethyl starch; HHS, Hypertonic hyperoncotic solutions; ICP, intracranial pressure; ICU, intensive care unit; IH, intracranial hypertension; INR, international normalized ratio; MAP, mean arterial pressure; PaCO2, arterial carbon dioxide pressure; PT, prothrombin time; SaO2, oxygen saturation.

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the supplement of colloid solution [1,6,15,33,37]. There is a growing consensus to use colloids in the treatment of severe head injury. However, there are still arguments between blood products and nonblood products [7,10,16,20,27]. The blood products are potentially hazardous substances, carrying risks of disease transmission, allergic reactions, and consequences of the administration of an acidotic, hypokalaemic solution containing the debris of dead and dying cells. In modern transfusion practice, it is not justified to use FFP as a volume expander. Limited and restricted blood transfusion has now become the consensus [7,16]. Hydroxyethyl starch (HES) is a derivative of starch consisting of glucose units bound by glycosidic bonds. In general, starch without hydroxylation groups is rapidly broken down by serum amylase. Through hydroxyethylation, the enzymatic degradation becomes more difficult, and the concentration of HES remains high. Hydroxyethyl starch has been widely used for volume expansion, hemodilution, and substitution of plasma in various situations [11,17,18,25]. Although the side-effects of older products have been reported worldwide, the application of medium-molecular-weight HES with a lower molar substitution ratio and C2/C6 ratio has demonstrated an adequate volume effect and relatively few adverse effects [12].

In the CPP-targeted therapy, combination of colloids and crystalloids has been used to maintain adequate cerebral flow and CPP [36,37]. To the best of our knowledge, there has been no relevant report about 10% HES used in this field. This study was undertaken to evaluate the clinical outcome after the use of 10% hydroxyethyl starch (HES 200/0.5) and the safety of its use in the treatment of severe head injury.

2. Subjects and methods

2.1. Subjects

From a retrospective chart review between September 2001 and February 2005, the patients with severe head injury in the neurosurgical intensive care unit (ICU) were enrolled in our study. Patients manifesting severe systemic injury with hypotension (systolic blood pressure less than 90 mm Hg on admission), a Glasgow Coma Scale (GCS) [39] score 3 with fixed and dilated pupils after resuscitation, a GCS score 3-4 with a family who refused aggressive treatment, and patients who had been admitted in the ICU for less than 48 hours were excluded.

Table 1
Fluid management protocol

1. Normal saline 1000 mL daily infusion
2. HES (10%, 200/0.5) 1000 mL infusion daily
3. NG tube feeding as early and as tolerated
4. Keep I/O balance with normal saline
5. Maintain CPP at or above 60 mm Hg
6. FFP only for coagulopathy (after day 2)

I/O indicates intake and output; NG, nasogastic.

Table 2
Management of increased intracranial pressure

1. Head up 30°, CPP > 60 mm Hg
2. CSF drainage if EVD available
3. Sedatives and NMB
4. Keep $ETCO_2$ 30-33 mm Hg
5. Osmotic diuretics (mannitol) infusion according to clinical ICP data
6. Decompressive craniectomy for brain edema

NMB indicates neuromuscular blockade; $ETCO_2$, end-tidal carbon dioxide; EVD, extraventricular drainage; CSF, cerebrospinal fluid.

2.2. Standard clinical management

Most of our patients received operations before being admitted to the ICU for evacuation of mass lesion such as epidural hematoma, subdural hematoma, or intraparenchyma hematoma. An intraparenchymal intracranial pressure (ICP) monitor (Codman electrode MicroSensor, Johnson & Johnson Medical, Ltd, USA) was used. The ICP monitor was connected to a Hewlett-Packard monitor model (66s-M116A) via a pressure transducer (Codman neuromonitor interface control unit, 82-6605) and module. The standard fluid management protocol (Table 1) and stepwise intracranial hypertension management [3,22,34] protocol (Table 2) were used. During the ICU stay, the patient's head was elevated at 30°. The neck was kept in the neutral position. $ETCO_2$ was maintained at around 30 to 33 mm Hg, and oxygen saturation on oximeter (SaO_2) 99% to 100%. Central venous pressure (monitored via the femoral vein) was maintained between 8 and 12 mm Hg. Mean arterial pressure (MAP) was monitored via the radial artery. Cerebral perfusion pressure (defined as MAP minus ICP) was kept higher than 60 mm Hg with a volume expander or inotropic agent, such as dopamine and Levophed, if needed. If ICP was greater than 40 mm Hg, unresponsive to nonoperative treatment modality, further craniectomy was then performed. Some patients received sedatives and neuromuscular blockers during the period of postoperative intensive care for ICP control.

2.3. Data collection

The data were collected daily for 7 days, which included ICP, MAP, CPP, intake, output, and the dosage of mannitol. Blood sample was taken for evaluation of renal function, coagulation function, and electrolyte every other day. Outcome was evaluated at 6 months after injury by the Glasgow Outcome Scale score [21], in which 'favorable outcome' was defined as a good recovery or a moderate disability, and 'unfavorable outcome' was defined as a severe

Table 3
Demographic data

No. of patients	78
Men	52
Women	26
Initial GCS (mean ± SD)	6.35 ± 1.38
Age (mean ± SD)	45.61 ± 21.80
ICP monitoring	n = 73

n Indicates patients who received ICP monitor implantation.

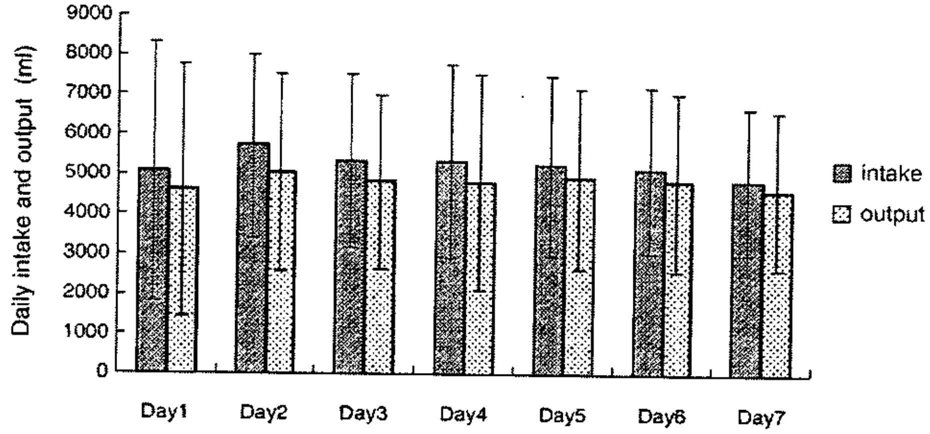

Fig. 1. The daily intake and output was presented as mean ± SD (N = 78) from day 1 to day 7. By means of colloid solution infusion, the daily intake and output could be maintained at optimal range (5000-6000 mL).

disability or a vegetative state (Table 5). The complication of coagulopathy was defined as prothrombin time (PT) international normalized ratio (INR) higher than 1.5. Renal function impairment was defined as serum creatinine level higher than 1.5. Pulmonary complication was defined as acute lung edema or adult respiratory distress syndrome.

2.4. Data analysis

All data were presented as the mean ± SD. Repeated measures analysis of variance was used for the fluid management between days. Statistical significance was defined as a probability value of less than .05. Commercially available software (version 10.0, SPSS, Inc, Chicago, Ill) was used.

3. Results

Originally there were 111 consecutive patients enrolled in this study; however, due to the exclusion criteria, only 78 patients ultimately were included. The clinical data of these patients were shown on Table 3. The average age was 45.61 ± 21.80 years. There were 52 men and 26 women. The initial GCS among these patients was 6.35 ± 1.38. Seventy-three patients underwent operations with ICP monitoring. There were 5 patients who received conservative treatment only. The daily intake and output are shown in Fig. 1. From days 1 to 7, the mean intake was 5220 ± 2320 mL/d, and mean output was 4793 ± 2414 mL/d. However, a decreasing trend of crystalloid solution and an increasing trend of oral intake were observed (Fig. 2). The percentage of ICP greater than 40 mm Hg was 5.48% (4/73) in the first day. The percentage was not changed until the end point of the study at day 7. Cerebral perfusion pressure less than 60 mm Hg was observed in 5.48% (4/73). Blood products used in the treatment course are shown in Table 4. It was demonstrated that many blood products were used in the first 2 days. We believe that it was surgery related. A repeated measure analysis among days shows that there was a significant difference ($P < .05$) between day 1 and days 3 to 7, as well as between day 2 and days 3 to 7 (Fig. 3). No

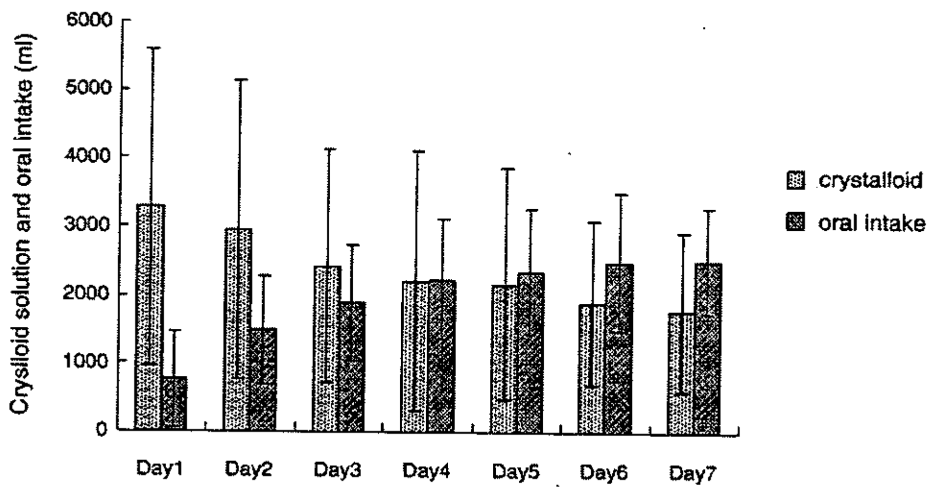

Fig. 2. The crystalloid solution and oral intake was presented as mean ± SD from day 1 to day 7, respectively (N = 78). The oral intake increased day-by-day, but the crystalloid solution decreased gradually from day 1 to day 7.

Table 4
Number of patients transfused within 1 week

	Day 1 N = 78	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
FFP	26 (33.3)	14 (17.9)	6 (7.6)	1 (1.2)	3(3.8)	3 (3.8)	2 (2.5)
PRBC	28 (35.8)	36 (46.1)	23 (29.4)	14 (17.9)	3 (3.8)	9 (11.5)	8 (10.2)
PLT	9 (11.5)	15 (19.2)	9 (11.5)	3 (3.8)	0	2 (2.5)	0
WB	7 (8.9)	7 (8.9)	3 (3.8)	1 (1.2)	0	0	0

Values are expressed as n (%).
PRBC indicates packed red blood cell; PLT, platelet; WB, whole blood.

anaphylactic reaction associated with HES during our treatment course was observed. The PT INR greater than 1.5 was seen only 7 (2.65%) times of 234 blood samplings. No renal function impairment occurred during our observation period. No patients developed acute lung edema or adult respiratory distress syndrome. The outcomes of our patients from chart review at 6 months are shown in Table 5. The rates of favorable outcome, unfavorable outcome, and mortality were 55.1%, 33.3%, and 11.6%, respectively.

4. Discussion

4.1. Limitations of our study

We have performed a retrospective review of our experience in using HES in a consecutive series of patients with TBI as a plasma expander and report the safety of this agent and, in a limited fashion, report the efficacy in maintaining plasma volume and CPP. It is important to select hyperoncotic fluids in these critically ill patients and avoid toxicities inherent in transfusion of blood products. However, it is difficult to compare with other study groups because many confounding factors may interact with each other. A different treatment protocol would make the clinical data quite different. Therefore, a prospective randomized study comparing these 2 groups with and without HES may be more convincing. For the complication of coagulopathy, we only performed the coagulation profile. In our study, the PT INR greater than 1.5 was seen only 7 times out of the 234 blood samplings (2.65%). However, to make a claim of safety for HES in this study, further evaluation of coagulation files by measuring platelets, PT, fibronectin, factor VIII: C, and von Willebrand factor antigen is needed. Besides, an optimal quantification of rebleeding or hematoma expansion after HES administration during the treatment course must by specified.

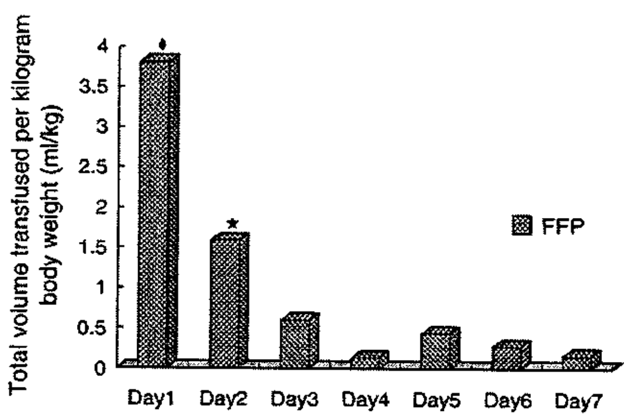

Fig. 3. The FFP transfused within 1 week. The FFP transfused in our patients (N = 78) from day 1 to day 7 was presented as total volume transfused/total body weight of patients (mL/kg). The mean transfusion amount of FFP in the first and second days were 3.80 ± 2.25 and 1.58 ± 0.51 mL/kg, respectively. The transfusions in the first and second days were surgically related. (♦ Indicates $P < .05$, significant difference between day 3-7 and day 1; ★, $P < .05$, significant difference between day 3-7 and day 2.)

4.2. Controversy of colloid and crystalloid

The controversy between crystalloid and colloid has dominated fluid therapy for last 50 years [31,43,44]. The debate has fluctuated from one side to the other as the knowledge of physiology has been extended and as different fluids have become available. It is reasonable to commence most of fluid regimens with crystalloid solutions [12,31]. However, in ongoing losses where plasma volume has been lost, it seems logical to use colloids for replacement [32,36-38,41]. Fluid balance is an important factor in determining the patient outcome from severe brain injury. A treatment protocol should include detailed specification of fluid management.

4.3. The characteristic of colloid

Many infusion solutions can be used for fluid management in severe head injury. There is growing evidence that colloid solutions are at least as beneficial as crystalloid solutions for volume replacement. The advantages of colloid solutions are rapid intravascular volume expansion, maintenance of oncotic pressure, and less tissue edema and pulmonary edema [8,14,17,32]. Forrest et al [13] reported that in critically ill hypovolemic patients who had a sepsis syndrome, volume expansion with a 10% HES preparation

Table 5
Outcome of patients

Glasgow Outcome Scale score		No. of patients	Outcome groups	%
Good recovery	5	22	Favorable outcome	55.1
Moderate disability	4	21		
Severe disability	3	14	Unfavorable outcome	33.3
Persistent vegetative state	2	12		
Death	1	9	Death	11.6

could increase the cardiac index, oxygen delivery, and filling pressures. Therefore, colloid solutions play an important role in volume replacement. There are 4 types of colloid solution: various plasma protein preparations derived direct from plasma, the gelatins, the dextrans, and the HESs. They have different molecular sizes, half-lives, colloid oncotic pressures, and costs.

The adverse effects that have so far been reported are anaphylatic reaction, renal function impairment, and coagulopathy [12,24-26].

4.4. The role of colloids in the treatment protocol

The crystalloids resembling the extracellular fluid, such as primary 0.9% normal saline and Ringer lactate, have been used widely in resuscitation. As they are distributed throughout the extracellular fluid, they produce limited plasma volume expansion usually of the order of about one quarter of the infused volume. They are readily filtered through the kidney and therefore maintain renal output, but they do reduce plasma oncotic pressure [12,44]. In the treatment of severe head injury, a large amount of mannitol is used (for the IH); hence, the urine output is greatly increased. When crystalloids alone are used, large crystalloid volumes are needed. Almost 3 to 4 times of the volume deficit must be administrated to provide adequate resuscitation and thus will result in large positive fluid balance [31]. Increased ICP after head trauma may compromise CPP, leading to cerebral ischemia and an increase in morbidity and mortality. To achieve a stable hemodynamic status and to increase CPP, many clinicians prefer the use of hyperoncotic colloid solutions such as human albumin [15,37], HES [32], and dextrans [2]. Since September 2001, our treatment protocol of severe head injury has included daily infusion of 1000 mL 10% HES solution. The purpose of HES infusion is to maintain adequate intravascular volume and to keep central venous pressure at 8 to 12 mm Hg. Therefore, a large volume of crystalloid solution could be avoided.

4.5. Why did we choose starch?

In the treatment of critically ill patients due to trauma or sepsis, albumin was proven to restore the volume deficit, but capillary leakage remained the key problem. Limited animal study [8] reported that HES 200/0.5 could ameliorate capillary leakage and become more beneficial than albumin in several aspects. However, whether HES is able to seal the leak in human patients must be clarified with additional studies. Colloid solutions are mandatory in CPP protocol for severe head injury [15,35,36]. The albumin/plasma/blood transfusions also serve the purpose of obtaining a normal colloid osmotic pressure favoring transcapillary absorption. A balanced fluid balance is part of the treatment protocol and is achieved by osmotic diuretics and an albumin infusion [33]. It has almost become a consensus that FFP should only be used in coagulopathy [7,16,26,32]. There are potential hazards to use blood products and plasma products for volume replacement. Thus, the HES seemed to us as a reasonable choice for substitution. In our study, FFP was used mainly in the first 2 days. We believe that it was surgery related according to the repeated measure analysis of variance between days. Under our treatment protocol, the amount of blood transfusion decreased, especially with regard to FFP. The difference was statistically significant ($P < .05$).

4.6. Limited experience with 10% HAES

Hypertonic hyperoncotic solutions by bolus infusion are one of the options for rapid hemodynamic control. Hypertonic hyperoncotic solutions are composed of (more or less) hyperoncotic colloids (6%-10% HES or dextran) and hypertonic crystalloids (7.2%-7.5% sodium chloride). Hypertonic hyperoncotic solutions have been investigated in the resuscitation of prehospital treatment. The containment of HES may serve to avoid compromising hemotasis, and associated manifest side-effects have only been rarely reported. However, the studies about the clinical use of HES in the treatment of head injury have been very few [4,19,29,30,35,38,40,42]. This study was retrospective, not randomized, and without a control group. However, this is probably the first study to document the safety of 10% HES and its good clinical outcome in the treatment of severe head injury.

5. Conclusions

The 10% HES (200/0.5) can be used in the treatment protocol of severe head injury. There is no definite bleeding complications documented by current dosage of HES. Besides, balanced fluid management can be achieved without causing serious pulmonary complications. We suggest that it can be used in the treatment of severe head injury following a standard protocol with a promising prospect and little adverse effect. However, a further randomized, prospective study is needed to define the actual benefit of HES in fluid management and clinical outcome.

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Trauma

Subdural intracranial pressure monitoring in severe head injury: clinical experience with the Codman MicroSensor

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Abstract

Background: Our main objective was to study the clinical outcome and complications of the subdural ICP monitoring with the CMS (Johnson and Johnson Medical Ltd, Raynham, MA) in severe head injury.

Methods: A retrospective analysis of patients with head injury with a GCS score of 8 or less was performed. Patients with severe systemic injury with hypotension (systolic blood pressure of <90 mm Hg on admission), a GCS score of 3 with fixed and dilated pupils after resuscitation, a GCS score of 3 to 4 whose family refused aggressive treatment, and those who were dead on arrival were excluded from this study. During the period from January 1997 to April 2004, 120 patients with severe head injuries were included and met criteria for insertion of a subdural ICP monitoring device (CMS).

Results: A total of 120 patients (84 males and 36 females), aged 16 to 80 years old (mean, 43.8 ± 14.4), were enrolled in the study. The average duration of ICP monitoring device use was 7.6 ± 0.4 days (range, 2-14 days). The overall clinical outcomes of these patients were as follows: mortality rate, 13.5%; percentage of unfavorable outcomes, 17.3%; percentage of favorable outcomes, 69.2%. There were no complications such as CNS infection or hemorrhage in this study.

Conclusion: A subdural transducer-tipped catheter (CMS) can be used as the first-line equipment for monitoring ICP in patients with severe head injury. The clinical results are similar with other recent studies, but no complication such as infection or hemorrhage occurred in this study.

Keywords: Severe head injury; Intracranial pressure monitoring; Complications; Subdural; MicroSensor

1. Introduction

Elevated ICP has been recognized as one of the most important factors affecting morbidity and mortality rates in patients who have had TBI; therefore, ICP monitoring has become routine in the management of severe head injuries [42]. The goal in the treatment of the patient with acquired brain injury is to minimize the impact of secondary injury. Secondary injury is the result of a complex set of events that can lead to a compromise in cerebral perfusion and tissue hypoxia and result in further neuronal death. Increased ICP is a major contributor to inadequate perfusion. Aggressive treatment of increased ICP requires measurement of the ICP, so that clinicians can assess the effectiveness of their interventions. The Guidelines for the Management of Severe Traumatic Brain Injury (published in 1995 and revised in 2000) [1,6] outline evidence-based recommendations for ICP monitoring to improve the treatment outcome of severe

Abbreviations: CBF, cerebral blood flow; CMS, Codman Micro Sensor; CNS, central nervous system; CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; CT, computer tomography; CVP, central venous pressure; $EtCO_2$, end-tidal carbon dioxide pressure; EVD, external ventricular drainage; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; ICP, intracranial pressure; ICU, intensive care unit; MAP, mean arterial pressure; $PaCO_2$, arterial carbon dioxide pressure; TBI, traumatic brain injury.

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Table 1
Demographic data

Demographic data	
Age	43.8 ± 14.4 y
Sex (F/M)	84/36
GCS score	6.2 ± 1.2
Duration of ICP monitoring	7.6 ± 0.4 d

F/M indicates females/males.

TBI in adults [18]. In 2004, the Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents was published, outlining similar recommendations for the pediatric population [1].

A variety of monitoring techniques and devices are available. Ventriculostomy is the first-introduced method of ICP measurement [28]. By use of a fluid pillar, the pressure is measured continuously. This method was first introduced into clinical practice by the Swedish neurosurgeon Nils Lundberg [28] in the late 1950s. Other methods of fluid-derived pressure monitoring are subdural and epidural pressure devices. The "gold standard" for the ICP measurement is still recognized to be the ventriculostomy and fluid pillar method, which allows for drainage of CSF, a potentially important means to lower elevated pressures [5,10,11,27,31]. Alternatively, several different types of fiberoptic monitoring systems are currently available and can be placed in the epidural space, subdural space, brain parenchyma, or ventricle [4,29,30,43,44].

Although ICP monitoring has played an important role in improving outcomes in patients with TBI, the procedure is not without risk, producing a low incidence of hemorrhagic or infectious complications [16,24,30,36,43]. We found an overall complication rate of 28% for patients in whom EVDs had been placed. Because of the severe swelling of the brain in patients with severe head injury, the ventricles were often compressed. This increased the difficulty of ventriculostomy [13,21], and the amount of cerebral fluid might not be sufficient. Some papers show that in patients with head trauma, although CSF drainage may lower ICP, these effects may only be transient in some patients and do not improve perfusion or oxygenation [12,22,23].

2. Methods

2.1. Subjects

A retrospective analysis of patients with head injuries with a GCS [39] of 8 or less was performed. Patients manifesting severe systemic injury with hypotension (systolic blood pressure of <90 mm Hg on admission), a GCS score of 3 with fixed and dilated pupils after resuscitation, those with a GCS score of 3 to 4 whose family refused aggressive treatment, and those who were dead on arrival were excluded from this study. During a 7-year period (January 1997–April 2004), 120 patients with severe head injuries were included and met the criteria for insertion of a subdural ICP monitoring device (CMS, Johnson and Johnson Medical Ltd).

2.2. Procedure

Criteria for ICP monitoring were standardized and this study included patients with an initial GCS score of 8 or less, with evidence of intracranial injury or elevated ICP (such as effacement of cisterns) on head CT scans. The data collected included age, sex, initial GCS, MAP, ICP, CPP, complications, and clinical results. Physiologic parameters such as MAP, ICP, and CPP were collected hourly for 7 days or until the time of discharge from the ICU.

2.3. Standard clinical management

During the stay in the ICU, the head of the bed was elevated by 30°. The neck was kept in a neutral position. Our treatment protocol excluded CSF drainage and induced hypothermia. Routine pharmacologic or physical measures were adopted to avoid fever if the body temperature was 37.5°C or higher. Mechanical ventilation was adjusted to keep $EtCO_2$ between 30 and 33 mm Hg. Patients underwent complete neurologic assessment by nursing staff hourly or more frequently if the condition was deteriorating.

2.4. Intracranial pressure monitoring and complications

A subdural ICP monitor (CMS) was used for monitoring the ICP. The ICP monitor was connected to a Hewlett-Packard monitor, model 66s-M116A, via a pressure transducer (Codman neuromonitor interface control unit, 82-6605) and module.

Table 2
Outcome: comparison with other series

	Death (%)	Unfavorable (%)	Favorable (%)
Eker et al [8]	47	10	42
Rosner et al [35]	29	11	59
In this study	13.3	17.5	69.2

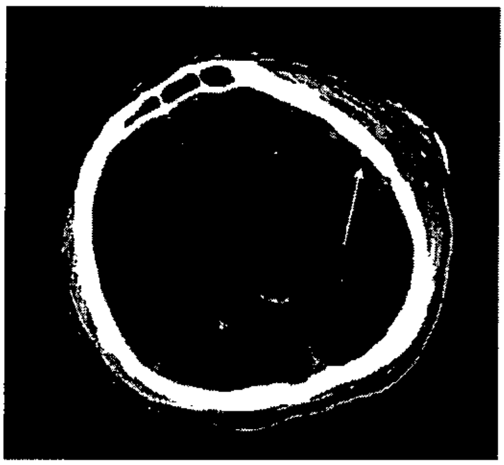

Fig. 1. The location of the subdural CMS on CT scan. The white arrow shows the position of the sensor.

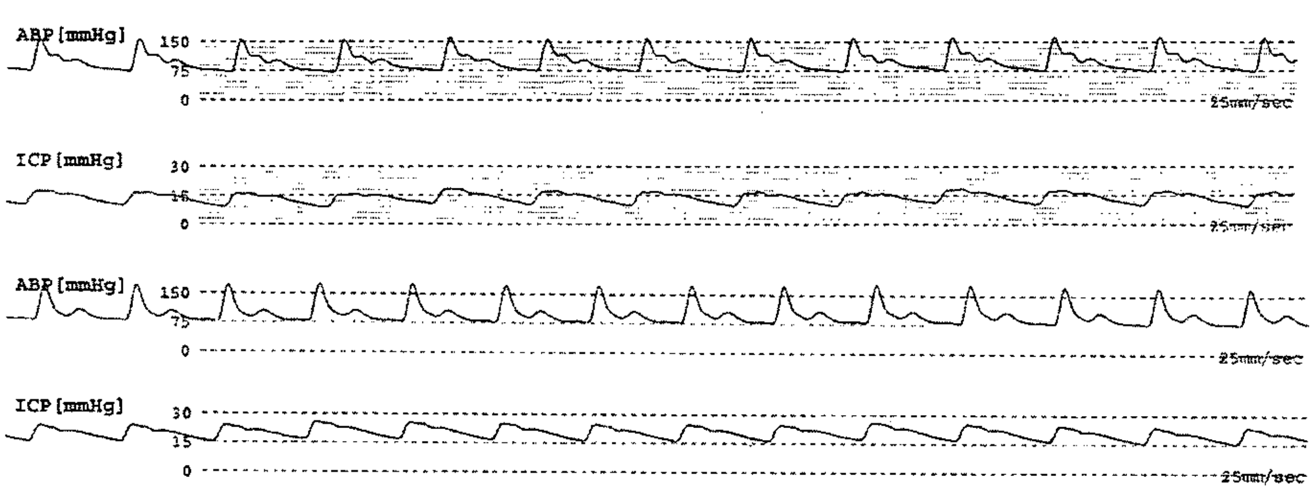

Fig. 2. The ICP waveform from subdural CMS monitoring.

Central nervous system infection, hemorrhage, and malfunction of the device were documented as complications. Central nervous system infection was defined as presentation of clinical signs of ventriculitis or meningitis with a positive finding of CSF culture or Gram stain. Cerebrospinal fluid was cultured only when a fever was present. Hemorrhage attributable to the placement of the monitoring device was defined as a new area of hemorrhage adjacent to the probe, which could be demonstrated on a postprocedure head CT scan.

2.5. Data analysis

Outcome was evaluated at 6 months after injury by the GOS [20] in which "favorable outcome" was defined as a good recovery or a moderate disability, and "unfavorable outcome" as a severe disability or a vegetative state.

χ^2, univariate, and multivariate studies were used for statistical analysis. Significance was determined at the 5% level. A commercially available software (SPSS version 10.0; SPSS, Inc, Chicago, Ill) was used for data processing and analysis.

3. Results

A total of 120 patients (84 males and 36 females), aged 16 to 80 years old (mean, 43.8 ± 14.4), were enrolled in this study. The basic demographic data are listed in Table 1. All patients received a subdural ICP monitoring device. The average duration of ICP monitoring device use was 7.6 ± 0.4 days (range, 2-14 days). As to the overall clinical outcomes of these patients, the mortality rate was 13.3%, the percentage of unfavorable outcomes was 17.5%, and that of favorable outcomes, 69.2% (Table 2).

A total of 120 procedures were performed without any clinical hemorrhagic complications. One hundred and two patients (85%) had postprocedure CT scans and no hemorrhagic complication was shown. There were 20 patients (16.7%) who had fever after surgery; of these, 16 were diagnosed to have pneumonia via chest x-rays or sputum culture, 2 were diagnosed to have urinary tract infection proved by urine culture, 1 had a positive finding on CVP tip culture, and 1 showed no obvious infection focus. There were no positive findings of CSF culture in these 20 febrile patients. All patients had a fair control under antibiotic treatment. A total of 12 patients received both EVD and subdural ICP monitoring device because of the intraventricular hemorrhage–induced acute hydrocephalus. In these 12 patients, the difference between data recorded by EVD and subdural ICP monitoring device was found to be −1 to −4 (Figs. 1 and 2). The daily ICP was recorded as the mean of 24 hours' ICP data. In the subgroup analysis of the first 7 days' ICP, the ICP data of the mortality group were significantly higher ($P < .05$) than that of the survival group (Fig. 3). The CPP data of the mortality group were significantly lower ($P < .05$) than that of the survival group (Fig. 4). In the survival patient (GOS, 3-5), the peak of the ICP trend was noted at days 3 to 4. The trend of ICP in

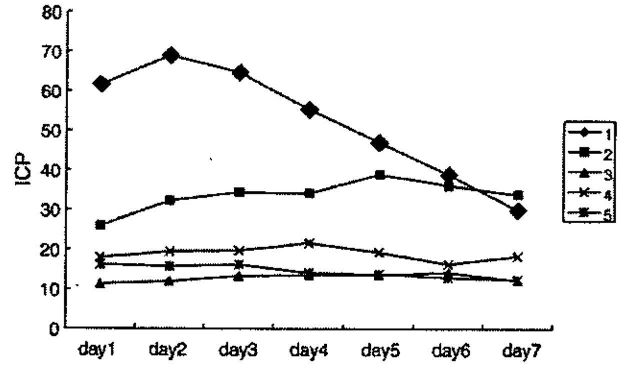

Fig. 3. The ICP in the mortality group was significantly higher ($P < .05$) than in the survival group. The figure in the right column represents GOS scores: 1, death; 2, vegetative; 3, severe disability; 4, moderate disability; 5, normal.

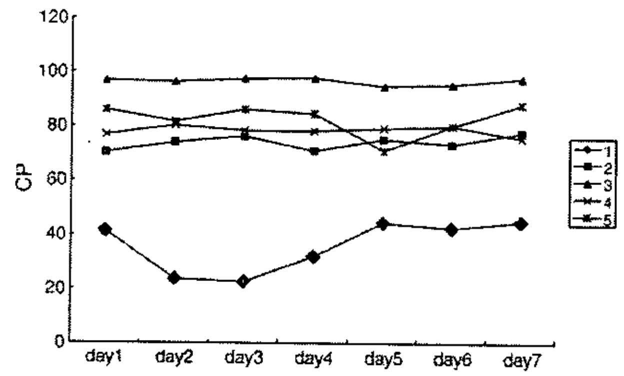

Fig. 4. The CPP in the mortality group was significantly lower ($P < .05$) than in the survival group. The figure in the right column represents GOS scores.

the vegetative group (GOS, 2) seems different from that of the other groups (GOS, 3-5). However, there was no statistical significance ($P = .08$).

4. Discussion

Elevated ICP has been recognized as one of the most important factors affecting morbidity and mortality rates in patients who have had severe head injury, and therefore, ICP monitoring has become routine in the management of severe head injuries in both adults and children [1,6]. A variety of monitoring techniques and devices are available, each with advantages and disadvantages. An EVD has been considered the gold standard for accurate ICP monitoring, and it allows for drainage of CSF, a potentially important means to lower elevated pressures. However, few studies have looked at the effectiveness of CSF drainage on ICP and CBF. Fortune et al [12] examined the impact of CSF drainage, mannitol, and hyperventilation on increased ICP and CBF. They found that although all treatments lowered ICP, only mannitol improved CBF. Two studies by Kerr et al [22,23] showed that CSF drainage may lower ICP, but these effects may only be transient and do not improve perfusion or oxygenation, especially in patients with traumatic brain injury. Cerebrospinal fluid drainage was not used in our study, but this did not produce worse results in clinical outcome in comparison with other studies (Table 2). Alternatively, several different types of transducer-tipped catheter systems are currently available that can be placed in the epidural space, subdural space, brain parenchyma, or ventricle [4,29,30,43,44]. Although ICP monitoring has become routine, there are no guidelines regarding whether to use a transducer-tipped catheter or an EVD when monitoring is desired after severe head injury. The device selected is, at present, dictated primarily by the surgeon's personal preference.

It has generally been agreed that the gold standard in ICP measurement is the use of a ventriculostomy. And we have to consider some problems such as the drift and the calibration number while using a transducer-tipped catheter. However, a number of papers [14,15,25] have shown that there is a good correlation between the ICP measured by ventriculostomy and by a transducer-tipped catheter. Koskinen and Olivecrona [25] showed that there is a good correlation between the ICP measured by ventriculostomy and the CMS. The drift from 0 was 0.9 ± 0.2 mm Hg, and no correlation with duration of use. Gray et al [15] compared a CMS placed subdurally with another CMS placed intraparenchymally. They found a good correlation between the values measured and a simultaneous reading difference between the 2 CMS devices of 0.1 ± 3.8 mm Hg.

As regards the complications after ICP monitoring, Anderson et al [2] found an overall complication rate of 28% for patients in whom EVDs had been placed and 6.5% for those in whom a fiberoptic intraparenchymal monitor was placed.

The 2 major complications of ICP monitoring are ventriculitis and hemorrhage. The reported infection rate [17,26,32,34,38,45] varies from 0% to 53% for EVDs and from 0.3% to 3.7% for transducer-tipped catheter devices. As to infection rates, regardless of definition, the risk of infection is approximately 10%. In most studies, the rate of infection is directly related to the duration of monitoring. Replacing the EVD after 5 days has been recommended on the basis of these studies. However, a study by Holloway et al [19] showed that there was no benefit in exchanging an EVD catheter at 5-day intervals. In this study, the average duration of CMS use was 7.6 ± 0.4 days (range, 2-14 days). There were no complications due to CNS infection in the patients. Pople et al [33] and Shapiro et al [37] also reported that fiberoptic intraparenchymal monitoring was associated with a very low infection rate.

Implantation of any device in the brain carries a potential risk of bleeding. There is a wide range in the reported incidences of this complication in the literature [3,7,9,16,36,40,41], from 0% to 17.6%. Blaha et al [3] reported an overall hemorrhage rate of 9.2% with intraparenchymal devices. Anderson et al [2] reported a 17.6% incidence of hemorrhage with intraventricular catheters with 1 bleeding requiring surgical intervention. Use of the ventricular catheter requires that the brain be fully penetrated, and some skill is necessary in the placement, especially in the case of small or shifted ventricles. It is not surprising that the higher reported hemorrhagic complication rates occurred with the use of intraventricular catheters. Jensen et al [21] and Gambardella et al [13] also reported that it would be difficult to place EVDs in patients with compressed or shifted ventricles.

5. Conclusions

An EVD has been considered the gold standard for accurate ICP monitoring, and it allows drainage of CSF, but there is a higher rate of infection and hemorrhage. In our experience with subdural CMS monitoring, there was no complication such as infection or hemorrhage. The lack of CSF drainage in our study did not bring about any worse clinical outcome in comparison with other studies. Therefore, we use a subdural transducer-tipped catheter (CMS) in patients with severe head injury as the first choice of equipment for monitoring ICP, and not an EVD.

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SENSORY AND MOTOR RECOVERY AFTER REPAIRING TRANSECTED CERVICAL ROOTS

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Abbreviations used in this paper:

aFGF, acidic fibroblast growth factor; bFGF, basic fibroblast growth factor; BDNF, brain-derived neurotrophic factor; CTB-HRP, cholerotoxin B-horseradish peroxidase; CNS, central nervous system; CNTF, ciliary neurotrophic factor; DREZ, dorsal root entry zone; DRG, dorsal root ganglion; PNS-CNS, peripheral nervous system-central nervous system; FGF, fibroblast growth factor; SD, Sprague-Dawley; SEP, somato-sensory evoked potential.

Abstract

Background: Adult mammal sensory axons avulsed through spinal dorsal root traction injuries, especially of the brachial plexus or cauda equina, cannot normally regenerate through axonal outgrowth from the dorsal root ganglion into the spinal cord, thus causing clinical conditions which require neuronal regeneration for sensory recovery, and for which no successful treatment has yet been reported.

Methods: To evaluate the sensory recovery of the forelimb after transection of their left cervical dorsal and ventral roots (C6-C8) at their spinal cord junctions, 22 Sprague-Dawley rats were randomly assigned to 3 groups: transection only (Control-1); transection, followed by repair using intercostal nerve grafts and fibrin glue (Control-2); transection, repair and application of acidic Fibroblast Growth Factor and fibrin glue (Experimental group).

Subsequent testing included: motor function (grasping-power), mechanical sensitivity to pain and touch (foot-withdrawal response to mechanical stimuli), temperature sensitivity (foot-withdrawal response to cold stimulus) and electrophysiological sensory responses (measurement of cortical somatosensory evoked potential). These tests were re-performed after re-transecting the repaired nerve roots to discount collateral innervation from adjacent nerve roots.

Results: Following transection and repair, testing showed recovery in both motor (grasping power) and sensory (touch, pain and temperature sensation) nerve functions. Neuronal regeneration was confirmed by the re-appearance of cortical somatosensory evoked potential, and by its disappearance after re-transection of the repaired cervical nerve roots.

Conclusion: Using our strategy for repairing transected cervical nerve roots, motor and sensory recovery was achieved in adult rats. The success of our study highlights possible treatment options for humans with avulsion injuries of the dorsal roots from the spinal cord.

Key words: regeneration, cervical root, somatosensory evoked potential, choerotoxin B horseradish peroxidase retrograde axonal labelling

INTRODUCTION

In adult mammals sensory nerve axons which have been avulsed through traction injuries to the nerve roots, especially of the brachial plexus or the cauda equina at their dorsal root ganglion (DRG) or dorsal root junctions with the spinal cord, are normally unable to regenerate through axonal outgrowth from the DRG, through the Dorsal Root Entry Zone (DREZ), across the Peripheral Nervous System-Central Nervous System (PNS-CNS) barrier, into the spinal cord. This neuronal regeneration is necessary for complete sensory recovery. Such avulsion or traction injuries to the nerve roots of the brachial plexus or the cauda equina therefore causes serious and debilitating clinical conditions for which no successful treatment has yet been reported.

Avulsion of one or more cervical nerve roots of the spinal cord that form the brachial plexus occurs in approximately 70% of severe brachial plexus traction injuries.(25) Unlike brachial plexus injury at other levels that are currently treated according to established surgical principles,(21, 24, 34) these brachial plexus traction injuries at the preganglionic level are believed to be beyond surgical repair(17) as they are considered to afflict the central nervous system (CNS).

Animal studies have shown that if continuity is restored between the spinal cord and the ventral roots of nerves at the lumbar(5) or cervical(4, 10) levels of the spinal cord, motor neuron axons can re-grow into their respective peripheral nerves with the concomitant recovery of motor function. The return of motor function after implantation of avulsed spinal nerve roots into the spinal cord has also been reported in one clinical case,(3) as well as in some animal studies.(11, 19)

However, unlike the axons of the motor neurons, sensory axons of spinal nerves in adult mammals, when interrupted at their dorsal root junctions with the spinal cord, are normally unable to regenerate through axonal outgrowth from the Dorsal Root Ganglion (DRG), through the Dorsal Root Entry Zone (DREZ), across the Peripheral Nervous System-Central Nervous System (PNS-CNS) barrier, and into the spinal cord. Therefore injury to dorsal roots, especially those for the brachial plexus and cauda equina, is still a serious clinical condition with no known treatment.

Our research was therefore designed to evaluate the possibility of sensory recovery of touch, pain and temperature, in Sprague-Dawley (SD) rats. This experiment involved the use of intercostal nerve grafts with subsequent application of acidic Fibroblast Growth Factor (aFGF) and Fibrin glue, to repair the roots of the left cervical nerves C6, C7 and C8, which form most of the brachial plexus and which, in this case, were transected at their dorsal and ventral nerve root junctions with the spinal cord.

The SD rats were then tested for both mechanical and electrophysiological motor and sensory function of the forelimb in order to confirm the recovery of these functions. Counter measures were carried out against the possibility that adjacent neuronal axons might have generated in compensation for the loss of these functions. We thus aimed to investigate the possibility of successful regeneration, in a clinical setting, of sensory and motor neuronal axons after repair of spinal nerve root avulsion caused by traction injuries.

MATERIALS AND METHODS

The design of our research to evaluate the possibility of motor and sensory recovery after the transection of the ventral and dorsal cervical nerve roots respectively, was done using a total of 22 adult female 250g Sprague-Dawley (SD) rats. These animals were then randomly assigned to one of three groups, namely Control-1 (7 SD rats), Control-2 (5 SD rats) and Experimental (or test) group (10 SD rats).

Control-1: Out of a total of 22 SD rats, 7 were operated on, on a heating pad under general isoflurane (0.75-1v/v, 3liters/min) anesthesia. In this operation, we exposed the vertebrae C2-T1, and a hemi-laminectomy was performed on the left side of the vertebrae C5, C6 and C7 to identify the dorsal and ventral roots of the corresponding levels. Following this we cut open the dura of the spinal cord, and the cervical nerve roots of C6, C7 and C8 were isolated, extracted and transected at their exit from the cervical spinal cord while making sure that no proximal stump remained on this region of the cervical spinal cord.

Control-2: The 5 SD rats that had been randomly assigned to this group were operated on as per the procedure mentioned above. Three intercostal nerves were then harvested and preserved in Hank Solution. Each of these three intercostal nerves was then cut transversely into two identical segments and each of these pair of graft segments was used to repair one spinal root - one segment to repair the ventral root and the other to repair the dorsal root of the transected cervical spinal root. This repair was done by anastomosing one end of the nerve graft to the severed nerve root using 10-0 prolene. The other end of the intercostal nerve graft was then implanted into the cervical spinal cord through a tiny incision of the pia mater. The grafts from the ventral root and dorsal root were inserted into the ventro-lateral and dorso-lateral aspect, respectively, of the cervical spinal cord. Finally, following the reparative procedure of the transected ventral and dorsal cervical nerve roots to the spinal cord, fibrin glue was applied to the surgical area to secure the anastomosis.

Experimental group: The remaining 10 SD rats that had been randomly assigned to this group underwent the same procedure as the rats in Control-2, including the repair of their dorsal and ventral nerve roots which had been transected for the purposes of this experiment. These rats, however, had acidic Fibroblast Growth Factor (aFGF) applied to the surgical area in order to decrease gliosis (an excess of astrocytes in the damaged areas of the CNS) and augment nerve fiber development, (12) as well as neuronal survival. (26) The aFGF was mixed into the fibrin glue. By mixing the aFGF into the fibrin glue, the entire surgical area was provided with aFGF in a slow-release form and promoted survival and sprouting of the motor neurons (15).

Re-transection: Of the 10 SD rats in the Experimental group, 2 rats were chosen that had shown full recovery of motor and sensory functions after the initial surgery. They were then re-operated on to re-transect the dorsal and ventral roots of the cervical nerves C6, C7 and C8, which had been transected and subsequently repaired in their initial surgery. Our goal in this case was to observe the effect of the re-transection and to also make sure that the recovery of the SD rats following their initial transection and subsequent repair was really the result of regeneration of the repaired roots and not from the re-innervation of the neighbouring roots.

BEHAVIORAL TESTS

Grasping power: The motor function of the SD rats was evaluated by testing the grasping power of their forelimbs using a commercial grip-strength meter (Grip-strength-meter 303500, TSE systems corp) for rats. This measurement involved placing the rat over a Perspex plate in front of a grasping trapeze. By pulling their tail, we impelled the SD rats to instinctively grab anything they could (in this case, the trapeze), to stop their involuntary backward movement. When our pulling force overcame its grip-strength, the animal lost its grip on the trapeze, and the peak preamplifier of the grip strength-meter showed a peak pull force which we then used to represent the grasping power of the tested limb. In order to ensure accuracy, we performed at least 5 trials per rat in each of the grasping power tests and both the average of and the maximum grasping power were recorded in each case.

Pain and touch sensation: The mechanical sensitivity of the forelimbs of the SD rats was quantified by using von Frey? filaments to test foot-withdrawal response to Graded Mechanical Stimuli . The rats were housed in small Lucite cubicles (20x8x8 cm) on an elevated metal wire mesh floor and the von Frey? filaments were applied from underneath the wire mesh to stimulate the plantar surface of the foot of the forelimbs of the rats. We then recorded the size of the smallest von Frey宸ilament to which we could elicit a foot-withdrawal response in each of the SD rats in the control-1 and the experimental groups. If there was constant responses to the mechanical stimuli, it was recorded as ? ? If there was no response to the mechanical stimuli at all times, it was recorded as ? ? If the response to the mechanical stimuli was present sometimes, but not always, it was recorded as ?

Temperature sensation: The SD rats?sensory function to temperature was tested using the foot-withdrawal response to a cold stimulus. This was done by delivering a drop of acetone (95%) to the dorsum of the foot of the left forelimb, using a dropper. Normally, there is a foot-withdraw response to the drop of acetone. All rats in the control-1 as well as the experimental groups were subjected to the temperature sensation test. If the foot-withdraw response existed and was present at all times, it was graded as ? ? On the contrary, if the foot-withdraw response was absent throughout the experimental period, it was graded as ? ? If the foot-withdraw to the drop of acetone occurred sometimes, but not always, it was recorded as ?

Electrophysiology: The somato-sensory evoked potential (SEP) of each SD rat was measured in the somatosensory cortex of their brains to test their electrophysiological sensory response and to confirm the recovery of this function and thus, confirm the successful regeneration of sensory neuronal axons after repair of the transected cervical nerve roots.

To record cortical SEPs, the cranium was exposed and four small-diameter holes were drilled bilaterally over the site of the somatosensory cortex of the brain, representative of the forelimbs. Stereotactic coordinates were measured at 1mm anterior and 2mm posterior to the bregma, both being 3mm lateral to the sagittal suture. (12) Four silver electrodes of 1mm diameter each were glued to the burr-holes to serve as epidural recording electrodes. Under anesthesia with isoflurane (0.75-1 v/v, 3 liters/min) and mounted on a stereotactic frame, the cortical SEPs of each rat were measured. A reference needle electrode was inserted into the nasion.

In order to evoke the cortical SEPs in the somatosensory cortex which correspond to the median nerve, each forepaw contralateral to its corresponding cortical electrode was stimulated using a pair of fine-needle electrodes. The stimulation frequency used was 2.11 Hertz, for a duration of 0.2 milliseconds. This stimulation was carried out by passing a current (2.0-5.0 mA)between the two fine-needle electrodes at a level that evoked the maximum cortical responses and small jerks in the forelimbs. The SEPs were amplified (amplification range: 10mA) and filtered (band pass, 20-2,000 Hz), and one hundred consecutive responses were averaged using a personal computer (Medelec system, Synergy). Finally, the cortical SEPs were recorded both before the operation and every 4 weeks afterwards for a total of 20 weeks. Seven of the 10 experimental group rats, 5 of the 7 control-1 group rats, all rats of the control-2 group and the 2 re-transected rats were tested for the cortical SEPs.

Morphological study: To confirm the presence of the regenerating sensory fibers, a morphological study was done using retrograde cholerotoxin B-horseradish peroxidase (CTB-HRP) labeling.

Two to four months post-surgery of their cervical spinal nerve roots, CTB-HRP was injected into both the palmar and dorsal sides of the forepaws of the SD rats of both Control-1 group and the Experimental group, on the side that was affected by this transection.

To confirm the regeneration and survival of neurons, the neurons thus labeled were then counted in the dorsal root ganglion (DRG). The labeled neuronal fibers or tracts were also looked for in the dorsal horn of the spinal cord.

RESULTS

Results of the Grasping power test for motor function: The grasping power of the SD rats in the Experimental group showed significant motor function recovery, in both the maximum grasping power as well as the average grasping power, compared to that of the rats in Control-1. However, there was no statistically significant difference between the maximum and the average grasping power of the rats in the Experimental group and Control-2, and likewise between the Control groups 1 and 2. (See Figure 1)

Results of the von Frey? filament test for pain and touch sensation: The mechanical sensitivity of the forelimbs of the SD rats was measured by using von Frey? filaments to test foot-withdrawal response to Graded Mechanical Stimuli.

Out of the 7 SD rats in Control-1, 6 rats showed no response to even the stimulation using the largest of the von Frey? filaments (6.65) during the first 3 months of the experiment. One rat, however, did show a response to stimulation using a 6.39 von Frey? filament; but this response was not consistent and was only observed occasionally.

In the Experimental group, however, all of the SD rats showed recovery of response to the von Frey? filament stimulation. Out of the 10 SD rats in this group, 9 rats showed a consistent response, with the response range being from 4.14 to 6.22 on the von Frey? filament scale. The remaining 1 SD rat showed a response to the simulation with the 6.65 von Frey? filament, but this response was inconsistent and was only observed occasionally. (see Table 1)

Results of the cold stimulation test for temperature sensation: The SD rats?sensory response to temperature was tested using the foot-withdrawal response to a cold stimulus.

Throughout the 3 to 6-month follow-up period, none of the 7 SD rats in Control-1 showed a response to the cold stimulus. They were therefore graded as ? ? according to our grading system.

All of the 10 SD rats in the Experimental group, however, showed a response to the cold stimulus. Out of these, 6 rats showed a constant and consistent response to the cold stimulus, which we scored at ? ? and the other 4 SD rats showed an irregular response to the cold stimulation, which we scored at ? (see Table 1)

Results of re-transection: Two of the SD rats in the Experimental group were subjected to re-explorative surgery. Both of these rats had had a full recovery, as garnered by our von Frey? filament stimulation and cold stimulation tests prior to the re-operation. This re-exploration further substantiated the results of our tests by showing the reparative grafts of the cervical nerve roots C6, C7, and C8 to be healthy. Furthermore, the anastomoses of the grafts with the cervical spinal cord and the transected roots were also shown to be solid. After re-transection of these previously repaired cervical nerve roots, however, any responses to von Frey? filaments and to cold stimulation disappeared, confirming that our results were due to the reparative process of the transected nerve roots and not due to the re-innervation of these nerve roots by adjacent nerve roots. (See Table 1)

Results of the SEP test for electrophysiological response: The somato-sensory evoked potential (SEP) of each tested rat was measured in the somatosensory cortex of their brains to test their electrophysiological sensory response and thus, to confirm the successful regeneration of sensory neuronal axons after reparation of the transected cervical nerve roots.

Post-transection of the cervical nerve roots, none of the rats in Control-1 registered any SEPs in the somatosensory cortex of their brains by the end of the 20-week post-operation period. While three of the 5 SD rats of Control-2 and 6 of the 7 nerve graft with aFGF rats tested for the cortical SEPs regained their cortical SEPs. The period required for the re-appearance of the SEPs by recovery varied, ranged from 4 to 20 weeks post-operation.

Of particular note is that the percentage of SD rats which showed recovery of SEPs in the Experimental group was significantly higher than that in Control-1 ($P \fallingdotseq 0$). The other paired comparisons did not show any significant differences (as determined by the Fisher exact test).

The reappearing SEPs were eliminated upon re-transection of the repaired roots, verifying that they originated from the re-grown axons rather than from re-innervation via adjacent intact roots. The regenerated SEPs , however, were often evoked with greater electrical stimulation than the original ones and amplitudes varied widely. Even so, the waveforms and interside comparison of latency (105.6 + 9.55%) did not show any significant differences from those of normal rats (based on the Mann-Whitney U test). (See Figure 2) For details of the evaluation of SEPs in this experiment, please refer to reference 22.

Results of the Morphological study using CTB-HRP labeling: CTB-HRP labeling was used to confirm the presence of the regenerating sensory fibers. The labeled neurons were counted in the dorsal root ganglion (DRG). The survival rate of the neurons in the DRG of the Experimental group showed that it had attained statistical significance in its difference with the neuronal survival rate of the Control -1. (See Figure 3)

In addition, CTB-HRP-positive fibers or tracts were also found in the dorsal horn of the spinal cord in all of the SD rats of the Experimental group. (See Figure 4) However, no such labeled neuronal fibers or tracts were found in the SD rats of the Control-1. The presence of these fibers confirmed that the regenerating sensory fibers did indeed originate from the DRG, and en route to the spinal cord, passed through the dorsal root entry zone (DREZ) and the PNS-CNS barrier.

DISCUSSION

In adult mammals, following the avulsion of the dorsal roots of the spinal nerves through traction injuries, the regeneration of the central processes of the dorsal root ganglion (DRG) stop abruptly at the dorsal root entry zone (DREZ).(6, 29) The DREZ is the place where the supporting structure of the nervous tissue (neuroglia), consisting of a fine web of tissue, encloses neuroglial cells, which are of three types: astrocytes, oligodendrocytes and microcytes. This is also where axonal growth is inhibited because the axons either turn around along the dorsal root or form swollen end bulbs abutting the astrocytes.(6, 29, 23, 33)

Some reports have shown that regeneration of the central primary sensory neurons in the dorsal spinal roots can be accelerated by peripheral nerve lesions.(8, 30, 31) However, most of the axons are still unable to re-enter the spinal cord and those that succeed, penetrate no further than the superficial dorsal horn of the spinal cord. These reports also suggest that adding some ntrinsic or extrinsic factors? 8) , can lead to the regeneration of the central processes of the DRG towards gaining entry into the spinal cord.

Recently, many reports have also documented that certain neurotrophic factors can stimulate axonal growth even in non-permissive environments.(14, 28, 32) Zhang Y et al. have shown in their recent study that gene therapy with adenoviral vector encoding a neurotrophin is capable of enhancing and directing the regeneration of a subpopulation of dorsal root axons through to the CNS environment in rats.(35) However, the regenerating axons in their study did not spread widely in the grey matter or away from the injection site and no sensory recovery was mentioned either.

Nevertheless, there are many neurotrophic factors present in different compartments around the motor neuron: ciliary neurotrophic factor (CNTF) is in the myelinating Schwann cells around the motor neuron axons; brain-derived neurotrophic factor (BDNF) is present in the hind limb buds innervated by motor neurons; fibroblast growth factor (FGF)-5 can be found in differentiated muscle, aFGF can be found in the motor neuron; and basic FGF (bFGF) is present in the astrocytes of the spinal cord.

Among these neurotrophic factors, acidic FGF (aFGF) is a normal constituent of the spinal cord which is expressed, for example, in motor neurons and primary sensory neurons. However, aFGF lacks a signal sequence, and it is therefore thought to be sequestered within synthesizing cells themselves, and perhaps only reaches the extracellular milieu after damage to the cell membrane. Consequently, aFGF may also be involved in repair after tissue damage (20).

Acidic FGF also decreases gliosis, which is caused by an excess of astrocytes following damage to the central nervous system. A study involving intraocular spinal cord grafts (12) has shown that aFGF can augment nerve fiber development and neuronal survival.(26)

Apart from the need to demonstrate effectiveness in neuron survival or nerve growth, in order for neurotrophic factors to be clinically useful, they must be also shown to be capable of localized delivery at the specified site, over a suitable time period after nerve injury, and at an appropriate and maintained concentration. (13) Therefore, by mixing aFGF into fibrin glue ? which is a good source for the slow-release of the trophic factor ? the entire surgical area can be provided with aFGF at a concentration that can be pre-determined and maintained in a slow-release form.

It has also been shown that aFGF delivered via fibrin glue has promoted survival and sprouting of the corticospinal tract in rats.(15) Moreover, aFGF, in contrast to several other members of the FGF family, appears to be a universal FGF-receptor ligand which may be able to functionally interact with the core of the FGF-binding domain,(27) and may therefore be capable of activating all other FGF receptor splice variants.

In our previous work, we found excellent motor recovery in the forelimbs of rats after repairing transected ventral roots of cervical nerves C5 and C6 with nerve grafting and application of aFGF with fibrin glue. (11, 19) In these previous studies we measured motor recovery by recording grooming reflex and electromyography , which showed excellent motor recovery in the repaired group.

However, in our current study, we have measured motor function recovery by testing grasping power and we have shown that the treated rats have significantly stronger grasping power compared to the non-treated rats. This finding is significant because grasping requires the recovery of intrinsic muscles of the hands. This would have much greater significance in a clinical setting because there has yet been no effective treatment for brachial plexus injury that can enhance the muscles distal to the elbows, (9) whereas our study shows that there may be a possibility of recovery of the muscles of the forelimb, including the intrinsic muscles of the hand.

In addition to the recovery of motor functions, the treated animals also showed significant recovery of both pain and temperature sensation. This recovery of sensory functions was confirmed by the reappearance of somatosensory evoked potential (SEP), as measured in the somatosensory cortex of the brain. Most strikingly, the recovery of both the sensory and motor functions disappeared again after re-transection of the grafted roots. The cortical SEP was also observed to have disappeared after re-transection. The loss of sensory and motor functions and of somatosensory evoked potential after re-transection confirms that the post-grafting recovery, with the addition of aFGF and fibrin glue, is by neuro-regeneration of the repaired grafts, from the dorsal root ganglion through to the spinal cord, and not by the compensatory collateral sprouting from adjacent cervical nerve roots.

In our previous study, we confirmed the protection conferred on motor neurons by aFGF mixed into fibrin glue. (19) In this study, however, we have also noted increased neuronal survival in the DRG due to the presence of aFGF mixed into fibrin glue. In addition, we have identified, through enzyme labeling, CTB-HRP-positive nerve fibers not only in the DRG but also in the dorsal horn of the spinal cord of the rats that had undergone the reparative grafting and application of aFGF in fibrin glue.

These findings indicate that our treatment strategy using intercostal nerve grafts along with aFGF in fibrin glue can enhance axon outgrowth from the DRG, through the DREZ, across the PNS-CNS barrier, into the spinal cord which leads to sensory recovery. In addition, it can confer both motor and sensory neuronal protection, thus increasing both motor and sensory neuronal survival after cervical spinal root injury.

CONCLUSION

Our experiment confirms that intercostal nerve grafts, along with aFGF in fibrin glue can effectively treat transected cervical spinal nerve roots in adult rats. The experimental animals not only showed good recovery of motor function, including that of the intrinsic muscles of the hand, but also showed good sensory recovery of both pain and temperature sensation.

Ours is the first report of recovery of sensory function subsequent to the repair of transected cervical spinal nerve roots in adult mammals. We believe that this simulation of a most difficult clinical condition through our animal model, and the success of our study, shed new light on the treatment of patients with brachial plexus and cervical nerve root injuries.

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FIGURE LEGENDS

Figure 1: (A): There is a statistically significant difference in average grasping power in the Experimental group when compared to the Control-1 group (C: Control-1; C': Control-2; E: Experimental group). (B): There is a statistically significant difference in maximal grasping power in the Experimental when compared to the Control-1 group (C: Control-1; C': Control-2, E: Experimental group).

Figure 2: There is a statistically significant difference in the reappearance of cortical somatosensory evoked potential (SEP) in the Experimental group when compared to the Control-1 group. (Fisher exact test, $p \fallingdotseq 0$)

Figure 3: The CTB-HRP labelled neuron number is significantly greater in the dorsal root ganglion of the Experimental group than in Control-1 (con: control-1 group; exp: experimental group). Student test showed statistically significant difference between control-1 and experimental groups in total ($p<0.001$), C7 ($p<0.001$) and C8 ($p<0.05$) DRG neuron numbers.

Figure 4: CTB-HRP positive nerve fibers (arrow) were noted in the dorsal horn of the spinal cord of the repaired rats. (CTB-HRP, immunostaining,200x).