PRACTICAL PEARL

Dexmedetomidine Controls Agitation and Facilitates Reliable, Serial Neurological Examinations in a Non-Intubated Patient with Traumatic Brain Injury

Julin F. Tang · Po-Liang Chen · Eric J. Tang · Todd A. May · Shirley I. Stiver

Abstract

Introduction We report the effective use of dexmedetomidine in the treatment of a patient with a history of chronic alcohol abuse and an acute traumatic brain injury who developed agitation that was unresolved if from traumatic brain injury, or alcohol withdrawal or the combination of both. Treatment with benzodiazepines failed; lorazepam therapy obscured our ability to do reliable neurological testing to follow his brain injury and nearly resulted in intubation of the patient secondary to respiratory suppression. Upon admission to hospital, the patient was first treated with intermittent, prophylactic doses of lorazepam for potential alcohol withdrawal based upon our institution's standard of care. His neurological examinations including a motor score of 6 (obeying commands) on his Glasgow Coma Scale testing, laboratory studies, and repeat CT head imaging remained stable. For lack of published literature in diagnosing symptoms of patients with a history of both alcohol withdrawal and traumatic brain injury, a diagnosis of agitation secondary to presumed alcohol withdrawal was made when the patient developed acute onset of tachycardia, confusion, and extreme anxiety with tremor and attempts to climb out of bed requiring him to be restrained. Additional lorazepam doses were administered following a hospital-approved protocol for titration of benzodiazepine therapy for alcohol withdrawal. The patient's mental status and respiratory function deteriorated with the frequent lorazepam dosing needed to control his agitation. Dexmedetomidine IV infusion at a rate of 0.5 mcg/kg/h was then administered and was titrated ultimately to 1.5 mcg/kg/h. After 8 days of therapy with dexmedetomidine, the patient was transferred from the ICU to a step-down unit with an intact neurological examination and no evidence of alcohol withdrawal. Airway intubation was avoided during the patient's entire hospitalization. This case report highlights the intricate balance between the side effects of benzodiazepine sedation for treatment of agitation and the difficulties of monitoring the neurological status of non-intubated patients with traumatic brain injury

Conclusion Given the large numbers of alcohol-dependent patients who suffer a traumatic brain injury and subsequently develop agitation and alcohol withdrawal in hospital, dexmedetomidine offers a novel strategy to facilitate sedation without neurological or respiratory depression. As this case report demonstrates, dexmedetomidine is an emerging treatment option for agitation in patients who require reliable, serial neurological testing to monitor the course of their traumatic brain injury.

Keywords Hypercarbia · Hypoxemia · Agitation · Alcohol withdrawal · Dexmedetomidine · Traumatic brain injury

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Humana Press

Introduction

Patients with a history of acute or chronic alcoholism who have sustained a mild to moderate traumatic brain injury are generally admitted to the neuro-intensive care unit for careful respiratory, hemodynamic, and neurological monitoring [1]. Agitation and alcohol withdrawal are common among hospitalized alcoholics [2]. Currently, the use of benzodiazepines is the most prevalent treatment for agitation and alcohol withdrawal. However, benzodiazepines indirectly suppress respiratory function, which may in turn cause hypercarbia requiring airway intubation. Hypercarbia can also increase intracranial pressure and, together with hypotension and hypoxemia, can increase the risk of poor neurological outcome in non-intubated traumatic brain injury patients. [3] This report describes a traumatic brain injured patient who developed agitation that was unclear if caused by alcohol withdrawal or traumatic brain injury or the combination of both but with stable neurological testing and CT imaging. The patient's agitation failed to respond to initial benzodiazepine therapy and was successfully treated with dexmedetomidine. Dexmedetomidine is a new α_2-agonist that provides sedation without suppressing respiratory function [4, 5]. With its unique combination of pharmacological properties, dexmedetomidine offers several advantages in the treatment of agitation and alcohol withdrawal for patients with traumatic brain injury. As proof of principle, we present a novel application of dexmedetomidine in traumatic brain injury that enables treatment of agitation without confounding side effects of neurological or respiratory compromise.

Case Report

A 69-year-old male with a history of chronic alcohol abuse was admitted to the neurosurgical intensive care unit after a fall while standing outside a bar. After a brief loss of consciousness, he became agitated and combative at the scene. In the emergency department, he had a Glasgow Coma Scale score of 14 with mild confusion and a serum ethanol level of 166 mg/dl. His head CT scan revealed a right acute on chronic subdural hemorrhage (1.0 cm in maximum thickness) together with 3 mm of midline shift (Fig. 1). In addition, a right temporal intraparenchymal hematoma ($3 \times 2 \times 2.5$ cm) together with left frontal and temporal subarachnoid hemorrhage were present. His past medical record was significant for an old basal ganglia stroke, history of a seizure disorder, and multiple admissions for alcohol withdrawal. His last alcohol intake was approximately 24 h before admission. The patient was admitted to the ICU for neurological monitoring and he received prophylactic treatment with thiamine (100 mg IV QD) and folate (1 mg IV QD). It is important to note that the patient's history together with the hospital's alcohol withdrawal protocol prompted the administration of benzodiazepines. He was started on "as needed" lorazepam for potential alcohol withdrawal. Vital signs at admission to the ICU were blood pressure 130/77, heart rate 97, temperature 35.9°C, and pulse oximetry 88% on room air. His oxygen saturation increased to 96% with temporary supplemental oxygen through nasal cannula, and he subsequently weaned back to room air and maintained saturations >95%. The chest X-ray revealed mild left basilar atelectasis. His hematological, coagulation, electrolyte, and glucose results were within normal limits. He obeyed commands without focal deficits. Due to the patient's past history of seizure disorder and current head trauma, phenytoin (100 mg Q8h) was initiated prophylactically. On hospital day 2, the patient became extremely agitated throughout the night with a temperature of 38°C, blood pressure of 158/95, and heart rate of 102. A presumed diagnosis of alcohol withdrawal was made based on the
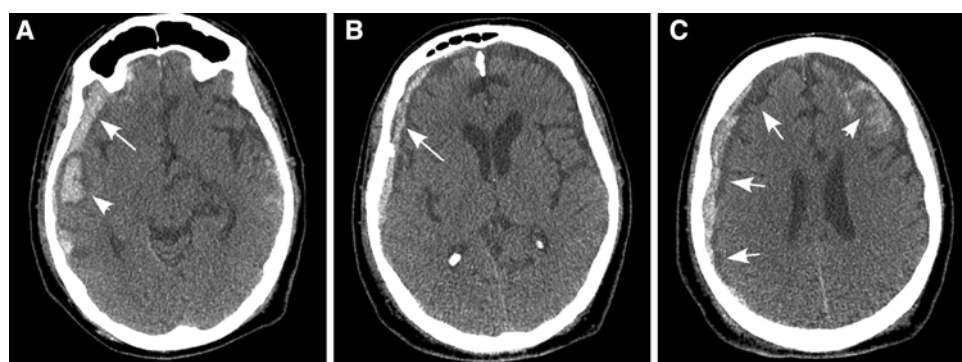

Fig. 1 Non-contrast CT scan of the brain at the time the patient was admitted to hospital. **a** An acute subdural hematoma (*long arrow*) and an intraparenchymal hematoma within the temporal lobe (*arrowhead*) exert mild mass effect with effacement of CSF in the basal cisterns. **b** The acute subdural hematoma (*long arrow*) causes mild 3 mm right to left midline shift. **c** Images at the vertex demonstrate an underlying chronic subdural hematoma (*short arrows*) in addition to the acute subdural hematoma. A contralateral left frontal subarachnoid hemorrhage (*arrowhead*) is also present

patient's vital signs, diaphoresis, and agitation combined with his history of alcohol consumption and prior admissions to hospital for alcohol withdrawal. His serum sodium, additional electrolytes, and glucose were normal. His phenytoin level was therapeutic (11 mg/l). In the absence of obvious signs of seizure activity, electroencephlograhy (EEG) was not performed. He was treated with additional doses of lorazepam following a hospital-approved protocol for dosing of benzodiazepine therapy titrated to grading scales of agitation due to alcohol withdrawal and sedation from the benzodiazepine treatments, as performed by the nurse on an hourly basis. However, the patient's mental status and respiratory function both deteriorated shortly after his lorazepam therapy was intensified, and this required rapid weaning of the lorazepam. At this point, the hospital's standard of care protocol, was not responding favorably to the condition of the patient. A repeat CT scan of the head showed no significant change from his admission study to account for his agitation or the depressed neurological status after starting the lorazepam treatments for alcohol withdrawal. His level of arousal returned to his previous baseline after the benzodiazepines had been weaned. However, his agitation persisted and vitals remained concerning for signs of alcohol withdrawal with early delirium tremens. The lesion burden on his CT

scan was significant, and we required pharmacological treatment that did not depress his level of consciousness. We also wanted to prevent respiratory depression and the need for intubation, which would further confound our ability to monitor serial neurological examinations reflective of his traumatic brain injury. He then was transitioned to dexmedetomidine IV infusion at a rate of 0.3 mcg/kg/h and titrated to 0.7 mcg/kg/h the following day. Despite the dexmedetomidine infusion, the patient again became severely agitated, precipitating the decision to revert back to benzodiazepine therapy. However, frequent dosing with lorazepam was required to control the patient's agitation and he became obtunded, having received > 30 mg of lorazepam over a period of 24 h. Faced with side effects of neurological obtundation and impending intubation from the benzodiazepines therapy, we elected to wean the lorazepam and restart dexmedetomidine at a much higher infusion rate. He stabilized on the dexmedetomidine and a follow-up head CT scan again revealed no significant changes. For the next several days, he received dexmedetomidine infusion at the rate of 1–1.5 mcg/kg/h for agitation compatible with alcohol withdrawal and early signs of delirium tremens. He required significantly smaller amounts of "as needed" lorazepam (8–12 mg/day) for breakthrough agitation (Fig. 2). He was easily arousable
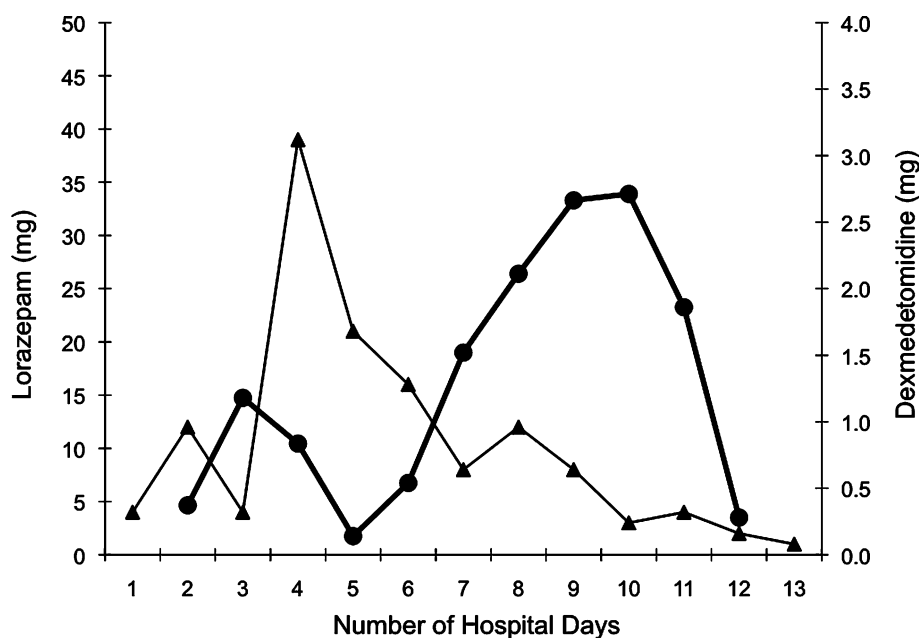

Fig. 2 Daily dosage requirements of lorazepam and dexmedetomidine. *Filled triangle* total daily dose of lorazepam, *filled circle* total daily dose of dexmedetomidine. Day 2: dexmedetomidine started at rate of 0.5 mcg/kg/h and titrated to 0.7 mcg/kg/h for 6 h based on body weight of 88 kg. Day 3: dexmedetomidine started at rate of 0.3 mcg/kg/h and titrated to 0.7 mcg/kg/h for 24 h. Day 4: dexmedetomidine started at 0.7 mcg/kg/h for 21 h and then titrated to off. During that period lorazepam "as needed dosing" totaled 5 mg. After the dexmedetomidine infusion was stopped, lorazepam requirements

markedly increased to a total of 34 mg. At times, the patient required 4 mg lorazepam every 15–30 minutes in addition to a lorazepam infusion at 2 mg/h to control his agitation. Day 5: dexmedetomidine started at 0.3 mcg/kg/h for 7 h and then titrated to off. Day 6: dexmedetomidine restarted at 0.3 mcg/kg/h and titrated to 0.7 mcg/kg/h after 10 mg of lorazepam was required for treatment of agitation within the first 10 h of the day. After day 6: the range of dexmedetomidine infusion rate was 0.3–1.5 mcg/kg/h

and intermittently responsive to verbal commands. On hospital day 9, his vital signs showed temperature 37.9°C, blood pressure 130/75, and heart rate 90. On hospital day 10, the patient developed hyponatremia consistent with cerebral salt wasting syndrome from his traumatic brain injury, and he was started on sodium chloride tablets. He also was started on propranolol for episodes of intermittent atrial fibrillation with ventricular rate ranging from 120 to 140. On hospital day 11, his neurological status improved, and he was able to verbalize his name and current address coherently. The dexmedetomidine infusion was tapered slowly without adverse sequelae. After 8 days of therapy with dexmedetomidine, the patient was transferred from the ICU to a step-down unit with an intact neurological status and no evidence of alcohol withdrawal. Airway intubation was avoided during the patient's entire hospitalization.

Discussion

Benzodiazepines have been the first-line treatment for agitation due to alcohol withdrawal for many years [6, 7]. Although the patient in this case also had the confounding element of traumatic brain injury, the initial therapeutic goal of treating alcohol withdrawal syndrome is to control agitation. Benzodiazepines are the therapy of choice because of their documented efficacy in reducing the duration of withdrawal symptoms, decreasing the incidence of seizures, and reduction in other adverse outcomes [6]. Symptom-triggered therapy (STT) using withdrawal severity scales such as the Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar) has been recommended by national guidelines for more than a decade [6]. STT allows individual titration of medication according to severity of symptoms and response to treatment. As compared to arbitrary fixed dose regimens, STT has the potential to control symptoms more quickly and avoid over-sedation. STT has been employed successfully in the ICU to manage alcohol withdrawal delirium [7]. Several years ago, San Francisco General Hospital implemented a strategy that employs around the clock benzodiazepine therapy for prevention of alcohol withdrawal in high risk patients and symptom-triggered benzodiazepine therapy for those with signs of active withdrawal. However, we have encountered problems with respiratory and neurological suppression, especially among those with liver disease or altered mental status from, for example, traumatic brain injury [8]. Recently, investigators at the Mayo Clinic reported a high level of misapplication of symptom-triggered benzodiazepine therapy among patients with abnormal mental status [9]. Side effects of respiratory and neurological depression during benzodiazepine treatment of agitation and alcohol

withdrawal have been challenging, especially in our head-injured patients. The incidence of endotracheal intubation as a consequence solely of benzodiazepine side effects is not rare [10, 11]. Both intubation, as well as benzodiazepine sedation impair reliable neurological monitoring, which is of paramount importance for patients with an acute traumatic brain injury.

Indeed, lorazepam treatment of the patient's agitation, described in this report, almost resulted in intubation secondary to respiratory and neurological suppression. There are a number of limitations to our study. Traumatic brain injury and sequelae from the injury, such as hyponatremia, can itself cause agitation. We acknowledge that establishing a definitive diagnosis of alcohol withdrawal in the setting of this patient's concomitant traumatic brain injury is difficult but we also cannot ignore the patient's significant history of chronic alcohol abuse and withdrawal episodes. Further, the patient's neurological status following his head injury had remained stable for the first 2 days in hospital. There was no change in the patient's level of arousal or GCS motor score of 6 (obeying commands), as might have been expected if the head injury had been the cause of his agitation. This together with the lack of any changes on repeat CT imaging strongly suggested that his brain injury was not the source of his agitation. Furthermore, biochemical and electrolyte dysfunction, while common following traumatic brain injury, were excluded by normal blood work test results. There is a strong possibility that the combination of traumatic brain injury and alcohol withdrawal could have caused the agitation and that the use of lorazepam exacerbated, instead of treated, the patient's condition. Improvements in the patient's orientation following initiation of dexmedetomidine treatment and similarly again later after weaning of the lorazepam when the patient had become obtunded and over-sedated also suggest that the patient's brain injury or sequelae of his injury were not the root cause of the behavioral change. At the same time, the patient's prior history of alcohol abuse, multiple hospital admissions for alcohol withdrawal, and vital signs of tachycardia, low-grade temperatures, and elevated blood pressure together with signs of tremor and attempts to climb out of bed, requiring the patient to be restrained, seemed most compatible with a diagnosis of alcohol withdrawal and early delirium tremens. Given the morbidity of delirium tremens, we opted to treat for a presumed diagnosis of agitation due to alcohol withdrawal, although the combination of both alcohol withdrawal and traumatic brain injury may have caused the agitation.

This case illustrates the risk of over-sedation with benzodiazepines of a patient with a history of alcohol withdrawal and traumatic brain injury who develops agitation. While the level of benzodiazepine medication required to treat alcohol withdrawal may be well-tolerated

under normal circumstances, patients with traumatic brain injury may be more sensitive to the side effects of such therapy. Failure to recognize the medication-induced sedation and misinterpretation of the drowsiness and agitation as neurological worsening due to the brain injury itself could potentially have led to surgical intervention. The patient's CT scan had a burden of injury that was concerning for the need for possible surgery. Fortunately, this patient's sedation level responded promptly to weaning of the benzodiazepines that was facilitated by use of dexmedetomidine. In this case report, we describe the novel application of dexmedetomidine to successfully treat agitation due to either presumed alcohol withdrawal, traumatic brain injury or the combination of both while avoiding neurological and respiratory compromise. The patient was initially treated with lorazepam at a dosage of 2 mg every 2–3 h, but as his agitation worsened, more frequent doses were required. At one point prior to restarting the dexmedetomidine, the patient required 4 mg of lorazepam every 15–30 min, in addition to a lorazepam infusion at 2 mg/h, to control his agitation. After restarting the dexmedetomidine infusion the second time, the patient's "as needed" lorazepam dosage requirements dropped to 8–12 mg per day. Fortunately, intubation was avoided by administering a centrally acting α_2-agonist as primary therapy for agitation with "as needed" benzodiazepine dosing as adjunctive therapy.

Dexmedetomidine, a selective central α_2-receptor agonist, was approved by the Food and Drug Administration for sedation during initial intubation and mechanical ventilation for no longer than 24 h. Unlike benzodiazepines, which act on the Gamma-aminobutyric acid (GABA) system and can cause respiratory suppression and increase the risk of delirium, dexmedetomidine does not inhibit respiratory drive nor does it depress the patient's neurological status. It ameliorates alcohol withdrawal symptoms via its effect on the locus ceruleus (LC) [12]. Alcohol is a central nervous system depressant. Patients who are undergoing withdrawal have depressed levels of GABA and elevated levels of catecholamines. This leads to a hyperadrenergic state and may cause hemodynamic instability. Dexmedetomidine can mitigate this adrenergic overload and produce a state of cooperative sedation [13]. Dexmedetomidine has been used to facilitate drug withdrawal and alleviate symptoms of alcohol withdrawal in non-head injury patients [13–16]. Dexmedetomidine decreases the hyperarousal state commonly associated with alcohol withdrawal through its central α_2-agonist activity. Unlike benzodiazepines, dexmedetomidine does not stimulate GABA. The differential GABA receptor specificity of dexmedetomidine over benzodiazepines is beneficial for the treatment of alcohol withdrawal, as GABA stimulation has been observed to increase the risk of inciting delirium [17].

Dexmedetomidine acts on the LC to suppress the adrenergic effects of alcohol withdrawal symptoms [13]. Healthy individuals treated with dexmedetomidine at low concentrations have decreased norepinephrine levels and decreased heart rates [18]. Dexmedetomidine treatment of non-alcohol-related delirium has also been shown to shorten the number of delirium- and coma-free days, as compared with lorazepam therapy [19]. While there are no reports specifically addressing the use of dexmedetomidine in traumatic brain injury, there appears to be consensus in the literature that dexmedetomidine causes no change or only slight decreases in intracranial pressure [20–23]. Furthermore, experimental studies have demonstrated a role for dexmedetomidine as a neuroprotective agent [24, 25]. A single study in healthy human volunteers by Drummond et al. [26] has reported that cerebral blood flow (CBF) and cerebral metabolic rate for oxygen ($CMRO_2$) are preserved during dexmedetomidine administration. However, dexmedetomidine has generally been observed to decrease cerebral blood flow without inducing a compensatory reduction in cerebral metabolism, thereby uncoupling the autoregulatory loop between flow and metabolism [27]. Despite its potential benefits, dexmedetomidine can have deleterious effects on cardiovascular and cerebrovascular functions which mandate close hemodynamic monitoring during infusion. Nakano recently reported that dexmedetomidine-induced cerebral hypoperfusion exacerbated ischemic brain injury in rats [28]. Hypotension was observed in 10 of 39 (26%) neurosurgical patients treated with dexmedetomidine infusions for sedation during intubation in the ICU [21]. Because of the FDA restriction on limiting the usage of dexmedetomidine very little has been reported about adverse effects from its long-term use. The most comprehensive study published to date mentioning adverse effects of prolonged use of dexmedetomidine is the SEDCOM study (Safety and Efficacy of Dexmedetomidine Compared with Midazolam). In this study, Riker et al. [29] showed that patients receiving dexmedetomidine had higher incidents of bradycardia compared to those patients receiving midazolam (42.2 vs. 18.9%) and those who required intervention for bradycardia increased but only at a level that was not statistically significant (4.9 vs. 0.8%). The hemodynamics in our patient were closely monitored in the neuro-intensive care unit without any hypotensive episodes and without the need for pressor agents. His systolic blood pressure remained >120 mmHg for most of the time during his dexmedetomidine treatment. He was also receiving propanolol 20 mg per nasogastric tube 3 times a day. His systolic blood pressure did drop to 95–100 on 3 occasions transiently, when the infusion was being titrated up to rates of 1.0–1.5 mcg/kg/h, but his pressure spontaneously recovered without need for pressors or other intervention. We recommend close continuous, hemodynamic monitoring in the intensive

care unit for all patients receiving dexmedetomidine infusions.

The current literature regarding the effects of dexmedetomidine on respiratory function is somewhat divergent depending on the dose administered and the methods used to assess ventilatory function. Following a dexmedetomidine bolus dose of 2 mcg/kg, Belleville et al. [4] noted a depression of the slope of the carbon dioxide response curve and a decrease in minute ventilation at an end tidal CO_2 (E_TCO_2) of 55 mmHg. This study further noted the onset of irregular breathing patterns with short periods of apnea in some of the patients. At an infusion rate of up to 1.5 mcg/kg/h, we did not observe any irregular or apneic periods in our patient's respiratory function. Propofol has been used as an alternative to benzodiazepines for alcohol withdrawal symptoms [30]. However, similar to benzodiazepines, propofol does not mitigate the side effects of respiratory suppression, and in our hospital, propofol cannot be used in non-intubated patients.

While rather expensive, dexmedetomidine offers a potential overall cost savings when balanced against the high costs of ventilatory care in the ICU. Early studies are beginning to recognize the high healthcare costs of over-sedation from use of benzodiazepines, as compared to propofol or dexmedetomidine, for sedation of mechanically ventilated patients in the ICU [31]. At San Francisco General Hospital the expense of ventilator care greatly exceeds that of either drug regimen and suggests that further studies would be useful to validate the cost-effectiveness of dexmedetomidine in the ICU.

In conclusion, continuous infusion of dexmedetomidine for several days enabled ongoing mental status assessment of a patient with a traumatic brain injury and numerous lesions on CT scan that typically carry risk for progression and neurological deterioration. This report, together with the known pharmacological advantages of dexmedetomidine over traditional benzodiazepine therapy for alcohol withdrawal challenge the efficacy of the current therapy compared to this novel, alternative agent. Additional studies are needed to validate the potential use of dexmedetomidine in treating agitation due to alcohol withdrawal in both intubated and non-intubated patients. Furthermore, the neuroprotective efficacy of dexmedetomidine offers a theoretical advantage that may extend to include all patients with traumatic brain injury who require sedation for indications other than agitation or alcohol withdrawal. Finally, this case report highlights the intricate relationship between sedation, alcohol withdrawal, and brain injury in non-intubated patients and demonstrates how, in this case study, dexmedetomidine proved an ideal agent for the management of a patient with agitation due to probable alcohol withdrawal and traumatic brain injury. Given the large numbers of patients with a history of alcohol abuse that suffer a traumatic brain injury, dexmedetomidine offers an alternative novel strategy to manage this common problem.

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