Journal of Critical Care 29 (2014) 287–290

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Comparison of the safety and efficacy of propofol with midazolam for sedation of patients with severe traumatic brain injury: A meta-analysis☆,☆☆

Jian-wen Gu, MD, PhD*, Tao Yang, MD, Yong-qin Kuang, MD, PhD, Hai-dong Huang, MD, Bin Kong, MD, Hai-feng Shu, MD, PhD, Si-xun Yu, MD, PhD, Jun-hai Zhang, MD

Department of Neurosurgery, Chengdu Military General Hospital, Chengdu 610083, China

ARTICLE INFO

Keywords:
Propofol
Midazolam
Traumatic brain injury
Sedation

ABSTRACT

Objective: To perform a meta-analysis to compare the safety and efficacy of propofol with midazolam for sedation of patients with severe traumatic brain injury.
Materials and Methods: Studies were included in the meta-analysis if they met the following criteria: randomized controlled trial of sedative-hypnotic agents including propofol and midazolam; patients had severe traumatic brain injury; the primary outcome was the Glasgow Outcome Scale score; secondary outcomes included mortality, therapeutic failure, intracranial pressure, and cerebral perfusion pressure. The data were analyzed using software for meta-analysis.
Results: Seven relevant studies were identified. Three of these studies were excluded: one was a single-arm study, one compared morphine and propofol, and for one the full text article could not be obtained. The remaining 4 studies were included in the meta-analysis. The results of the meta-analysis showed that propofol and midazolam have similar effects on the Glasgow Outcome Scale score, mortality, intracranial pressure, and cerebral perfusion pressure.
Conclusion: Our meta-analysis of 4 studies showed that there are no important differences between propofol and midazolam when administered to provide sedation for patients with severe traumatic brain injury. Further randomized, controlled trials comparing propofol with midazolam for sedation of such patients are needed.

1. Introduction

Traumatic brain injury (TBI) is a very significant medical problem throughout the world, and the cause of considerable mortality and morbidity. In the United States, the annual incidence of visits to emergency departments because of TBI is 403 per 100,000, while the incidence of hospital admissions because of TBI is 85 per 100,000 [1]. The effects of the mortality and morbidity on society are particularly pronounced because TBI occurs most commonly in younger adults [1]. Indeed, TBI is the most frequent cause of disability and death among adults aged less than 45 years [2]. The medical cost associated with TBI are, unsurprisingly, considerable [3].

Patients with TBI often require sedation to induce amnesia, anxiolysis, and to facilitate appropriate treatment [4]. Sedation may also help ameliorate hypoxia, hypercapnia, systemic hypertension, and intracranial hypertension [5]. A concern with giving sedatives is that systemic blood pressure may decrease, leading to a decrease in cerebral perfusion pressure (CPP) and other adverse consequences [5]. Other issues that must be considered are the effects of the sedative on factors such as re-perfusion injury and secondary brain injury. Clearly, determining which sedative(s) offer optimal safety as well as efficacy is of critical importance.

Drugs from several different classes, including benzodiazepines, anesthetic agents, α2-adrenergic receptor agonists, antipsychotics, and opioid analgesics, are all used to sedate patients with TBI [4–6]. Two of the more widely used sedatives for such patients are propofol and midazolam [5]. These agents have different pros and cons. For instance, propofol is highly lipid soluble, crosses blood-brain barrier rapidly, and therefore has a rapid onset of action [5,6]. Propofol also has relatively rapid renal clearance and very strong anxiolytic and amnesic properties, but does not have any analgesic effect [5,6]. Midazolam also has a relatively rapid onset and offset of action (compared with other benzodiazepines used for sedation), and possesses anxiolytic, amnesic, and anticonvulsant properties [5].

Several systematic reviews have compared the efficacy and safety of propofol with that of midazolam for the sedation of critically ill patients [7–9]. All 3 of these reviews reported that these sedatives have similar safety and efficacy. No systematic review or meta-

☆ Sources of Funding: None to declare.
☆☆ Conflict of Interest: The authors have stated that there is no conflict of interest to declare.
* Corresponding author. Tel./fax: +86 28 86570361.
E-mail address: gujianwen5000@gmail.com (J. Gu).

0883-9441/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jcrc.2013.10.021

analysis published to date, however, has compared the safety and efficacy of propofol with that of midazolam for the sedation of patients with severe TBI. The purpose of this meta-analysis was to perform such a comparison.

2. Methods

2.1. Search strategy

Medline, EMBASE, Current Contents, and the Cochrane database were searched using combinations of the following terms: severe brain injury, severe head injury, TBI, sedation, propofol, midazolam, hypnotic agents, safety, and efficacy. The search was carried out in July 2013.

2.2. Eligibility criteria

To be included in the meta-analysis, studies had to be randomized controlled trials of sedative-hypnotic agents, including propofol and midazolam, involve patients with severe TBI, and be published in English language journals.

Studies were excluded from the meta-analysis if they were randomized controlled trials that compared 2 types of analgesic agents in an analgesia-based sedation regimen or if they included patients who did not have TBI.

2.3. Data extraction

Data were extracted from eligible studies by 2 independent reviewers. Any disagreement between the 2 reviewers was resolved by consulting with a third reviewer.

The following data were extracted: first author, number of patients, age of patients, sex of patients, Glasgow Outcome Scale (GOS) score, mortality, and safety outcomes (proportion of patients for whom sedation was ineffective, jugular oxygen saturation [JOS], intracranial pressure [ICP], cerebral perfusion pressure [CPP], and sedation and anesthesia doses).

The primary meta-analysis outcome was the GOS score. The secondary meta-analysis outcome was mortality. Safety outcomes were summarized for each eligible study.

2.4. Data analysis

The proportion of patients with GOS scores of 4 or 5 and mortality rates were compared between patients who received midazolam and those who received propofol. A χ^2-based test of homogeneity was performed using Cochran's Q statistic, and I^2, the percentage of the total variability in effect estimates among trials that was due to heterogeneity rather than chance, was calculated. An I^2 >50% was taken to indicate heterogeneity between studies, and a random-effects model of analysis was used. Otherwise, fixed-effects models were used. Summary statistics (odds ratio [OR] with the corresponding 95% confidence interval [CI]) are shown. Combined ORs and 95% CIs were calculated and a 2-sided $P < .05$ was taken to indicate statistical significance. All analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ).

3. Results

3.1. Literature search

The results of our literature search are shown in Fig. 1. A total of 178 records were identified through searching and screening for relevance. Of these, 172 were not relevant, 6 underwent full text review, and 4 [10–13] met the criteria for inclusion.

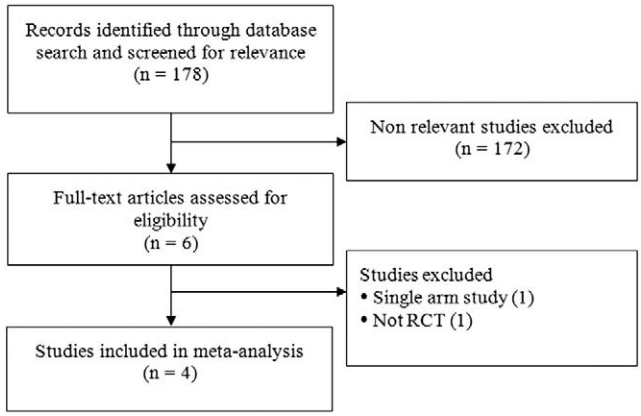

Fig. 1. Flow diagram of study selection. RCT, randomized controlled trial.

3.2. Study characteristics

The characteristics of the studies identified are summarized in Table 1. The number of patients in the studies ranged from 14 to 34 in the midazolam group and from 13 to 33 in the propofol group. Patients were of similar ages (generally in their late 30's) in the 3 studies [10,11,13] reporting age data. The majority (≥66.7%) of patients in each of the studies were male.

The studies reported by Sandiumenge Camps et al [11] and Sanchez-Izquierdo-Riera et al [10] included a variety of severe trauma patients, including patients with severe TBI, whereas the studies reported by Tanguy et al [13] and Ghori et al [12] only included patients with severe TBI. Hence, only the studies by Tanguy et al [13] and Ghori et al [12] were included in the meta-analyses of GOS scores and mortality. Sandiumenge Camps et al [11] used 2% propofol for sedation, whereas Sanchez-Izquierdo-Riera et al [10] used 1% propofol. The other 2 studies did not report the percentage of propofol administered. Although all 4 studies were randomized controlled trials comparing propofol and midazolam, the study by Ghori et al [12] was a double-blind study, the study Tanguy et al [13] was a single-blind study, and the study by Sandiumenge Camps et al [11] was unblinded. Sanchez-Izquierdo-Riera et al [10] did not provide any information with regard to blinding.

There were several differences among the studies with respect to drug administration. All patients in the studies reported by Sanchez-Izquierdo-Riera et al [10] and Sandiumenge Camps et al [11] received morphine chloride, all patients in the study by Ghori et al [12] received morphine sulfate, and all patients in the study by Tanguy et al [13] received fentanyl. There were differences among the studies in the protocols for administering midazolam and propofol. In the studies reported by Sanchez-Izquierdo-Riera et al [10] and Sandiumenge Camps et al [11], patients in the midazolam group were given IV midazolam 0.1 mg/kg per hour (maximal dose = 0.35 mg/kg per hour) and the patients in the propofol group were given IV propofol 1.5 mg/kg per hour (maximal dose = 6 mg/kg per hour). In the study reported by Ghori et al [12], patients in the midazolam group were given IV midazolam 0.1 to 0.3 mg/kg per hour and patients in the propofol group were given IV propofol 1.5 to 5 mg/kg per hour. In the study reported by Tanguy et al [13], patients in the midazolam group were initially given IV midazolam 0.03 mg/kg per hour and the dose was increased in increments of 0.01 mg/kg, while patients in the propofol group were initially given IV propofol 1 mg/kg per hour (maximal dose = 5 mg/kg per hour).

There were similarities and differences among the studies in outcome measures. GOS scores were assessed in the studies reported by Ghori et al [12] and Tanguy et al [13], whereas Sanchez-Izquierdo-Riera et al [10] and Sandiumenge Camps et al [11] did not assess GOS