行政院國家科學委員會專題研究計畫　成果報告

台灣地區嚴重頭部外傷病人使用 propofol 之前瞻性跨院隨機臨床試驗

計畫類別： 個別型計畫
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執行期間： 93 年 08 月 01 日至 94 年 07 月 31 日
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計畫主持人： 邱文達
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行政院國家科學委員會專題研究計畫成果報告

台灣地區嚴重頭部外傷病人使用 Propofol 之前瞻性跨院隨機臨床試驗

A prospective, Multi-center, Randomized, Placebo-controlled Trial to Evaluate the Use of Propofol in Head Injured Patients in Taiwan

計畫編號：NSC93-2314-B038-053
執行期限：93 年 08 月 01 日至 94 年 07 月 31 日
主持人：邱文達　台北醫學大學傷害防治學研究所
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一、中文摘要

研究背景

本研究以跨院前瞻性、隨機臨床試驗，探討 propofol 於頭部外傷病患之神經重症照護的角色。藉由此研究，期能提供嚴重頭部外傷病患一項新的藥物治療選擇。

方法

本研究收集 2003 年 1 月至 2004 年 12 月間，台北市立萬芳醫院、臺大醫院、及淡水馬紀念醫院之所有頭部外傷患者，排除條件為沒有接受積極治療者、年齡超過 79 歲或未滿 12 歲者。收集資料包括基本資料、診斷、臨床症狀、GCS 昏迷指數、顱內壓、腦灌流壓、使用藥物及劑量、治療結果等變項。

結果

本研究共收集 151 人，其中 47 人合於排除條件，總計收案 104 位患者納入研究，其中 44 人投與 propofol，60 位未投與。平均年齡 40.8±22 歲，投與組與未投與組分別為 41.91±20.41 歲、43.48±23.19 歲 (p=0.097)。加護病房前三天之平均顱內壓在投與組、未投與組分別為 17.23±9.0mmHg、33.19±32.56mmHg (p=0.017)及 71.10±15.32mm Hg、43.20±29.92mm Hg (p＜0.001)。前五天之平均腦灌流壓投與組、未投與組分別為 71.10±15.32 mm Hg、43.20±29.92mm Hg (p＜0.001)。投與組之死亡率較未投與組低(81.82% vs. 46.67%, p＜0.001)。

討論

本研究證實，propofol 的使用對於加護病房頭部外傷患者有較好的預後。故 propofol 可被推薦用於頭部外傷患者的手術後照護。

Abstract

Background. The present study is a multi-center, prospective, randomized, controlled trial to evaluate the efficacy of propofol, a new choice of pharmacotherapy in head injured patients.

Methods. Head-injured patients admitted to Taipei Municipal Wan Fang Hospital, National Taiwan University Hospital, and Tamshui Mackay Memorial Hospital during January 2003 to December 2004 were enrolled. Patients were excluded if aggressive treatment did not perform, or the age of patients was less than 12 or older than 79 years old. The patients' demographics, clinical lab data, Galscow coma scale (GCS) score,

intracranial pressure (ICP), cerebral perfusion pressure (CPP), concurrent medications, and therapeutic outcomes were collected.

Results. The total number of patients admitted to the hospitals was 151, with 47 patients excluded according to the criteria. Among the 104 patients met the inclusion criteria, 44 were given with propofol and 60 without. Average age was 40.8 ± 22 for the all patients, with 41.91 ± 20.41 and 43.48 ± 23.19 for the propofol group and non-propofol group, respectively. (p=0.097) There was no significant difference in the baseline GCS between the propofol and nonpropofol groups, respectively. (5.86 ± 1.84 vs. 5.66 ± 1.59, p=0.729) Mean ICP for the first 3 days in the intensive care units (ICU) was 17.23 ± 9.0mm Hg in the propofol group and 33.19 ± 32.56 in the non-propofol group, respectively. (p=0.017) Mean CPP for the first 5 days in the ICU was 71.10 ± 15.32mm Hg in the propofol group and 43.20 ± 29.92mm Hg in the nonpropofol group. ($p < 0.001$) A higher survival rate was found in the propofol group than non-propofol group. (81.82% vs. 46.67%, $p < 0.001$)

Conclusions. The use of propofol in the intensive care units demonstrated a better clinical outcomes for head injured patients in the recovery conditions. Propofol can be considered to help the head-injured patients in the post surgery care.

二、報告內容

前言

The Brain Trauma Foundation and American Association Neurological Surgeons have proposed the Guidelines for the Management of Severe Head Injury to provide evidenced-based new treatment recommendations to reduce the mortality and morbidity. Carefully controlling intracranial pressure (ICP), maintaining cerebral perfusion pressure (CPP) and hyperventilation, and use of vasopressors and sedatives have been identified as mainstay therapies in this guideline.[1] A recent position paper from the Society of Critical Care Medicine[2] also provided valuable guidelines on the sustained use of sedatives and analgesic agents in critically ill adults. Although literature has discussed the application of many agents used, they provide little specific guidance in the head-injured population. There were only few studies that directly compare the effectiveness and adverse effects of different agents in this group of patients. The drug of choice for sedation in head-injured patients still warrants new studies to provide evidences.

文獻探討

Sedatives are widely used in the management of head injured patients in recent years[3], with advantages to decrease agitation, anxiety, metabolism, and ICP.[3-5] The general purposes of using sedatives in the intensive care units (ICU) are to provide amnesia, hypnosis, and pain-free, as well as to relieve agitation and anxiety.[6] These agents may additionally provide useful reductions in cerebral metabolism and decrease raised ICP in head-injured patients.[6] High ICP and low CPP are serious threats after head injury.[7] It was suggested that ICP of 20mmHg is an indication to initiate therapy, including sedatives, mannitol, diuretics, or hyperventilation. [8-11], and CPP below 70 to 80mmHg is the threshold of significant poor outcome.[3-6] Sedation enables the manipulation of respiration, which is essential in the treatment of raised ICP.[6] Sedatives not only make head-injury patients a stable phase but also improve outcome such as ICP and CPP, thus required careful consideration to select the best regimen.

Sedation regimens for head-injured patients are quite variable.[12] Agents used in these patients included benzodiazepines (e.g. midazolam), barbiturates (e.g. pentobarbital and thiopental), narcotics (e.g. morphine and fentanyl), and propofol. Among the above sedatives, pentobarbital is recommended to decrease high ICP in head-injured patients by the Guidelines for the Management of Severe Head Injury proposed by the Brain Trauma Foundation and American Association Neurological Surgeons.[1] However, a recent meta-analysis[13] found no evidence that barbiturate therapy in head-injured could improve outcome. The conclusions of this meta-analysis are in conflict with expert recommendation provided in internationally accepted guidelines.[14] Thus it is important to compare with data other agents to search a more ideal sedative agent than pentobarbital for head injured patients.

The use of short-acting sedative-anesthetic agent propofol has been increased recently in head trauma patients, with little has been known regarding its safety and efficacy.[12] With an unique pharmacokinetics and pharmacodynamics characteristics, propofol is considered as a well-used in head-injured patients.[3] Propofol is a phenolic derivative with highly lipophilic. It has a sleep-inducing effect, and reduces brain metabolism, CBF and ICP.[5] The pharmacokinetic properties of propofol are characterized by a three-compartmental model: rapid initial distribution from blood into tissues, rapid redistribution and metabolic clearance, and a slow return from poorly perfused tissues into the bloodstream even after long-term infusions.[15] Propofol has the advantage of a short half-life, which allows intermittent neurological examination.[16] Propofol is also frequently used in recent years to treat patients with intracranial hypertension. In noncomparative studies in patients with head injury, propofol has been shown to maintain mean CPP>60mm Hg and reduce or maintain mean ICP[4,17] and these treatments are provided to increase the survival rate in head-injured patients. Studies on propofol in head injury patients should be done to further improve outcome of therapy.

目的

The objective of the present multi-center, prospective, randomized clinical trial was to compare the influence of propofol on the survival rates in treating severe head trauma patients.

研究方法

Trauma patients admitted to Taipei Municipal Wan Fang Hospital, National Taiwan University Hospital, and Tamshui Mackay Memorial Hospital during January 2003 to December 2004 were enrolled. Patients were included if meeting the following criteria: age ≥12 years old and ≤79 years old; sustained a closed or penetrating traumatic brain injury resulting in a post resuscitation Glasgow Coma Score (GCS) sore of 3 to 13; and requirement for mechanical ventilation and ICP monitor. Patients were excluded if aggressive treatment did not perform, or the age of patients was below 12 or above 80 years old.

The variables collected were age, sex, body weight, symptoms, wound date, admission date, GCS score at admission, diagnosis, complications, surgery date, ICU length of stay, discharge date, with or without ICP monitoring, and therapeutical outcome (discharge or death). Clinical data for the first 5 days in the ICU included mean daily ICP, mean daily CPP, mean daily arterial carbon dioxide partial pressure (PaCO2), mean daily fluid balance, and the required daily doses for mannitol, sedative agents, vasopressors, neuromuscular blockers.

All statistical analyses were performed using the Statistical Package for the Social

Science (SPSS 10.0, SPSS Inc., Chicago) computer software program. Statistical significance for all analyses was defined as p value less than 0.05. 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 X^2 test with Chi-square or Fisher's exact test.

結果

Among the 151 patients admitted during the study period, 47 were excluded because aggressive treatment did not perform, or the age of patients was less than 12 or older than 79 years-old. The data of the remaining 104 patients were therefore analyzed. Of the 104 subjects, 71 were male and 33 were female. The average age was 40.8±22 years old and the median GCS was 6 (range 3-10) on admission.

Among the 104 patients met the inclusion criteria, 44 were given with propofol and 60 without. Baseline and interventional physiological data were shown in Table 1. The two groups did not differ in age, body weight, sex, and baseline GCS score. The mean age was 41.91±20.41 years old for the propofol group and 43.48±23.19 years old for the non-propofol group. (p=0.097) There were 65 head trauma patients with ICP monitoring, including 36 in the propofol group and 29 in the nonpropofol group. PaCO2 was monitored in 99 patients, including 43 in the propofol group and 56 in the nonpropofol group. (p=0.397)

A higher survival rate was found in the propofol group than non-propofol group (81.82% vs. 46.67%, p＜0.001). Compared the propofol group with the nonpropofol group, there was a statistically significant in mean ICP for the first 3 days in the ICU. (17.23±9.0mmHg vs. 33.19±32.56 mmHg, p=0.017, respectively). Mean CPP for the first 5 days in the ICU was 71.10±15.32 mmHg in the propofol group and 43.20 ± 29.92 mmHg in the non-propofol group, respectively. (p ＜ 0.001) Vasopressors were given to 45 patients, including 12 in the propofol group and 33 in the nonpropofol group. (p<0.001) There were 101 patients given with mannitol, including 44 in the propofol group and 57 in the nonpropofol group, respectively. (p=0.138)

討論

The data of present study demonstrated that propofol effectively increased survival rate in head-injured subjects, which may be resulted from propofol decreasing ICP and maintaining CPP. The two groups with or without administration of propofol did not differ in the treatment of hyperventilation and mannitol. A statistically significant difference between the two groups in the mean ICP and CPP for the first 3 days was found. This difference induced by propofol has decreased ICP to be below 20mm Hg and maintained CPP above 70mm Hg, which were reached the suggested targets endorsed by current guidelines to improve the survival rate in head-injured patients.

The influence of sedatives used in head-injured patient has been investigated in few studies with results that each agent improved outcome at different degree of effectiveness. In a randomized, double-blinded trial with moderate or severe head injured patients, ICP and CPP were generally similar in groups treated with 2% propofol (n=23) or morphine (n = 19), but on day 3 ICP was lower in patients treated with propofol than that with morphine (14mm Hg vs. 18mm Hg; p<0.05).[18] In a further small comparative study of patients with severe head injury, propofol produced adequate control of ICP in all patients (n = 10), whereas adequate control was achieved in only three of seven patients receiving morphine plus midazolam.[19] In comparative studies, the effect of propofol on ICP in patients following head injury was similar to

that of fentany [20] or pentobarbital plus morphine.[21] Although studies has been done on use of barbiturates, benzodiazepines, narcotics, these of studies were limited to small sample size and thus the choice of sedatives was still unknown. The data of current study further provided the evidence of propofol to be considered as an alternative drug in the treatment of head-injured patients.

The use of propofol is limited by few side effects in head-injured patients. The commonly adverse effects associated with propofol include hypotension and hypertriglyceridaemia. Propofol has a cardiovascular depressant effect, which can lead to hypotension (incidence of 26%)[15] and a reduced heart rate. Hypertriglyceridaemia is associated with propofol infusions of >3 days. Other adverse effects associated with propofol include respiratory acidosis during weaning from the ventilator (3–10%), green discolorations of the urine and the rare occurrence of anaphylactic reactions.[22-24] The occurrences of these adverse effects are rare, but they may make a poor outcome in recovery phase. A regimen of propofol, which includes dosage and administration model, should be investigated deeply in the future.

結論

The data of current study proved that propofol improved the recovery phase in patients with head injury. Propofol decreased ICP to be below 20mm Hg and maintained CPP above 70mm Hg, and the survival rate in the propofol group was significantly higher than that in the nonpropofol group. Propofol can be suggested to use in the treatment of head-injured patients due to the beneficial clinical outcomes and unique pharmacokinetic/pharmacodynamic characteristics. Further studies are warranted to study the best regimen and monitoring plans on the use of propofol in head injury patients.

Table 1. Demographics

	Propofol group(N=44)	**Non-propofol group(N=60)**	**P value**
Gender			
Male N(%)	31(70.75)	40(66.67)	0.832
Female N(%)	13(29.55)	20(33.33)	
Age	**41.91 ± 20.41**	**43.48 ± 23.19**	
12-19yrs N(%)	8(18.18)	10(16.67)	0.097
20-39yrs N(%)	13(29.55)	20(33.33)	
40-64yrs N(%)	13(29.55)	11(18.33)	
65-79yrs N(%)	10(22.72)	19(31.67)	0.811
Body Weight (kg)	**66.66 ± 15.47**	**64.64 ± 12.65**	
			0.963
Baseline GCS	**5.86 ± 1.84**	**5.66 ± 1.59**	
			0.729

Table.2 Comparison of drug uses in the propofol and non-propofol groups

With or Without	Propofol (N=44)	Non-propofol (N=60)	p value
Sedatives N(%)			
Propofol	44(100.00)	0(0.00)	
Midazolam (Dormincum®)	14(31.82)	0(0.00)	
Lorazepam (Ativan®)	0(0.00)	0(0.00)	
Others	1(2.29)	0(0.00)	
Vasopressors N(%)	**12(27.27)**	**33(54.10)**	**<0.001***
Dopamine	6(13.64)	16(26.23)	
Norepinephrine(Levophed®)	5(11.36)	13(21.31)	
Epinephrine (Bosmin®)	0(0.00)	3(4.92)	
Others	1(2.27)	1(1.64)	
NMB N(%)	**11(22.92)**	**0(0.00)**	**<0.001***
Atracurium	9(18.75)	0(0.00)	
Pancuronium (Pavulon®)	0(0.00)	0(0.00)	
Vecuronium	0(0.00)	0(0.00)	
Others	2(4.12)	0(0.00)	
Mannitol N(%)	**44(100.00)**	**57(93.44)**	**0.138**

ICP=intracranial pressure, CPP=cerebral perfusion pressure, PaCO2=arterial carbon dioxide partial pressure, ETCO2=…,

NMB=Neuromuscular blockers. *Statistically significant by Chi-Square test（P<0.05）

Table 3. Outcomes of patients in the propofol and non-propofol groups

	Propofol group (N=44)	Non-propofol group (N=60)	p value
Survival Rate N(%)	**36(81.82)**	**28(46.67)**	**<0.001***
Mean GCS in first 5days	**71.10 ± 15.32**	**43.20 ± 29.92**	**<0.001†**
-Day1	6.48 ± 1.69	5.67 ± 2.26	0.041†
-Day2	7.06 ± 2.61	5.67 ± 2.63	0.013†
-Day3	7.34 ± 3.41	5.81 ± 3.11	0.026†
-Day4	7.94 ± 3.61	6.16 ± 3.48	0.027†
-Day5	8.08 ± 3.68	6.07 ± 3.49	0.027†
Mean ICP in first 3 days(mmHg)	**17.23 ± 9.0**	**33.19 ± 32.56**	**0.017†**
-Day1	15.71 ± 10.33	31.43 ± 26.60	0.009†
-Day2	17.77 ± 9.06	43.38 ± 39.35	0.003†
-Day3	19.67 ± 10.52	39.71 ± 42.91	0.043†
Mean CPP in first 5 days(mmHg)	**71.10 ± 15.32**	**43.20 ± 29.92**	**<0.001†**
Mean PaCO2 in first 5days(mmHg)	**23.15 ± 8.12**	**24.71 ± 8.34**	**0.350**

ICP=intracranial pressure, CPP=cerebral perfusion pressure, PaCO2=arterial carbon dioxide partial pressure, ETCO2=…,

NMB=Neuromuscular blockers.

* Statistically significant by Chi-Square test (p<0.05)

†Statistically significant by Independent T test (p<0.05)

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附件一

行政院國家科學委員會補助專題研究計畫成果報告

台灣地區嚴重頭部外傷病人使用 propofol 之前瞻性跨院隨機臨床試驗

計畫類別：☑ 個別型計畫　　□ 整合型計畫
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計畫主持人：邱文達 台北醫學大學傷害防治研究所
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計畫參與人員: 林天仁　黃子娟

成果報告類型(依經費核定清單規定繳交)：☑精簡報告　□完整報告

本成果報告包括以下應繳交之附件：
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□赴大陸地區出差或研習心得報告一份
□出席國際學術會議心得報告及發表之論文各一份
□國際合作研究計畫國外研究報告書一份

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執行單位：台北醫學大學傷害防治學研究所

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