應用減少腦部神經膠質細胞纖維化提升腦部氧氣分壓與維持最佳腦部血液灌流壓於治療嚴重頭部外傷之研究

Application of Decreasing Brain Tissue Gliosis, Elevating Brain Tissue O2 Partial Pressure, and Maintaining Optimal Cerebral Perfusion Pressure in Treatment of Severe Traumatic Brain Injury

中文摘要

1997 年以前，台灣地區的頭部外傷發生率、死亡率及嚴重度均為世界上最嚴重的地區，主要原因為機車的高使用率與安全帽的低配戴率。為了因應這個嚴重的問題，我們進行了一連串的研究。在過去二十年來把我們所進行的研究方法、對象及內容大致分成八大研究主題，分別簡述如下：(一)頭部外傷流行病學研究：一開始進行全國性頭部外傷病人收集，發現台灣地區頭部外傷的發生率為鄉村地區較高，且其中機車車禍導致頭部外傷佔了七成，研究中顯示機車騎士配戴安全帽的比例甚低，因此建議推動安全帽的強制立法是減輕及防止頭部外傷的最重要政策。(二)介入研究：本研究針對安全帽立法前後做一完整趨勢研究比較，並從中瞭解到安全帽的使用確實有其必要性。研究顯示機車事故中，在安全帽立法後，戴安全帽者發生意識喪失、顱骨骨折、顱內出血等情形，皆較立法前少。顯示安全帽的立法確有其功效。(三)神經行為調查研究：本研究的目的，主要是將 Levin et al.(1998)所發展的神經行為量表(Neurobehavioral Rating Scale，簡稱 NRS)，進行台灣地區的初步驗證工作，以瞭解頭部外傷病人之行為改變模式及與受傷嚴重性和持續性之間的關係。研究結果在不同程度的頭部外傷受試中，NRS 的「認知語言」因素及「焦慮」因素上是有顯著差異的。(四)脊髓損傷流行病學研究：安全帽立法後，為探討創傷性頸脊髓損傷與機車安全帽使用的相關性。研究結論是安全帽並不會造成更高之頸脊髓損傷機率。(五)國際合作性研究：對於發展中國家而言，頭部傷害是一個複雜和困難的問題。這些國家通常都缺乏人力資源和設備。跟歐洲和美洲相較下，發展中國家還是有較大的頭部傷害問題。 (六)嚴重頭部外傷研究：腦部外傷是造成死亡與嚴重殘障的主要原因。根據美國的統計資料, 每一年的頭部外傷人數約為一百五十萬人，其中大約有一百萬人因為頭部外傷而到醫院的急診室就診及處理。其中總共住院的病人數約有二十三萬五千人，九萬名病人造成嚴重殘障。。另外每年因為腦部外傷而死亡的的人數大約有 5 萬人。頭部外傷照護之主要目的是降低其死亡率及殘障程度，並盡可能的提高傷者之生活品質。對於嚴重之頭部外傷病患採用加護重症照顧可顯著降低死亡率及殘障程度，美國更於 1995 年正式發表嚴重頭部外傷處理準則(Guidelines of management in severe head injury)，其中主張嚴重病患應裝置顱內壓(Intracranial pressure, ICP)監測，及腦灌流壓(Cerebral perfusion pressure, CPP)的維持，藉此以避免腦部缺血所造的細胞壞死，經過五年之評估，認為此一新觀念確

實有其臨床效果。(七)輕度頭部外傷研究：本國際合作專案爲一個跨國及跨文化之世代研究計畫，邀集澳洲、義大利、印度、美國、阿根廷及台灣六國共同參加。計畫於各國都以同樣的研究方法及標準化的表格進行同步研究。希望能藉此了解在不同的國家及不同的文化背景之下，輕度頭部外傷病患之傷害的早期指標與後期結果間的關係。 (八)嚴重頭部外傷診療指引研究：本研究邀請台灣地區神經科學領域北、中、南、東，台灣地區醫學中心及區域醫院共 32 位專家學者，經過多次的會議討論及研討會，共同制訂台灣版嚴重頭部外傷治療共識(Guidelines)。依計畫之執行方向，製訂八大主題：1.急診處置 Management in ER (ER: Emergency Room). 2. 顱內壓監測 ICP monitor. 3. 腦灌流壓與輸液之原則 CPP and Fluid management. 4. 鎮定劑之使用 Sedation. 5. 營養 Nutrition. 6. 顱內壓上升之處置 Management of Intracranial Hypertension. 7. 癲癇之預防治療 Seizure Prophylaxis. 8. 二線療法 Second Tier Therapy

其中之嚴重頭部外傷研究部份正是本論文之研究主題，本論文之研究方向主要是真對四大方向進行相關之基礎及臨床研究，其結論與摘要如下：(甲)減少腦傷後癲癇發生之機率。本研究藉由玻尿酸與細胞表面上相關受器的交互作用，影響細胞的活動和增生能力。腦部損傷後的病人，恢復神經功能，多在受傷後半年內快速進行，然而在半年之後，隨著疤痕組織形成及穩定，神經功能的恢復也日趨穩定，也就是恢復的速度也日趨緩慢。在這次實驗中，實驗組中，無論是 4 週，8 週，或是 12 週的老鼠，中樞神經系統受傷表面疤痕組織中 GFAP+細胞的數目都較對照組的老鼠受傷腦部表面少。受傷後神經疤痕組織的厚度及神經膠質化的程度也較趨於緩和。這些增厚的疤痕組織常常被認爲與阻礙神經發展恢復，甚至於被認爲與頭部外傷後的癲癇，特別是慢性長期性的癲癇有關。 (乙)提升血液中之氧分壓。在本次試驗中，我們顯示出腦部外傷病人的 GCS 昏迷指數在接受高壓氧治療的族群比起控制組有顯著的進步。這個結果顯示出高壓氧對於腦部外傷病人 GCS 昏迷指數的恢復有正面的影響。關於 GOS (Glasgow 預後量表)的進步上，接受高壓氧治療的病人，在三個月的追蹤兩組並沒有差別，但在高壓氧治療六個月後的追蹤，GOSb=4 的族群有得到一些進步。這表示高壓氧治療須要更多時間來表達影響，高壓氧可以幫助輕度神經功能缺失的病人恢復並回到日常生活，在這前瞻性的試驗中，我們可以定出以下結論，高壓氧治療可以改善腦部外傷病人的昏迷指數恢復同時幫助輕度神經功能殘障的病人恢復，而能享有較好的人生。(丙)盡快降低水腫之程度。血液透析不平衡症候群(dialysis disequilibrium syndrome－DDS)是一種在血液透析治療過程中，發生急性神經學功能上的異常表現。我們發現幾乎所有急性及慢性腎衰竭的病患，在接受血液透析的時候，都發現顱內壓上升的情形。在我們這個研究中，顱內壓的波動在血液透析治療過程中的第二個小時內急遽的上升，而且在滿第二個小時顱內壓上升到最高峰。在腦部手術後病患需要血液透析治療時。於本研究中藉由改變血液透析的治療方式，例如：減少每次血液透析的總量和流速，增加血液透析的頻率，達到更緩和的方式去清除尿素分子，降低腦內出血腎衰竭的病人產生血液透析不平衡症候群的機

會。(丁)提升腦部血液之灌流量以減少腦傷後之二度傷害。我們的研究結果顯示，有放置顱內壓監測器的病患不但存活率較高，Glasgow outcome scale 也較佳，昏迷指數較差的病患，死亡率相對的較高，約在百分之八十左右。在昏迷指數三分到五分的這一組當中，維持腦灌流壓高於 70 毫米汞柱不但可以降低死亡率，對於短期及長期的預後也有改善。針對昏迷指數六分到八分者，將腦灌流壓維持在 60 毫米汞柱以上即足夠。針對嚴重腦幹功能損傷的病患，維持腦灌流壓高於 70 毫米汞柱可以明顯的改善預後。對於死亡率的控制更佳，若能夠避免因為要維持較高的腦灌流壓而發生的併發症，將腦部的灌流壓維持在 70 毫米汞柱以上對於腦外傷的病患來說應是有所助益的。
臨床上治療嚴重腦外傷的方法主要為：減少腦傷後癲癇發生之機率，提升血液中之氧分壓，盡快降低水腫之程度，及提升腦部血液之灌流量以減少腦傷後之二度傷害。以本論文之研究結論主要是真對上述之四大方向進行進一步之探討。
根據本論文之四大主題主要是針對嚴重頭部外傷診療指引建立相關之研究及理論基礎，希望借由本論文中粗淺且簡單之結論拋磚引玉，誘導國內從事相關研究工作之專家群能一起全心投入頭部外傷相關之研究，進而建立本土化之研究結論，如此才能完備建立嚴重頭部外傷診療指引時所需之所有基礎，也只有在具有本土化之研究結論的嚴重頭部外傷診療指引才有足夠之說服力去大力推行此診療指引在台灣地區甚或亞洲地區確實的落實。

英文摘要

Before 1997, Taiwan was one of the areas with the highest incidence and mortality rate of traumatic brain injuries (TBI) in the world. This situation mainly resulted from a large number of motorcyclists, of whom only very few wore a helmet. In order to tackle this serious problem, we carried out several studies on TBI in the past few years. According to different subjects, material and methods, there were seven main topics of studies, which were:1. Epidemiological study of TBI: We initiated a nationwide brain injury survey. We found that incidence of TBI was higher in the rural area than in the urban area of Taiwan. Seventy percent of the TBI were due to motorcycle accidents and most of the motorcycle riders did not wear a helmet. So we asserted that the mandatory helmet use law would be the most important and effective policy to reduce and to prevent TBI in Taiwan. 2. Intervention study of TBI: We started a complete study comparing the trend of TBI before and that after the mandatory helmet use law. We found that after the helmet use law, there was a reduction of the rate of consciousness disturbance, skull fracture and intracranial hemorrhage in the motorcycle related accidents. We concluded that the helmet use law intervention was effective and the continue education for the use of helmet and re-enforcement of the helmet use law were essential to maintain a satisfactory rate of helmet use in motorcyclists.

3. Study of neurobehavioral: With the use of the neurobehavioral rating scale (NRS) of Levin et al. (1987), we investigated the relationship of neurobehavioral disturbances in TBI patients with the severity and duration of head injury. NRS factors “cognitive language” and “anxiety” were significantly different in head injury subgroups with different degree of brain injury. 4. Epidemiological study of spinal cord injury: After the helmet use law, the incidence of TBI in Taiwan was proved to be successfully declined, but the use of helmet might increase the risk of spinal cord injury. In order to investigate the correlation of helmet use with spinal cord injury, we collected the registered and telephone interview data from the “Head and Spinal Cord Injury Study Group, R.O.C” for important after injury evaluation. The result showed that the use of helmet would not cause cervical spine injury. 5. International collaborative program: TBI is a tough and complicated issue for developing countries. However, most of these countries have limited resources and facilities for TBI prevention and treatment. Kraus, Jennett and Frankowski reported in 1990 that the annual incidence rate of head injury was 132–430/105, and the annual morality rate was 9–32/105. Although every country has their own method, definition and strategies in their TBI databases collection, the comparative results between developing countries and developed countries showed that the developing countries faced a more serious problem of TBI. 6. Quality of life study of severe TBI: The main goal of the TBI patients care is to reduce the severity of disability, mortality rates, and their quality of life as much as possible. Since 1970, many researches showed that application of intensive care on severe TBI patients significantly decreased the severity and mortality rates. USA published the “Guidelines of management in severe head injury” in 1995, suggesting the use of intracranial pressure monitors to control not only the intracranial pressure, but also to maintain the cerebral perfusion pressure. That was a breakthrough concept that could clinically help to avoid cell necrosis due to ischemia of brain tissues and was now widely used in Europe and America after a 5 years evaluation. 7. Study of minor TBI: This is an international collaborative cohort study of six countries (Australia, Italy, India, USA, Argentina and Taiwan) with standardized method of study and forms. We aim to find out the risk and prognostic index of patients with minor traumatic brain injury, and provide patients with better quality of care. 8. Guidelines for management of severe TBI in Taiwan: We invited 32 neurosurgical experts from medical centers and local regional hospitals in different parts of Taiwan to join the Taiwan TBI guideline consensus meetings and conferences. We chose eight topics of guideline development:

- Management in emergency room
- ICP monitor
- CPP and fluid management

- Use of sedation
- Nutrition
- Management of intracranial hypertension
- Seizure prophylaxis

Second tier therapy

Within this dissertation, 4 major basic and clinical researches for the severe traumatic brain injury were conducted. 4 major conclusions were summarized as following: (1) HA application could effectively reduce the gliosis in brain cortex not only on the thickness of the scarring and also in glia cell proliferation. All these change was believed to be related with the lesser chance of post traumatic or post operative seizure incidence. (2) HBOT could elevate the brain oxygenation; promote the GCS improvement, and also the 3 months outcome, esp. in GOS change. But the timing when the HOBT implement need further clarification. (3) Slower speed of hemodialysis, more frequently dialysis could reduce the severity of brain edema effective. These subtle changes for the patient who need dialysis could reduce IICP incidence and increase the survival rate for these patient also. And (4) Improved cerebral perfusion, esp. for the patient with extreme poor GCS after the brain trauma could be indicated for the better outcome and better survival rate. But the high complication rate should be also monitored closely to avoid the further disaster during the maintenance patient's CPP.

These entire 4 major topics was only the beginning of the clinical trial for the development of the treatment guideline of severe traumatic brain injury. We hope in the near future, some more researchers could join into this field of research. With all there efforts evidence-based guideline could be then setup and well accepted by the clinical practice.