Research Article

Propofol Compared to Dexmedetomidine as Primary or Adjunctive Sedation in Traumatic Brain Injury

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Abstract...

Objective: Propofol has been the standard of care for sedation management in traumatic brain injury (TBI). Dexmedetomidine has been increasingly used for sedation in TBI as an alternative to propofol, but data are limited in this population. The objective of this study was to evaluate the safety and efficacy of dexmedetomidine compared to propofol for sedation in mechanically ventilated patients with TBI.

Methods: This retrospective analysis included mechanically ventilated critically ill patients with TBI who received propofol or dexmedetomidine for more than six hours between June 1, 2016 and August 31, 2018. The primary efficacy outcome was the percentage of time spent within target sedation range, defined as the goal Richmond Agitation Sedation (RASS) score. Secondary outcomes included hospital and ICU lengths of stay, duration of mechanical ventilation, incidence of agitation and delirium, need for additional sedative agents, and need for interventions for elevated intracranial pressure (ICP). Safety outcomes included the prevalence of hypotension and bradycardia.

Results: This analysis included 83 patients, with 64 patients in the propofol group and 19 patients in the dexmedetomidine group. Time at target RASS goal was significantly higher in patients receiving dexmedetomidine compared with propofol (34.5% vs 0%, p = 0.003). Hospital and ICU length of stays were significantly longer in the dexmedetomidine group (20 vs 8 days, p <0.001 and 14 vs 6 days, p = 0.014, respectively). The incidence of agitation was significantly higher in the dexmedetomidine group (52.6% vs 18.8%, p = 0.007). More patients in the dexmedetomidine group required additional sedative agents (73.7% vs 42.2%, p = 0.019). There were no significant differences in duration of mechanical ventilation, the number of patients requiring interventions for elevated ICP, incidence of delirium, and all safety outcomes.

Conclusion: This study adds to the data about the safety and efficacy of dexmedetomidine use in patients with TBI. In patients with TBI, primary or adjunctive sedation with dexmedetomidine may be associated with increased time in the target RASS range compared to propofol. Dexmedetomidine appears to be as safe as propofol in patients with TBI, with similar rates of hypotension and bradycardia between the two agents.

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Background

Sedative agents are a cornerstone in the management of critically ill patients with traumatic brain injury (TBI) to facilitate mechanical ventilation, to manage agitation and to treat elevated intracranial pressure (ICP) [1]. Additionally, sedative agents and opioids are frequently utilized in this population to reduce metabolic rate, manage or prevent seizures, and improve patient synchrony with the mechanical ventilator [2,3]. Traditionally, propofol has been the standard of care for sedation management in TBI. However, propofol is associated with adverse events including propofol-related infusion syndrome (PRIS) and hemodynamic instability which could potentially decrease cerebral perfusion pressure in patients with TBI [4,5]. The most recent Brain Trauma Foundation guidelines recommend using propofol for management of elevated ICP, but caution against the use of high doses of propofol given the known morbidity [2].

There has been an increasing use of alternative sedative agents, such as dexmedetomidine, in patients with TBI; however, there remains a paucity of data regarding the use of this agent in this population [6-8]. Dexmedetomidine has been shown to be an effective sedative in other critically ill patient populations, with adverse effects most notable for hypotension and bradycardia [9-11]. Specifically, the MIDEX and PRODEX randomized controlled trials demonstrated that dexmedetomidine offered similar time at target sedation compared to midazolam and propofol use, respectively [11]. Given the lack of data regarding dexmedetomidine in patients with TBI, the safety and efficacy of the use of dexmedetomidine in these patients needs to be further elucidated. The objective of this study was to evaluate the safety and efficacy of dexmedetomidine compared to propofol for sedation in mechanically ventilated patients with TBI.

Methods

This study was a single-center, retrospective chart review that was conducted at Brigham and Women's Hospital (BWH) in Boston, MA and was approved by the Partners Healthcare Institutional Review Board. Reports were generated in the electronic medical record using International Classification of Diseases 10 codes for the diagnoses of TBI, trauma, subdural hemorrhage, subarachnoid hemorrhage, intracranial hemorrhage, intraventricular hemorrhage, and intraparenchymal hemorrhage to identify all patients admitted to the neuroscience, surgical, and/or trauma intensive care units (ICU) at BWH with a TBI between June 1, 2016 and August 31, 2018. Patients were excluded if they were less than 18 years of age, were not intubated during the course of their sedation, received propofol or dexmedetomidine for less than six hours, had bleeding that was not traumatic in origin, or if they received propofol or dexmedetomidine for procedural sedation only. Patients were included in the propofol group if they received propofol as a sedative agent for greater than six hours. Patients were included in the dexmedetomidine group if they received dexmedetomidine alone or as an adjunct to propofol for sedation for greater than six hours. Patients initially started on propofol and transitioned to dexmedetomidine had data points censored prior to initiation of dexmedetomidine and were included only in the dexme-

detomidine group. Data were only collected in these patients from the time dexmedetomidine was initiated until the end of therapy; any data points during propofol administration were not collected or included in the analysis.
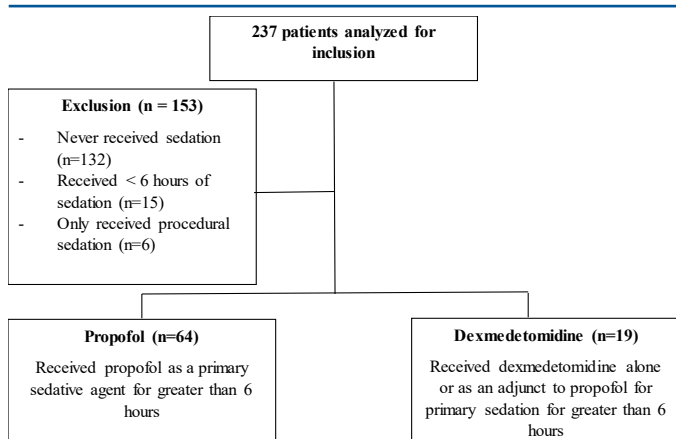
Baseline patient demographics collected were age, sex, race, BMI, admission serum creatinine, admission Glasgow Coma Scale (GCS), and injury mechanism. Physiological variables collected were delirium and sedation scores. Other data points collected included hospital and ICU length of stay, intracranial pressure lowering interventions, and length of mechanical ventilation. Data were collected for the length of the sedative infusion or until extubation, whichever occurred first.

The primary outcome analyzed in this study was the percentage of time spent within target sedation range, defined as goal Richmond Agitation and Sedation Scale (RASS) score as set by the treatment team. The goal RASS was obtained from the sedative medication order in the electronic medical record, as it is a required part of any continuous sedation medication order at our institution. Secondary outcomes included hospital length of stay, ICU length of stay, need for additional sedative agents (defined as concurrent administration of a continuous sedative other than propofol or dexmedetomidine), in-hospital mortality, duration of mechanical ventilation, incidence of agitation (defined as RASS greater than +1), incidence of delirium (defined as a positive documentation of the Confusion Assessment Method for the ICU), and the number interventions made for elevated ICP. Elevated ICP interventions were defined as surgical interventions including the placement of an external ventricular drain, the need for a craniectomy or hemicraniectomy, a decompressive Burr Hole, the placement of a ventriculoperitoneal shunt, and/or the use of hyperosmolar agents such as hypertonic saline and/or mannitol. Safety outcomes included the prevalence of hypotension and bradycardia, and the incidence of PRIS. Consistent with previous literature, hypotension was defined as a systolic blood pressure less than 90 mmHg and bradycardia was defined as a heart rate of less than 50 beats per minute [4,8,12]. PRIS was defined as occurring if there was documentation of such reaction by the medical team in the electronic medical record.

Data for the primary outcome are presented as median plus interquartile range (IQR). Data for the secondary and safety outcomes are presented as medians plus IQR, as well as percentages. Categorical data were analyzed utilizing Chi-square or Fischer Exact tests. Continuous non-parametric data, including the primary outcome, were analyzed utilizing Mann-Whitney U test. A p-value of less than 0.05 was considered statistically significant for all outcomes.

Results

A total of 236 patients were screened for inclusion in this study (Figure 1); 153 patients did not meet criteria for inclusion, with a majority excluded due to diagnosis of a mild TBI who never required sedation with propofol or dexmedetomidine. In total, 83 patients were included in the analysis, with 64 patients included in the propofol group and 19 patients included in the dexmedetomidine group (Figure 1). Eleven patients in the dexmedetomidine group also received concomitant propofol.

Figure 1: Flow diagram of inclusion and exclusion criteria.

Flow diagram text:

237 patients analyzed for inclusion

Exclusion (n = 153)
- Never received sedation (n=132)
- Received < 6 hours of sedation (n=15)
- Only received procedural sedation (n=6)

Propofol (n=64)
Received propofol as a primary sedative agent for greater than 6 hours

Dexmedetomidine (n=19)
Received dexmedetomidine alone or as an adjunct to propofol for primary sedation for greater than 6 hours

Table 1: Baseline demographics by group.

Characteristic	Propofol group (n = 64)	Dexmedetomidine Group (n = 19)	p-value
Age*, years	67 [52-78]	53 [28-66]	p = 0.048
Male^	50 (78.1)	16 (84.2)	p = 0.75
Race^			
- White	47 (73.4)	16 (84.2)	p = 0.542
- African American	3 (4.7)	2 (10.5)	p = 0.322
- Asian	2 (3.1)	1 (5.3)	p = 0.547
- Other	12 (18.8)	0 (0)	p = 0.059
BMI*, kg/m²	27.7 [24.9-31.8]	25.5 [23.2-29.9]	p = 0.28
Admission GCS*	6 [3-11]	6 [3-12]	p = 0.589
Mechanism of injury^			
- Blunt	51 (79.7)	17 (89.5)	p = 0.502
- Penetrating	1 (1.6)	0 (0)	p = 1
- Undefined	12 (18.7)	2 (10.5)	p = 0.513

* Data presented as median [IQR]
^ Data presented as n (%)
BMI: Body Mass Index; CGS: Glasgow Coma Scale; IQR: Interquartile Range

Table 2: Primary and Secondary outcomes.

Primary Outcome			
	Propofol group (n = 64)	Dexmedetomidine group (n = 19)	p-value
Percentage of time at goal RASS*	0 [0-21.3]	34.5 [14.7-42.9]	p = 0.003
Secondary Outcomes			
Characteristic	Propofol group (n = 64)	Dexmedetomidine group (n = 19)	p-value
Hospital LOS, days*	8 [5-17]	20 [17-30]	p < 0.001
ICU LOS, days*	6 [3-13]	14 [7-22]	p = 0.014
Duration of mechanical ventilation, hours*	67 [24-153]	118 [33-267]	p = 0.267
In-hospital mortality^	26 (40.6)	1 (5.3)	p = 0.004
Incidence of delirium^	8 (12.5)	11 (57.9)	p = 0.058
Incidence of agitation^	12 (18.8)	10 (52.6)	p = 0.007
Need for additional sedatives^	27 (42.2)	14 (73.7)	p = 0.019
Patients requiring pharmacologic ICP intervention^	23 (35.9)	4 (21.1)	p = 0.275
Patients requiring surgical ICP interventions^	34 (54.7)	8 (42.1)	p = 0.335
-EVD placement^	24 (37.5)	8 (42.1)	p = 0.717
-Hemicraniectomy or craniectomy^	24 (37.5)	3 (15.8)	p = 0.076
-Burr Hole Decompression^	2 (3.1)	1 (5.3)	p = 0.661
VP Shunt Placement^	0 (0)	1 (5.3)	-

* Data presented as median [IQR]
^ Data presented as n (%)
RASS: Richmond Agitation Sedation Score; LOS: Length of Stay; ICP: Intracranial Pressure; EVD: External Ventricular Drain;
VP: Ventriculoperitoneal

Table 3: Safety outcomes.

	Propofol group (n = 64)	**Dexmedetomidine group (n = 19)**	**p-value**
Total hypotensive events	45	24	p = 0.976
Total bradycardic events	25	21	p = 0.728
Incidence of PRIS	1 (1.6)	-	-

Data presented as n (%)
PRIS: Propofol Related Infusion Syndrome

Discussion

This analysis found that patients receiving dexmedetomidine spent more time at goal RASS compared to patients receiving propofol. Compared with previously published literature, this study demonstrated a much lower percentage of time spent in target RASS with both propofol (median 0%) and dexmedetomidine (median 34.5%) compared to a median percentage of time at target RASS of 60-90% seen in other studies, although these were not performed in the TBI population [13-15]. Alternatively, the results in this study are similar to a study by Pajoumand, et al. where TBI patients who received dexmedetomidine for sedation spent more time at target RASS (mean 16 hours per day or 66.7%) compared to propofol8. In the current study, over half of the patients in the propofol group never achieved the targeted RASS goal. One explanation could be due to the severity of their neurologic injury, leading to lower baseline neurologic function and level of arousal. Although the baseline GCS was similar between the dexmedetomidine and propofol group with a median score of six, patients could have experienced a progression of their injury and decline in degree of functionality throughout their hospital course. There is also a potential for discrepancies between the ordered RASS goal and the actual RASS goal, which may have been lower to manage elevated intracranial pressure or to facilitate synchrony with the ventilator. Propofol is used in the TBI population for management of ICP elevations, which may require larger doses and deeper levels of sedation [2]. Nevertheless, there were no differences observed between both pharmacological and surgical interventions between the dexmedetomidine and propofol groups.

Patients on dexmedetomidine had a higher incidence of agitation and a higher percentage of these patients required additional sedative agents for the management of their sedation compared to patients on propofol. These findings suggest that although dexmedetomidine may lead to more time spent in target RASS, it might not offer adequate levels of sedation in the TBI population. This finding is consistent with other studies which focused on dexmedetomidine for sedation in both the neurocritical and general critically ill populations which found that dexmedetomidine provided lighter levels of sedation [7,14]. Agitation in TBI patients can lead to ICP elevations and potentially worsen outcomes [16,17]. Further research is needed to confirm these findings and clarify the relationship between increased agitation with dexmedetomidine and the effect on clinical outcomes in this patient population.

There was a longer ICU and hospital LOS in the dexmedetomidine group, which contrasts with previous literature showing no difference in these measures between propofol and dexmedetomidine; however, these studies did not include patients with traumatic brain injury [18,19]. A 2020 study in neurocritical care patients also demonstrated no difference in both hospital and ICU length of stay between propofol and dexmedetomidine [20]. It has been previously shown that patients with TBI have extended ICU and hospital length of stay (an increase of 2.5 ICU days and 4.2 hospital days) compared to the general hospitalized population, a finding which is also seen in our study [21]. The higher mortality rate observed in the propofol group could also have affected the differences observed in ICU and hospital LOS between the groups. Our findings contrast with previous studies that have reported no difference in mortality when these agents were used [12,22]. The increased rate of mortality may reflect the severity of illness of the patients who received propofol, with those surviving long enough more likely to be transitioned to dexmedetomidine during the course of their ICU stay.

There have been variable results in the literature regarding hemodynamic outcomes in TBI when using dexmedetomidine and propofol [4,8,20]. In this study, no difference in the prevalence of hypotensive or bradycardic events was seen. This finding contrasts with a study by Pajoumand, et al. [8] showing an increased rate in hypotension in patients with TBI receiving regimens containing dexmedetomidine versus propofol alone. However, this finding is consistent with the studies by Erdman, et al. [4] and Owusu, et al. [20], which found no significant differences in the rates of both hypotension and bradycardia. Although there was a numerically higher prevalence of hypotensive and bradycardic events in the propofol group, this result was nonsignificant. Hemodynamic fluctuations have been noted in patients with TBI, which could explain the differences in results between this study and previous literature [23]. PRIS is a rare condition with an estimated incidence of 1.1% in critically ill adults and was only seen in chart review in one patient in this study [24]. The small sample size of this study and the low incidence of PRIS limits the ability to draw conclusions from this finding.

Limitations

There are several limitations to this study. The small sample size and uneven distribution between the groups makes it difficult to draw definitive conclusions from these data. This was a single-center, retrospective study which limits the generalizability to other institutions. There was wide variability in frequency of documentation of key values such as RASS which may have affected the primary outcome. In addition, there may have been discrepancies between the ordered RASS goal in the medication order and the verbalized RASS goal which was not reflected in the electronic medical record. Finally, patients in the dexmedetomidine group could also concurrently be on propofol, which could confound the results seen in this group. Eleven patients that concurrently received both dexmedetomidine and propofol were assigned to the dexmedetomidine group as we thought it was important to analyze whether patients on dexmedetomidine required the use of additional sedatives (including propofol) to achieve the target RASS goal; however, as eleven patients in the dexmedetomidine group were on propofol concurrently, this limits the ability to draw conclusions about the use of dexmedetomidine as a single agent for sedation in patients with TBI.

Conclusion

In summary, dexmedetomidine as primary or adjunctive sedation in patients with TBI may maintain target RASS for a higher percentage of time compared to propofol. However, dexmedetomidine may lead to higher rates of agitation and an increased need for additional sedative requirements in this patient population. Further research is needed to clarify the impact of this increase in agitation and requirement for additional sedative agents on clinical outcomes. Finally, dexmedetomidine appears to be as safe as propofol in patients with TBI, with similar rates of hypotension and bradycardia between the two agents.

Declarations

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of conflicting interests: The Author(s) declare(s) that there is no conflict of interest.

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References

1. James ML, Olson DM, Graffagnino C. A pilot study of cerebral and haemodynamic physiological changes during sedation with dexmedetomidine or propofol in patients with acute brain injury. Anaesth Intensive Care. 2012; 40: 949-957.

2. Carney N, Totten AM, O'Reilly CBS, et al. Guidelines for the management of severe traumatic brain injury. Neurosurgery. 2017; 80: 6-15.

3. Skoglund K, Enblad P, Marklund N. Monitoring and sedation differences in the management of severe head injury and subarachnoid hemorrhage among neurocritical care centers. J Neurosci Nurs. 2013; 45: 360-368.

4. Erdman MJ, Doepker BA, Gerlach AT, et al. A comparison of severe hemodynamic disturbances between dexmedetomidine and propofol for sedation in neurocritical care patients. Crit Care Med. 2014; 42: 1696-1702.

5. Devlin JW, Skrobik Y, Gelinas C, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med. 2018; 46: e825-e873.

6. Burry L, Dryden L, Rose L, et al. Sedation for moderate-to-severe traumatic brain injury in adults: a network meta-analysis. Cochrane Database of Systematic Reviews 2017, Issue 4. Art. No.: CD012639.

7. Humble SS, Wilson LD, Leath TC, et al. ICU sedation with dexmedetomidine after severe traumatic brain injury. Brain Inj. 2016; 30: 1266-1270.

8. Pajoumand M, Kufera JA, Bonds BW, et al. Dexmedetomidine as an adjunct for sedation in patients with traumatic brain injury. J Trauma Acute Care Surg. 2016; 81: 345-351.

9. Tang JF, Chen PL, Tang EJ, May TA, Stiver SI. Dexmedetomidine controls agitation and facilitates reliable, serial neurological examinations in a non-intubated patient with traumatic brain injury. Neurocritical Care. 2011; 15: 175-181.

10. Wang X, Ji J, Fen L, Wang A. Effects of dexmedetomidine on cerebral blood flow in critically ill patients with or without traumatic brain injury: a prospective controlled trial. Brain Injury. 2013; 27: 1617-1622.

11. Jakob SM, Ruokonen E, Michael Grounds R, et al. Dexmedetomidine for Long-Term Sedation Investigators: Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: Two randomized controlled trials. JAMA. 2012; 307: 1151-1160

12. Stevens V and Johnson, A. Association of dexmedetomidine infusion rates with first incidence of hypotension and bradycardia. Crit Care Med. 2019; 47: 450

13. Tran A, Blinder H, Hutton B, English SW. A Systematic Review of Alpha-2 Agonists for Sedation in Mechanically Ventilated Neurocritical Care Patients. Neurocrit Care. 2018; 28: 12-25.

14. Shehabi Y, Howe BD, Bellomo R, et al. Early Sedation with Dexmedetomidine in Critically Ill Patients. N Engl J Med. 2019; 380: 2506-2517.

15. Winings NA, Daley BJ, Bollig RW, et al. Dexmedetomidine versus propofol for prolonged sedation in critically ill trauma and surgical patients. Surgeon. 2020; S1479-666X(20)30047-0.

16. Rangel-Castillo L, Gopinath S, Robertson CS. Management of Intracranial Hypertension. Neurol Clin. 2008; 26: 521-541.

17. Farahvar A, Gerber LM, Chiu YL, et al. Response to intracranial hypertension treatment as a predictor of death in patients with severe traumatic brain injury. J Neurosurg. 2011; 114: 1471-1478.

18. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA. 2009; 301: 489-499.

19. Maldonado JR, Wysong A, van der Starre PJ, et al. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. Psychosomatics. 2009; 50: 206-217.

20. Owusu KA, Kurczewski L, Armahizer MJ, et al. DEXmedetomidine compared to PROpofol in NEurocritical Care [DEXPRONE]: A multicenter retrospective evaluation of clinical utility and safety. J Crit Care. 2020 Jul 24; 60: 79-83.

21. Tardif PA, Moore L, Boutin A, et al. Hospital length of stay following admission for traumatic brain injury in a Canadian integrated trauma system: A retrospective multicenter cohort study. Injury. 2017; 48: 94-100.

22. Ng KT, Shubash CJ, Chong JS. The effect of dexmedetomidine on delirium and agitation in patients in intensive care: systematic review and meta-analysis with trial sequential analysis. Anaesthesia. 2019; 74: 380-392.

23. Krishnamoorthy V, Rowhani-Rahbar A, Chaikittisilpa N, et al. Association of Early Hemodynamic Profile and the Development of Systolic Dysfunction Following Traumatic Brain Injury. Neurocrit Care. 2017 Jun; 26: 379-387.

24. Roberts RJ, Barletta JF, Fong JJ, et al. Incidence of propofol-related infusion syndrome in critically ill adults: a prospective, multicenter study. Critical Care. 2009; 13.