

Impact of Dexmedetomidine on Hospital and Intensive Care Unit Stay Duration in Adult Traumatic Brain Injury Patients: A Systematic Review

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Background: Traumatic brain injury is a pressing public health issue worldwide that leads to profound disability and mortality. Medical guidelines recommend sedation and analgesia, with dexmedetomidine emerging as a promising option, given its unique pharmacological properties. However, the effect of dexmedetomidine in reducing the length of hospital stay in patients with traumatic brain injury remains unclear. This systematic review aimed to assess the effect of dexmedetomidine administration on traumatic brain injury management based on severity, with a specific focus on hospital and intensive care unit length of stay.

Methods: A systematic search following the PRISMA guidelines identified relevant studies from various databases. Eligible studies involving adult patients with traumatic brain injury and dexmedetomidine interventions were selected and assessed for the risk of bias. The extracted data included the study characteristics, intervention details, and outcome measures.

Results: Eight studies, three of which were randomized controlled trials, met the inclusion criteria. Dexmedetomidine has shown potential benefits in mitigating traumatic brain injury length of stay, particularly in patients with severe traumatic brain injury. However, the findings on hospital length of stay varied, preventing a definitive conclusion regarding the effectiveness of dexmedetomidine in reducing length of stay. Heterogeneity among the studies was the main factor in the reported variable results.

Conclusion: Dexmedetomidine has a promising role in traumatic brain injury management with evidence suggesting reduced intensive care unit length of stay with dexmedetomidine administration. A comprehensive understanding of dexmedetomidine dosing strategies and their long-term effects is crucial to optimize patient outcomes. A multifaceted approach to traumatic brain injury management will help enhance the therapeutic utility of dexmedetomidine and improve the care and outcomes of traumatic brain injury patients worldwide.

Keywords: traumatic brain injury, dexmedetomidine, length of stay, ICU outcomes, sedation, hemodynamics

Introduction

Traumatic brain injury (TBI) poses a substantial global health challenge, impacting millions of people annually.¹ It leads to severe health complications, increased mortality rates, and imposes significant economic burdens. Unlike chronic illness patients, trauma patients often face acute physiological disturbances, necessitating comprehensive analgesic management.^{2,3} Through extensive research, healthcare professionals and institutions have developed clinical protocols to enhance TBI treatment and improve patient outcomes.^{4,5}

TBI is a clinical diagnosis traditionally classified using the Glasgow Coma Scale (GCS). GCS scores 13–15 are mild brain injuries, 9–12 are moderate, and 3–8 are severe. In addition to structural damage, a broad spectrum of physiological changes secondary to TBI occur in the brain including increase intracranial pressure, brain swelling, and decrease blood supply among other changes. The challenges in TBI management are the wide spectrum of different presentations of other traumatic injuries and complications. While mild head injuries (GCS 13–15) typically have excellent outcomes and often do not require specific sedative interventions, a widely accepted approach involves using sedatives and analgesics to modulate intracranial pressure, decrease cerebral oxygen consumption, prevent seizures, and aid in mechanical ventilation.^{6–10} Dexmedetomidine is highlighted as a promising sedative for TBI patients due to its ability to induce sedation without causing respiratory depression. It offers the advantages of lacking active metabolites, providing combined analgesic and sympatholytic effects, and not disrupting neurological assessments or the process of ventilator weaning.¹¹ Existing TBI guidelines from the Trauma Brain Foundation presently furnish only Level IIB endorsement for the infusion of propofol and barbiturates, underscoring the insufficiency and inadequacy of current studies.¹² Various reviews and a meta-analysis have thoroughly examined the systemic and intracranial hemodynamic effects of dexmedetomidine.^{13–15} Recently, anticipation surrounded the A2B trial, designed to explore the effects of alpha-2 agonists within the general intensive care unit (ICU) population.¹⁶

The widespread preference for dexmedetomidine is attributed to its selective function as an alpha-2-adrenergic receptor agonist.¹⁷ This specificity allows dexmedetomidine to target the locus coeruleus in the brainstem and the spinal cord to provide sedative and analgesic effects.¹⁷ This property is especially beneficial for trauma patients, who endure more severe pain compared to general ICU patients and therefore have an elevated risk of developing opioid use disorders and other complications after discharge.^{13,18} In summary, dexmedetomidine is indicated for sedation in TBI patients due to its ability to reduce intracranial pressure, modulate sympathetic hyperactivity, and provide analgesia without respiratory depression, offering advantages over traditional sedatives like propofol or midazolam.

This systematic review sought to comprehensively evaluate the impact of administering dexmedetomidine to patients with TBI on both hospital and ICU length of stay based on disease severity.

Methods

Search Strategy

A comprehensive literature search was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to identify relevant studies across multiple databases, including PubMed, ScienceDirect, Scopus, and Web of Science, up to March 2024. The search strategy was meticulously formulated to include Medical Subject Headings terms and pertinent keywords related to traumatic brain injury and dexmedetomidine (ie, “traumatic brain injury”, “TBI”, “head injury”, “brain trauma”, “dexmedetomidine”, “Precedex”, “Dex”, “alpha-2 agonist”, etc) in English only. The authors decided not to perform a meta-analysis due to the heterogeneity and discrepancies among the selected studies.

Study Selection

Two authors screened the titles and abstracts of the retrieved articles to identify the relevant studies. These articles were then thoroughly assessed for eligibility based on predefined criteria that included a confirmed adult TBI diagnosis and interventions involving dexmedetomidine as well as reporting the length of hospital and/or ICU stay. Additionally, a stated assessment of TBI severity based on the GCS and/or Abbreviated Injury Scale (AIS) scores was required for inclusion. Because of the heterogeneous nature of trauma in medicine, the studies included patients with isolated TBI as well as those with multiple injuries. The exclusion criteria were administration of dexmedetomidine before hospitalization or in battlefield settings and animal studies, review articles, case reports, studies unrelated to TBI, and studies that did not report relevant outcomes. Any disagreements between the reviewers were resolved through constructive discussions and consensus.

Data Extraction

A comprehensive data extraction process was performed using a standardized form to obtain key data from the eligible studies. Essential information such as author name, publication year, country of study, study design, sample size, patient characteristics (age, sex), intervention specifics (dosage, duration), injury mechanism, TBI severity, and inclusion and exclusion criteria were carefully noted. Moreover, outcome data, including length of hospital and ICU stay, mechanical ventilation duration, initial GCS scores, and GCS score at discharge, were documented.

Risk of Bias Assessment

The risk of bias within the included studies was evaluated using tools tailored to the study designs. For randomized control trials (RCTs), the Cochrane risk of bias tool was employed, which assesses various domains, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting, and other biases. Each domain was evaluated as having low, high, or unclear risk of bias.¹⁹ For observational studies, the Newcastle–Ottawa scale was utilized.²⁰ This scale evaluates the quality of nonrandomized studies based on three domains: selection of study groups, comparability of groups, and ascertainment of outcomes. Each domain was assessed using specific criteria and the studies were awarded stars based on their adherence to these criteria. A higher number of stars indicates a lower risk of bias. Two independent reviewers assessed the risk of bias for each included study. Discrepancies were resolved through discussion and consensus among authors.

Results

Study Selection

An initial comprehensive search across the included databases identified 1650 articles. After eliminating duplicates, 1240 articles remained for further evaluation. The screening of titles and abstracts resulted in the identification of 69 articles deemed potentially relevant for inclusion. Subsequently, these articles underwent a full-text review, resulting in the final selection of three randomized trials^{21–23} and five observational studies^{24–28} that met the predetermined inclusion and exclusion criteria (Figure 1). No study was excluded from the final selection.

Baseline Characteristics

The baseline characteristics of the included studies are shown in Table 1. All studies were conducted in ICU settings, with those by Huang et al including patients after neurosurgical interventions.²³ The follow-up durations varied, ranging from short-term assessments during ICU stay to longer-term evaluations extending for up to 6 months after injury, as observed by Liu et al.²⁷ The sex distributions varied, with some studies reporting a predominance of men, reflecting the demographic diversity in TBI populations. Geographical diversity was evident, with studies conducted in the USA, Canada, China, Iran, and Egypt highlighting the global burden of TBI and allowing the exploration of regional variations in management practices. The sample sizes varied from 41 to 352 individuals across studies and exhibited disparities between observational studies and RCTs. The age ranged from 24 to 65 years. The risk of bias for the included RCTs and observational studies is shown in Tables 2 and 3, respectively.

Hospital Length of Stay

Hospital length of stay varied significantly across the studies, with mean lengths ranging from 19.8 to 48 days. It was observed that the administration of dexmedetomidine may be linked to shorter hospital stays when compared to the control groups or the administration of other sedatives such as propofol and midazolam, as indicated by reports from Liu et al and Tang et al.^{22,23} However, contrasting results were found by Khallaf et al and Huang et al, who revealed minimal to no reduction in the length of hospital stay with dexmedetomidine administration.^{22,23} Additionally, some studies such as those by Pajoumand et al, Bilodeau et al, and Humble et al, did not include comparative groups for length of hospital stay, yet still reported median lengths ranging from 15 to 27 days.^{24–26}

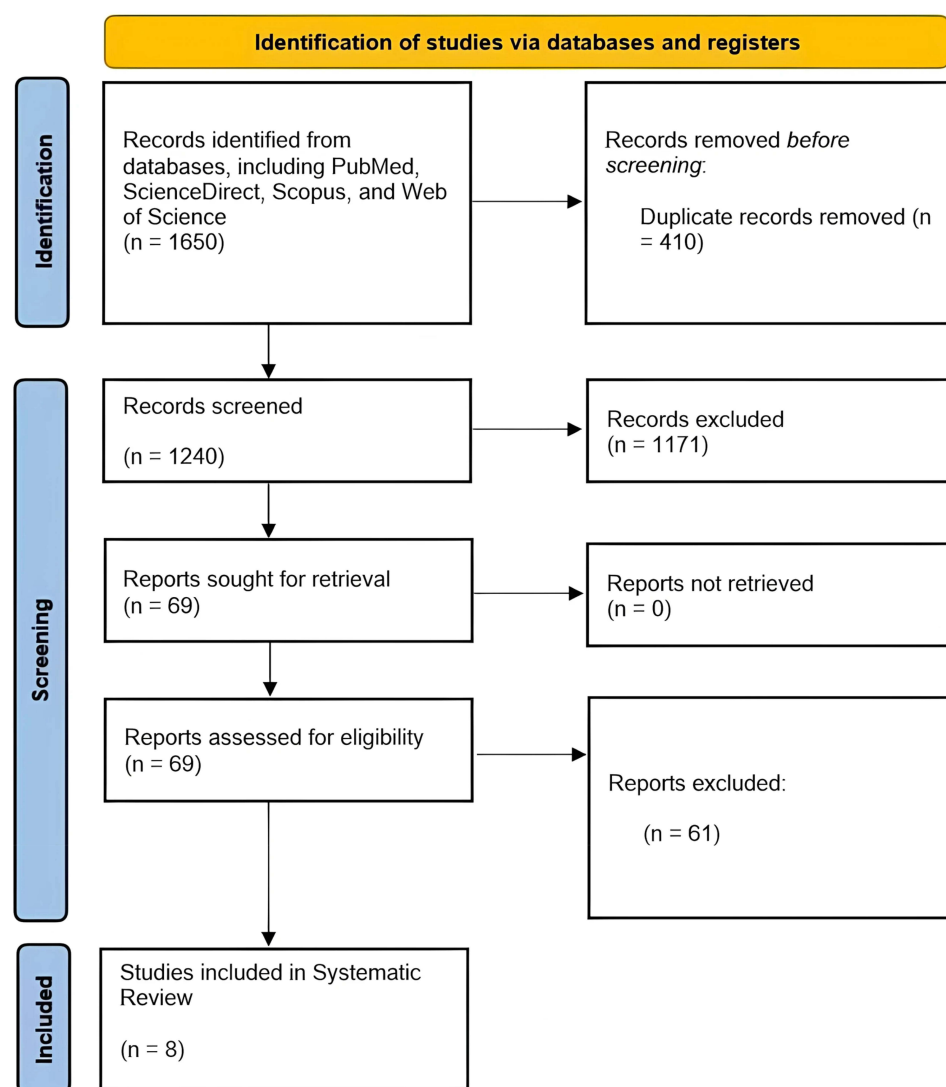


Figure 1 Flowchart illustrating the study selection process, including identification, screening, eligibility, and inclusion of studies, according to the PRISMA guidelines. **Notes:** PRISMA figure adapted from Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34. Creative Commons. doi: 10.1016/j.jclinepi.2009.06.006.²⁹

Studies Reporting on Mild to Moderate Traumatic Brain Injury

Studies conducted by Khallaf et al and Bilodeau et al focused on patients with GCS scores indicative of mild to moderate TBI.^{22,24} Khallaf et al found that patients sedated with dexmedetomidine had a slightly longer hospital stay than those sedated with propofol alone or in combination with dexmedetomidine. However, Bilodeau et al did not note direct comparisons with other interventions regarding the length of hospital stay, but did observe a median stay of 27 days in all patients sedated using either dexmedetomidine, propofol, or benzodiazepines. The longest hospital stay reported in the study by Bilodeau et al was 38 days, which is notably shorter than the mean of 48 days observed by Khallaf et al, despite including patients with lower initial GCS scores of 6 to 8.

Studies Reporting on Moderate to Severe Traumatic Brain Injury

Four observational studies^{25–28} and one RCT²³ investigated a cohort of 839 patients with a GCS score <13. Tang et al and Huang et al investigated a cohort exclusively comprising patients with severe TBI and found that those in the dexmedetomidine group had shorter mean hospital lengths of stay than those sedated with propofol or midazolam.^{23,28} Specifically, Tang et al reported a reduction in the mean hospital length of stay of 5 days, while Huang et al reported a

Table 1 Baseline Characteristics of Included Studies

Author and Year	Design and Sample Size	Age (Years Mean $\pm$ SD)	Gender	Inclusion	Exclusion	TBI Severity	Control	Intervention and Dosage	DEX vs Other	DEX vs Other	Follow Up time	Results
			Male, n (%)						ICU LOS, (Mean $\pm$ SD, d)	Hospital LOS, (Mean $\pm$ SD, d)		
Khallaf et al, 2019 ²²	RCT 60* (DEX 20) (PROP 20) (DEX + PROP 20)	DEX (39.3 $\pm$ 8.5) PROP (38.7 $\pm$ 11) DEX + PROP (39.3 $\pm$ 10.2)	DEX 19 (95) PROP 16 (80) DEX + PROP 18 (90)	-Age between 18 and 80 years-ASA I-III- GCS $\geq$ 8-Agitated and restless patients in need of sedation and close follow-up- Diagnosis of TBI by CT or abnormal posturing-Placement of an ICP monitor as part of standard of care	- Patients requiring mechanical ventilation on admission- Atrioventricular (AV) block with heart rate < 45/min- Severe pre-admission hemodynamic instability	TSS Dex (28.95 $\pm$ 4.2) TSS PROP (30.95 $\pm$ 5.7) TSS DEX + PROP (30.85 $\pm$ 6.4) GCS PROP (14 patients Mild, 6 Moderate) GCS DEX (16 patients mild, 4 moderate) GCS DEX + PROP (15 patients mild, 5 moderate)	PROP, DEX + PROP	Dexemtidine Loading dose: 1 μ g/kg followed by IV infusion: 0.4–1 μ g/kg/h	DEX (24.1 $\pm$ 2.8) PROP (23.5 $\pm$ 3) DEX + PROP (22.9 $\pm$ 3.1)	DEX 48 $\pm$ 3.1) PROP (46.6 $\pm$ 3.8) DEX + PROP (46.4 $\pm$ 4.2)	2–48h	- Heart rate decreased over time, with significantly lower values in the DEX and mixed groups- No significant differences in tachycardia, bradycardia, and hypertension - Significantly lower incidence of hypotensive episodes in the DEX and mixed groups- Significantly lower incidence and duration of delirium in the DEX and mixed groups
Pajoumand et al, 2015 ²⁶	Observational study 198* DEX only (222 patient-days) DEX + PROP (148 patient-days) PROP only (599 patient-days) NEITHER (59 patient-days)	40.1 $\pm$ 17.9	157 (80.1)	-Age $\geq$ 18 years- Admission to the STC Neurotrauma or Multitrauma Critical Care Unit-TBI defined as a head AIS score > 2-Mechanical ventilation > 24 hours- Anticipated ventilation and sedation duration of at least 2 or more days following enrollment-Receiving continuous infusions of benzodiazepines, PROP and/or DEX for sedation	- Patients not mechanically ventilated- Undergoing therapeutic hypothermia following cardiac arrest- Expected survival < 24 hours following time of injury	Mild (GCS 13–15): 37 (18.9%) Moderate (GCS 9–12): 40 (20.4%) Severe (GCS 3–8): 119 (60.7%) median AIS: 4	PROP, DEX + PROP	Dexemtidine Minimum dose: 0.4 μ g/kg/h Maximum dose: 0.9 μ g/kg/h	14(9–22)§	17(12–23)§	1–7days	- The Dex-only group had the highest mean daily estimate of 16.0 hours spent in the target RASS range.- Mean peak ICP differed between groups on some days, but the differences were clinically insignificant.- Hypertension was the most common adverse event, with the highest incidence in the “NEITHER” group.- There were no significant differences in adverse events between the sedation groups.

(Continued)

Table 1 (Continued).

Author and Year	Design and Sample Size	Age (Years Mean $\pm$ SD)	Gender	Inclusion	Exclusion	TBI Severity	Control	Intervention and Dosage	DEX vs Other	DEX vs Other	Follow Up time	Results
			Male, n (%)						ICU LOS, (Mean $\pm$ SD, d)	Hospital LOS, (Mean $\pm$ SD, d)		
Tang et al, 2017 ²⁸	retrospective study ⁹⁰ * DEX (50) PROP or midazolam (40)	46.76 $\pm$ 15.41 Dex (47.50 $\pm$ 15.12) Control (45.83 $\pm$ 15.92)	62 (68.9) DEX 37 (74) Control 25 (62.5)	- Older than 18 years old- Suffered sTBI- Underwent an operation	- Serious hepatic or renal dysfunction - Serum creatinine > 445 μ mol/L and/or blood urea nitrogen > 20 mmol/L in preoperative lab exam- Unstable hemodynamics at NICU admission, such as bradycardia and hypotension- Death occurring within 24 hours after surgery	Severe	PROP or midazolam	DexemtidineLoading dose: 0.8 μ g/kg followed by within 10 min Continuous infusion: 0.25–0.75 μ g/kg/h	17.90 $\pm$ 14.93Dex (15.70 $\pm$ 13.07) Control (20.65 $\pm$ 16.74)	25.87 $\pm$ 18.40Dex (23.50 $\pm$ 16.58) Control 28.53 $\pm$ 20.28	3 months	- Patients in the Dex group had significantly lower PSH-AM scores compared to the control group.- Patients meeting the “probable” PTSD criterion had lower scores in the Dex group compared to control. - More patients in the Dex group met the “unlikely” PTSD criterion compared to control.- No significant differences between groups in mortality, ICU stay, hospital stay, or functional outcomes.
Bilodeau et al, 2021 ²⁴	Retrospective observational study ⁴¹ *	49 (26–64) [†]	37 (90)	- Patients admitted to the ICU of the Hôpital Sacré-Coeur de Montréal for TBI between January 1, 2017 and December 31, 2017- Received Dex for the management of agitation	- Patients who received Dex solely for sedation, not agitation	Median initial GCS (25–75th percentile) 9 (6–14)Median Marshall score (25–75th percentile) 2 (1–2)	NR	Dexemtidine, PROP, BenzodiazepinesMean average rate: 0.62 μ g/kg/h (SD 0.25)Mean minimum rate: 0.26 μ g/kg/h (SD 0.15)Mean maximum rate: 0.96 μ g/kg/h (SD 0.33)	11 (7–17) [§] Mechanical ventilation: 2.7 $\pm$ 2.9	27 (15–38) [§]	2 days before initiation - 6 days after initiation	- Hypotension occurred in 31 out of 41 (76%) patients and bradycardia in 22 out of 41 (54%) patients receiving Dex- Dex had to be discontinued in 1 out of 41 (2%) patients due to hypotension/ bradycardia- The proportion of agitated patients decreased from 100% to 63% during Dex treatment

Huang et al, 2022 ²³	RCT151* DEX (77) Midazolam (74)	DEX (52.2 ± 13.5) Midazolam (51.8 ± 12.8)	Dex 52 (67.5) Midazolam 52 (70.3)	-Patients aged ≥ 18- Patients transferred to the ICU after craniotomy within 24 h	- Sedation duration < 24 h- Long-term use of benzodiazepines before this study (more than 3 months)- Pregnancy- GCS score was 3 and electrocerebral silence- Serious hepatic or renal dysfunction- Death occurring within 24 h after surgery- Craniotomy for brain tumor during this period- Refusal to sign informed consent	Dex GCS (6.5 ± 3.1)Midazolam GCS (5.7 ± 2.3) which indicate severe TBI	Midazolam	DexentidineNR	Dex 9.5 ± 7.7 Midazolam 11.9 ± 11.6	Dex 23.5 ± 19.8 Midazolam 25.3 ± 18.2	28 days	- No significant difference in 28-day mortality between Dex group (14.3%) and midazolam group (24.3%) (p = 0.117)- No significant difference in theta/beta ratio (TBR), delta/alpha ratio (DAR), and (delta + theta)/(alpha + beta) ratio (DTABR) between the two groups on day 1 or day 3- TBR and DTABR were significantly increased in the Dex group- DTABR was significantly increased in the midazolam group - DAR was significantly increased on the right side in the Dex group (p = 0.006)- DAR was significantly increased on both the left (p = 0.006) and right (p = 0.002) sides in the midazolam group
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Table 1 (Continued).

Author and Year	Design and Sample Size	Age (Years Mean $\pm$ SD)	Gender	Inclusion	Exclusion	TBI Severity	Control	Intervention and Dosage	DEX vs Other	DEX vs Other	Follow Up time	Results
			Male, n (%)						ICU LOS, (Mean $\pm$ SD, d)	Hospital LOS, (Mean $\pm$ SD, d)		
Soltani et al, 2021 ²¹	RCT60* DEX (30) Haloperidol (30)	Haloperidol (36.8 $\pm$ 10.1) DEX (40.1 $\pm$ 15.2)	Dex 73.5% Haloperidol 61.7%	- Age between 18–65 years- Requiring mechanical ventilation- APACHE II score > 48- RASS score between –5 to +4- Elapsed time of at least 48 hours after ICU admission	- Patient dissatisfaction- Allergy to haloperidol- History of dementia, Parkinson's, old Brain injury, malignant neuroleptic syndrome- Chronic use of antipsychotic drugs- Long QT interval (> 500 ms)- Family history of dystonic drug reactions- Torsades de pointes syndrome- Pregnancy- Admission to ICU for less than 48 hours- Extrapyramidal symptoms after haloperidol administration- Chance of survival less than 48 hours	Moderate	Haloperidol	Dexentidineiv infusion: 0.5 μ g/kg Dex	Dex (12.2 $\pm$ 5.2) haloperidol (11.8 $\pm$ 3.0) Mechanical Ventilation: Dex (6.3 $\pm$ 2.5) haloperidol (17.0 $\pm$ 3.7)	NR	1–7 days	- Significant differences between the two groups in agitation score (RASS) and APACHE II score 3–7 days after intervention, with the Dex group showing lower agitation and more stable condition.- Incidence of delirium (assessed by CAM-ICU) was significantly lower in the Dex group compared to the haloperidol group at 5–7 days after intervention.

Humble et al, 2016 ²⁵	Retrospective, observational study ^{85*} Dex (85)out of 85 patients: propofol (51) midazolam (35)	35 (24–51)†	73 (86)	- Adult patients (age ≥ 18 years)- sTBI (head AIS ≥ 3, GCS ≤ 8)- Received Dex infusion during ICU stay- ICU LOS ≥ 96 hours	NR	Severe	PROP or midazolam	Dexentidine, propofol, midazolamMedian infusion dose: 0.49 µg/kg/h (IQR 0.38–0.74)	9 (5–13)§ Mechanical Ventilation:7 (4–13)§	15 (11–22)§	70h (24h pre infusion - infusion - 24h post infusion)	- Patients showed significant decreases in systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) during the Dex infusion- There was no significant change in the incidence of hypotension - Patients had significant increases in their GCS scores and Riker Sedation-Agitation Scale (RASS) scores from before the infusion to after the infusion - Patients required significantly less sedation and narcotic pain medication during the Dex infusion compared to before the infusion
Liu et al, 2024 ²⁷	Retrospective cohort ^{352*} Dex infusion during the first 5 days following ICU admission (77) not exposed to early Dex (275)	39.8 ± 16.5	78%	- Adults aged 17 years or older- msTBI, defined as GCS score less than 13 after resuscitation- Underwent ICU admission and received mechanical ventilation within the first 24 hours of ICU admission	- Patients without complete medication records- Patients with unknown timing of ICU admission- Patients who died before 48 hours following ICU admission	Moderate-Severe	PROP, midazolam, ketamine	PROP, midazolam, ketamine, and Dex NR	14.6 (0.8) #Dex infusion during the first 5 days following ICU admission 12.3 (1.1)# not exposed to early Dex 15.2 (0.9)#	22.9 (1.1) #Dex infusion during the first 5 days following ICU admission 19.8 (1.3) #not exposed to early Dex 23.9 (1.4)#	6 months	-Variation exists in the early sedation choice among mechanically ventilated patients with msTBI.-Early exposure to Dex was not associated with improved 6-month functional outcomes in the overall population of patients with msTBI.- However, early Dex exposure may have clinical benefit in patients with indications for ICP monitoring.

Notes: * Total across all groups for each metric (age, sample size, male, female, ICU los, Hospital Los, GCS). † age presented as median (IQR). § LOS presented as median (IQR). # LOS presented as Mean (SE).

Abbreviations: DEX, Dexmedetomidine; PROP, Propofol; GCS, Glasgow Coma Scale; ICU, Intensive Care Unit; LOS, Length of Stay; TBI, Traumatic Brain Injury; msTBI, Moderate-severe traumatic brain injury; sTBI, severe traumatic brain injury; ASA, American Society of Anesthesiologists; ICP, Intracranial Pressure; CPP, Cerebral Perfusion Pressure; RASS, Richmond Agitation-Sedation Scale; AIS, Abbreviated Injury Scale; NR, Not Reported.

Table 2 Assessment of Risk of Bias in Included Studies Using the Cochrane Risk of Bias Tool for Randomized Controlled Trials

	Soltani 2021 ²¹	Khallaf 2019 ²²	Huang 2022 ²³
Random sequence generation (selection bias)	+	+	+
Allocation concealment (selection bias)	+	+	?
Blinding of participants and personnel (performance Bias)	+	+	+
Blinding of Outcome Assessment (detection bias)	?	+	–
Incomplete Outcome Data (attrition bias)	+	+	+
Selective Reporting (reporting bias)	+	+	+
Other Bias	+	+	+

Notes: (+) indicates a low risk of bias; (–) indicates a high risk of bias; (?) indicates unclear or missing information, which preventing prevents a conclusive assessment.

Table 3 Risk of Bias Assessment of Observational Studies Using the Newcastle-Ottawa Assessment Scale

Study Name	Selection				Comparability		Outcome		
	Representation of the Intervention Cohort	Selection of the Non-Intervention Cohort	Has the Correct Intervention Been Utilized?	Outcome of Interest Present at the Start of Study?	Are The Cohorts Comparable Based on The Design or Analysis: Age, sex, and Injury Severity?	Are The Cohorts Comparable Based on The Design or Analysis? Additional Factors	Was The Outcome Assessed?	Was the Follow-Up Long Enough For Measured Outcomes to Occur?	Was the Cohort Follow-Up Long Enough?
Pajoumand 2016 ²⁶	*	*	–	–	*	*	*	*	*
Bilodeau 2021 ²⁴	*	–	*	*	*	*	*	*	–
Liu 2024 ²⁷	*	*	*	–	*	–	*	*	*
Humble 2016 ²⁵	*	–	*	*	–	–	*	*	*
Tang 2017 ²⁸	*	*	*	*	–	–	*	*	*

Notes: (*) indicates a low risk of bias; (–) indicates a high risk of bias.

reduction of 1.8 days. Humble et al exclusively examined individuals with severe TBI who received dexmedetomidine infusion, and found that the median length of hospital stay was 15 days.²⁵ Similarly, Liu et al have observed a 4-day reduction in mean hospital length of stay in patients with moderate to severe TBI with early exposure to dexmedetomidine—within the first 5 days of ICU admission—compared with those with late exposure to dexmedetomidine.²⁷ The study by Pajoumand et al included 198 patients with all severities of TBI, with only 37 having mild TBI, and reported a median length of hospital stay of 17 days.²⁶

ICU Length of Stay

In the double-arm studies, the mean ICU length of stay ranged from 9.5 to 24.1 days in the dexmedetomidine groups and 11.8 to 23.5 days in the control groups. Conversely, the median ICU length of stay in single-arm studies varied from 9 to 14 days. Several reports have demonstrated a decrease in ICU length of stay when dexmedetomidine was administered compared to when alternative interventions were used.^{22,23,28} A study by Liu et al revealed that early administration of

dexmedetomidine resulted in a shorter ICU stay than late administration.²⁷ Conversely, Soltani et al found that patients in the haloperidol group had a shorter ICU length of stay than those in the dexmedetomidine group.²¹ Unfortunately, the timing of dexmedetomidine administration varies significantly, and has been poorly documented in some studies.

Studies Reporting on Mild to Moderate Traumatic Brain Injury

Two RCTs^{21,22} and one observational study²⁴ included cohorts with mild to moderate TBI. In their study, Khallaf et al observed a marginal increase in the ICU length of stay in patients administered propofol alone, whereas the administration of a combination of dexmedetomidine and propofol resulted in a mean reduction in ICU stay of 1.2 days when compared with the administration of dexmedetomidine alone. In contrast, a study by Soltani et al showed that administration of haloperidol was more effective in reducing ICU length of stay than administration of dexmedetomidine. Additionally, Bilodeau et al conducted a single-arm study revealing that the administration of a combination of dexmedetomidine and other sedatives, namely, propofol and benzodiazepines, resulted in a median ICU stay of 11 days.

Studies Reporting on Moderate to Severe Traumatic Brain Injury

Three studies focused only on patients with severe TBI, namely, those by Tang et al, Huang et al, and Humble et al, and have found an overall reduced ICU length of stay.^{23,25,28} The studies conducted by Tang et al and Huang et al compared a dexmedetomidine group with a propofol or midazolam group and have demonstrated a reduction in the mean ICU length of stay by 4.95 and 2.4 days, respectively. Additionally, a single-arm study by Humble et al revealed a median ICU stay of 9 days for patients administered dexmedetomidine in conjunction with propofol or midazolam. Furthermore, a cohort study conducted by Liu et al showed that those who were administered dexmedetomidine within the first 5 days of admission had a mean reduction in ICU length of stay of 2.9 days when compared with unexposed patients. Moreover, the single-arm study by Pajoumand et al, which included patients with a wide range of TBI severities, with a minimal proportion of patients with mild TBI, found a median ICU stay of 14 days.²⁶

Discussion

Managing patients with TBI in a clinical setting requires a multifaceted approach aimed at optimizing outcomes and minimizing complications.^{30,31} Dexmedetomidine holds promise in this regard. This systematic review aimed to thoroughly evaluate the effect of dexmedetomidine on the length of hospital and ICU stay in adult patients with TBI.

Our results highlight the potential benefits of incorporating dexmedetomidine into treatment regimens for TBI of varying severity, particularly in conjunction with other sedatives, to optimize patient outcomes and resource utilization. The existing literature supports the notion that dexmedetomidine exhibits enhanced efficacy in reducing hospital stay when combined with other sedatives, particularly propofol and midazolam. However, despite the importance of considering the severity of TBI to fully comprehend the impact of dexmedetomidine, the current body of evidence does not provide conclusive recommendations in this regard mainly due to the quality of the studies. Therefore, further research is required in this field.

Sedation and analgesia are critical components in the management of patients with TBI. These interventions are used to control agitation, facilitate mechanical ventilation, and reduce the risk of secondary brain damage.^{32–34} Dexmedetomidine, an alpha-2 adrenergic agonist, has emerged as a noteworthy sedative due to its unique properties: it induces sedation, provides analgesic effects, and reduces sympathetic nervous system activity, all while exerting minimal impact on respiratory function.^{35–37} Recent studies underscore its efficacy when administered intravenously, either as a primary sedative in ICU patients requiring mechanical ventilation or during surgical procedures not involving endotracheal intubation.^{38–41}

Notably, precaution is advised when using dexmedetomidine in patients with hypotension or bradycardia, as it may worsen these conditions and lead to complications such as heart block or severe ventricular dysfunction.^{42,43} Furthermore, a contemporary study has identified a potential link between the use of dexmedetomidine and elevated mortality rates in individuals under 65 years of age, when compared to traditional sedatives like propofol or midazolam.⁴⁴

A scoping review conducted by Hatfield et al provides a detailed elaboration of the cerebral physiology and systemic hemodynamics in patients with TBI who have been sedated using dexmedetomidine.⁴⁵ The review highlights the similarities observed when dexmedetomidine is used independently and in combination with standard sedation options, particularly in terms of hemodynamic stability. Our study findings are in line with the results presented by Hatfield et al, suggesting that the reduced or sustained length of hospital stay in patients with TBI could be attributed to the comparable or even superior safety and efficacy of dexmedetomidine compared to that of other sedatives. This indicates that dexmedetomidine may offer promising efficacy in sedating patients with TBI in terms of both safety and reducing the length of hospital stay.

Individuals with severe TBI exhibit a higher susceptibility to complications arising from autonomic dysfunction.^{46,47} In their comprehensive review, Tang et al²⁸ conducted the sole study examining dexmedetomidine capacity to mitigate post-traumatic sympathetic hyperactivity (PSH). PSH, which correlates with TBI severity, is associated with adverse hospital outcomes, including prolonged ICU stays, extended mechanical ventilation periods, and increased infection rates. Recent case reports have also demonstrated dexmedetomidine's efficacy in alleviating PSH symptoms.^{48,49} Dexmedetomidine's sympatholytic properties may potentially inhibit norepinephrine release, offering a viable approach for managing autonomic dysregulation, either as a monotherapy or in combination with medications such as beta blockers.⁵⁰ Current research has not identified any significant differences in intracranial pressure changes, and there is limited data regarding the efficacy of additional sedatives, hyperosmolar therapy, mannitol administration, and external ventricular drain insertion for managing intracranial pressure.^{51–53} While dexmedetomidine has been demonstrated to have no effect on brain oxygenation and to reduce the requirement for narcotics and additional sedatives in TBI patients, it is hypothesized that its protective effects are mediated through anti-inflammatory mechanisms.⁵⁴ These mechanisms involve the inhibition of NF- κ B and NLRP3 inflammasome activation by attenuating endoplasmic reticulum stress-induced apoptosis.^{55,56} Karakaya et al⁵⁷ have also demonstrated that various dexmedetomidine doses can effectively mitigate neuroinflammation. Despite divergent opinions on dexmedetomidine's side effects, particularly its potential to induce hypotension and bradycardia, researchers concur that further studies are necessary to evaluate its impact on TBI patients. The observed reduction in ICU length of stay associated with dexmedetomidine administration has significant implications for healthcare resource utilization by alleviating the burden on healthcare facilities and diminishing the risk of complications such as hospital-acquired infections and delirium, ultimately contributing to improved patient outcomes.

Limitations and Future Perspectives

The present research provides valuable insights into dexmedetomidine's potential benefits for reducing hospital and intensive care unit stays in critically ill patients with traumatic brain injury; however, it has several limitations. Additional research, particularly randomized controlled trials (RCTs) that address confounding factors, is essential to strengthen the evidence and elucidate dexmedetomidine's true impact on this patient population. The implementation of a standardized protocol would minimize inconsistencies and enhance study comparability, thereby enabling more definitive conclusions regarding dexmedetomidine's efficacy for patients with traumatic brain injury. Subsequent studies should examine intensive care unit length of stay while considering specific comorbidities and complications associated with early versus late dexmedetomidine administration. Trauma to other regions of the body should be interpreted with TBI population especially for effects of sedatives, length of stay, and mortality. Mixing different anesthetics is practice of sedating patients, hence, studying a combined regimen of sedatives in trauma population would match the common practice.

Conclusion

This comprehensive review elucidates the efficacy of dexmedetomidine in reducing ICU and hospital stays for TBI patients. An analysis of eight selected studies demonstrates dexmedetomidine's potential to decrease ICU duration across various TBI severity levels, particularly in severe cases, although evidence regarding hospital stay reduction remains inconclusive. The investigators acknowledge the methodological challenges inherent in designing a well-controlled study for sedation use in trauma cases. Future research should focus on optimizing dosing and timing protocols, identifying TBI patient subgroups that may derive maximal benefit from dexmedetomidine, and investigating its long-term impact on

functional outcomes and quality of life among TBI survivors. Addressing these research gaps will enable researchers to enhance dexmedetomidine's therapeutic value and improve overall care and outcomes for TBI patients.

Abbreviations

ICU, Intensive Care Unit; TBI, Traumatic Brain Injury; GCS, Glasgow Coma Scale; AIS, Abbreviated Injury Scale; RCT, Randomized Control Trials; PSH, Post-traumatic Sympathetic Hyperactivity.

Data Sharing Statement

All data supporting the findings of this study are available within the paper. Raw data can be provided upon request.

Ethics Approval and Consent to Participate

This article does not include any interventions that require consent to participate. Confidential data were used in the preparation of this manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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