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Multicenter evaluation of propofol for head-injured patients in Taiwan

Wen-Ta Chiu, MD, PhD[a], Tien-Jen Lin, MD[a], Jia-Wei Lin, MD[a], Sheng-Jean Huang, MD[b], Cheng-Kuei Chang, MD, PhD[c], Hsiang-Yin Chen, PharmD[d,*]

[a]*Department of Neurosurgery, Taipei Medical University-Wanfang Hospital, Taipei Medical University, Taipei 116, Taiwan*
[b]*Department of Neurosurgery, National Taiwan University Hospital, Taipei 100, Taiwan*
[c]*Department of Surgery, Division of Neurosurgery, Mackay Memorial Hospital, Taipei 104, Taiwan*
[d]*Department of Pharmacy, Taipei Medical University-Wanfang Hospital and School of Pharmacy, Taipei Medical University, Taipei 110, 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.

* Corresponding author. Tel.: +886 2 29307930x1157; fax: +886 2 8662 1163.
E-mail address: shawn@tmu.edu.tw (H.-Y. Chen).

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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 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.

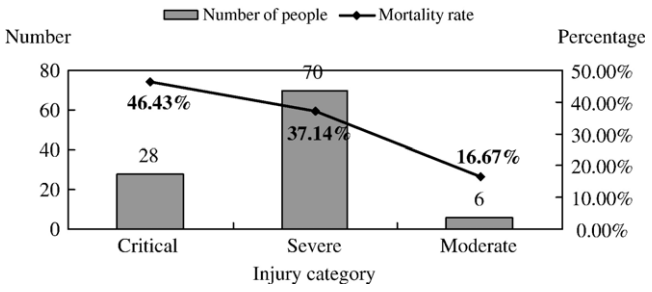

Fig. 1. The relationship between mortality rate and injury category. [a]Injury categories: critical, if GCS score was between 3 and 4; severe, if GCS score was between 5 and 8; and moderate, if GCS was between 9 and 13.

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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References

[1] Albanese J, Martin C, Lacarelle B, et al. Pharmacokinetics of long-term propofol infusion used for sedation in ICU patients. Anaesthesiology 1990;73:214-7.

[2] Albanese J, Viviand X, Potie F, et al. Sufentanil, fentanyl, and alfentanil in head trauma patients: a study on cerebral hemodynamics. Crit Care Med 1999;27:407-11.

[3] Alvarez del Castillo M. Monitoring neurological patients in intensive care. Curr Opin Crit Care 2001;7:49-60.

[4] Bailie GR, Cockshott ID, Douglas EJ, et al. Pharmacokinetics of propofol during and after long term continuous infusion for maintenance of sedation in ICU patients. Br J Anaesth 1992; 68:486-91.

[5] Barrientos-Vega R, Mar Sanchez-Soria M, Morales-Garcia C, et al. Prolonged sedation of critically ill patients with midazolam or propofol: impact on weaning and costs. Crit Care Med 1997;25:33-40.
[6] Bauer TM, Ritz R, Haberthur C, et al. Prolonged sedation due to accumulation of conjugated metabolites of midazolam. Lancet 1995;346:145-7.
[7] Bayliff CD, Schwartz ML, Hardy BG. Pharmacokinetics of high dose pentobarbital in severe head trauma. Clin Pharmacol Ther 1985; 38:457-61.
[8] Bullock R, Chesnut RM, Clifton G, et al. Guidelines for the management of severe head injury. Brain Trauma Foundation. Available at: http://www2.braintrauma.org [Accessed in 2000].
[9] Carrasco G, Molina R, Costa J, et al. Propofol vs midazolam in short-, medium-, and long-term sedation of critically ill patients: a cost-benefit analysis. Chest 1993;103(2):557-64.
[10] Cook S, Palma O. Propofol as a sole agent for prolonged infusion in intensive care. J Drug Dev 1989;2(Suppl 2):65-7.
[11] Cremer OL, Moons KGM, Bouman EAC, et al. Long-term propofol infusion and cardiac failure in adult head-injured patients. Lancet 2001;357(9250):117-8.
[12] Cruz J, Jaggi JL, Hoffstad OJ. Cerebral blood flow, vascular resistance, and oxygen metabolism in acute brain trauma: redefining the role of cerebral perfusion pressure? Crit Care Med 1995;23:1412-7.
[13] Cruz J. An additional therapeutic effect of adequate hyperventilation in severe acute brain trauma: normalization of cerebral glucose uptake. J Neurosurg 1995;82:379-85.
[14] de Nadal M, Ausina A, Sahuquillo J, et al. Effects on intracranial pressure of fentanyl in severe head injured patients. Acta Neurochir Suppl (Wien) 1998;71:10-2.
[15] Farling PA, Johnston JR, Coppel DL. Propofol infusion for sedation of patients with head injury in intensive care: a preliminary report. Anaesthesia 1989;44:222-6.
[16] Hollrigel GS, Toth K, Soltesz I. Neuroprotection by propofol in acute mechanical injury : role of GABAergic inhibition. J Neurophysiol 1996;76:2412-22.
[17] Kelly DF, Goodale DB, Williams J, et al. Propofol in the treatment of moderate and severe head injury: a randomized, prospective double-blinded pilot trial. J Neurosurg 1999;90:1042-52.
[18] Kumar MA, Urrutia VC, Thomas CE, Abou-Khaled KJ, Schwartzman RJ. The syndrome of irreversible acidosis after prolonged propofol infusion. Neurocrit Care 2005;3(3):257-9.
[19] Lauer ML, Connolly LA, Schmeling WT, et al. Opioid sedation does not alter intracranial pressure in head injured patients. Can J Anaesth 1997;44:929-33.
[20] Levy ML, Aranda M, Zelman V, et al. Propylene glycol toxicity following continuous etomidate infusion for the control of refractory cerebral edema. Neurosurgery 1995;37:363-71.
[21] Bullock MR, Chestnut RM, Clifton GL, et al. Management and prognosis of severe traumatic brain injury. Brain Trauma Foundation. Available at: http://www.braintrauma.org [Accessed in 2003].
[22] McCollam JS, O'Neil MG, Norcross ED, et al. Continuous infusions of lorazepam, midazolam, and propofol for sedation of the critically ill surgery trauma patient: a prospective, randomized comparison. Crit Care Med 1999;27:2454-8.
[23] McKeage K, Perry CM. Propofol: a review of its use in intensive care sedation of adults. CNS Drugs 2003;17:235-72.
[24] Muizelaar JP, Marmarou A, Ward JD, et al. Adverse effect of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. J Neurosurg 1991;75:731-9.
[25] Nordby HK, Nesbakken R. The effect of high dose barbiturate decompression after severe head injury: a controlled clinical trial. Acta Neurochir 1984;72:157-66.
[26] Okomoto PM, Kawaguchi DL, Amin AN. Evaluation of propofol infusion syndrome in pediatric intensive care. Am J Health Syst Pharm 2003;60(19):2007-14.
[27] Ortolani O, Conti A, Sall-Ka B, Salleras JP, Diouf E, Kane O, Roberts SJ, Novelli GP. The recovery of Senegalese African blacks from intravenous anesthesia with propofol and remifentanil is slower than that of Caucasians. Anesth Analg 2001;93(5):1222-6.
[28] Ortolani O, Conti A, Chan YK, Sie MY, Ong GS. Comparison of propofol consumption and recovery time in Caucasians from Italy, with Chinese, Malays and Indians from Malaysia. Anaesth Intensive Care 2004;32(2):250-5.
[29] Papazian L, Albanese J, Thirion X, et al. Effect of bolus doses of midazolam on intracranial pressure and cerebral perfusion pressure in patients with severe head injury. Br J Anaesth 1993;71: 267-71.
[30] Pinaud M, Lelausque JN, Chetanneau A, et al. Effects of Diprivan on cerebral blood flow, intracranial pressure and cerebral metabolism in head injury patients. Ann Fr Anesth Reanim 1991;10:2-9.
[31] Pocaccio F, Stocchetti N, Citerio G, et al. Guidelines for the treatment of adults with severe head trauma (part II). Criteria for medical treatment. J Neurosurg Sci 2000;44:11-8.
[32] Roberts I. Barbiturates for acute traumatic brain injury. Cochrane Database Syst Rev 2000;CD000033.
[33] Robertson C. Critical care management of traumatic brain injury. In: Winn HR, editors. 5th ed. Youmans neurological surgery, vol 4. Philadelphia: Elsevier Inc; 2004. p. 5103-44.
[34] Ronan KP, Gallagher TJ, George B, et al. Comparison of propofol and midazolam for sedation in intensive care unit patients. Crit Care Med 1995;23:286-93.
[35] Rosner MJ, Rosner SD, Johnson AH. Cerebral perfusion pressure: management protocol and clinical results. J Neurosurg 1995;83(6): 949-62.
[36] Sanchez-Izquierdo-Riera JA, Caballero-Cubedo RE, Perez-Vela JL, et al. Propofol versus midazolam: safety and efficacy for sedation the severe trauma patient. Anesth Analg 1998;86:1219-24.
[37] Stocchetti N, Rossi S, Buzzi F, et al. Intracranial hypertension in head injury: management and results. Intensive Care Med 1999; 25(4):371-6.
[38] Thompson KA, Goodale DB. The recent development of propofol (DIPRIVAN). Intensive Care Med 2000;26(Suppl 4):S400-4.
[39] Urwin SC, Menon DK. Comparative tolerability of sedative agents in head-injured patients. Drug Saf 2004;27(2):104-33.