Chapter 35

INTENSIVE CARE UNIT SEDATION IN THE TRAUMA PATIENT

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INTRODUCTION

Critical illness can be a traumatic and anxiety-provoking experience. A multitude of factors can contribute to patients' anxiety in the intensive care unit (ICU), including the constant disruptions and stimulation from alarms, mechanical ventilation and the inability to speak, multiple healthcare providers, frequent vital-sign checks, continuous ambient light, inadequate analgesia, and the associated sleep deprivation, all of which can lead to anxiety and increased stress.[1] The stresses of ICU admission have been associated with a 4% to 15% rate of posttraumatic stress disorder among ICU survivors.[2,3] Combined with posttraumatic stress disorder among veterans returning from Iraq and Afghanistan, the rate of which has been estimated at 17%,[4] resultant morbidity may be significant. Appropriate use of sedative agents may decrease some of these stresses

by providing anxiolysis and amnesia and improving tolerance to mechanical ventilation.[5] Additionally, sedation reduces the stress response and improves tolerance of routine procedures performed in the ICU.[6]

While the patient is sedated and undergoing transport, routine monitoring should consist, at a minimum, of continuous pulse oximetry and electrocardiography readings, and regular blood pressure and respiratory rate monitoring.[7-9] Additionally, depending on patient factors, monitoring with more invasive devices, including taking intraarterial blood pressure,[9] central venous pressure, pulmonary arterial pressure, intracranial pressure, and, potentially, capnography, may be beneficial.[10] An additional supply of sedatives should be available when sedated critically ill patients are being transported.[11]

SEDATION SCALES

A sedation scale is critically important because its use has demonstrated fewer instances of over sedation,[12] more precise sedative dosing, shorter duration of mechanical ventilation, and less use of vasopressor therapy.[13] Use of a validated sedation assessment scale was recommended in the 2002

Society of Critical Care Medicine (SCCM) clinical practice guidelines for the sustained use of sedatives in the critically ill adult.[7] Despite this recommendation, survey data show that sedation scales are used by only approximately 50% of intensivists[14] and in a similar percentage of consecutive patients receiving

TABLE 35-1

THE RICHMOND AGITATION-SEDATION SCALE

Score	Term	Description	
+4	Combative	Overtly combative, violent, immediate danger to staff	
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive	
+2	Agitated	Frequent nonpurposeful movement, fights ventilator	
+1	Restless	Anxious but movements not aggressive or vigorous	
0	Alert and calm		
−1	Drowsy	Not fully alert, but has sustained awakening (eye opening/eye contact) to voice (>10 seconds)	Verbal stimulation
−2	Light sedation	Briefly awakens with eye contact to voice (<10 seconds)	
−3	Moderate sedation	Movement or eye opening to voice (but no eye contact)	
−4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation	Physical stimulation
−5	Unarousable	No response to voice or physical stimulation	

Procedure for RASS Assessment
1. Observe patient
   • Patient is alert, restless, or agitated. — Score 0 to +4
2. If not alert, state patient's name and say to open eyes and look at speaker.
   • Patient awakens with sustained eye opening and eye contact. — Score −1
   • Patient awakens with eye opening and eye contact, but not sustained. — Score −2
   • Patient has any movement in response to voice but no eye contact. — Score −3
3. When no response to verbal stimulation, physically stimulate patient by shaking shoulder and/or rubbing sternum.
   • Patient has any movement to physical stimulation. — Score −4
   • Patient has no response to any stimulation. — Score −5

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mechanical ventilation in another study.**[15]** No specific recommendation has been made by the SCCM favoring any of the myriad scales available. Important features of a sedation scale include rigorous multidisciplinary development; ease of administration, recall, and interpretation; well-defined discrete criteria for each level; assessment of agitation; demonstration of interrater reliability for relevant patient populations; and evidence demonstrating validity in the population in which it is to be used.[16] Several sedation scales, including the Richmond Agitation-Sedation Scale (RASS; Table 35-1),[17] Ramsay Sedation Scale,[18] Sedation Agitation Scale,[19] Motor Activity Assessment Scale (MAAS),[20] and Adaptation to the Intensive Care Environment (ATICE) instrument[21] offer many of these desired characteristics.

Most sedation assessments operate in a similar fashion. First, the patient's level of consciousness is observed to evaluate wakefullness. If the patient is not awake, verbal stimulation is usually the next step, followed by physical stimulation if the patient does not respond to the verbal cue. In the Ramsay Seda-

tion Scale, RASS, and ATICE, a position on the scale is assigned given the patient's response to increasing levels of stimulation. Some scales, like the RASS and ATICE, also incorporate the patient's ability to follow commands. The opposite of sedation, agitation, is important to measure because it may compromise care, raise metabolic requirements, and increase morbidity and mortality.[15] The Sedation Agitation Scale, MAAS, RASS, and ATICE all identify and grade the patient's degree of agitation.[17,19–21]

The RASS has been validated, used in critically ill trauma patients, and shown to correlate well with other methods of monitoring sedation.[17,22] Its scoring system includes a positive number corresponding to restlessness or agitation and a negative number corresponding to sedation, with the higher absolute value correlating with a more extreme behavioral state. This system is intuitive and allows for easier evaluation and recall. The three-step assessment can be done quickly, usually in 30 to 60 seconds, and has favorable interrater reliability.[16] The author recommends the RASS as the first-choice sedation scale in clinical settings.

SEDATIVES

The ideal sedative should have a rapid onset of action and recovery after discontinuation, a predictable dose response, analgesic benefit, and a neutral effect on hemodynamics; it should not result in accumulation, respiratory depression, delirium, or associated toxicity.[5] Because no such sedative exists, providers must choose the most appropriate drug based on medication availability, pharmacokinetics, pharmacodynamics, the patient's comorbidities, and institutional protocols (Table 35-2).

Benzodiazepines

Benzodiazepines (diazepam, lorazepam, and midazolam) are the most commonly administered sedatives.[23] They potentiate the effects of γ-aminobutyric acid (GABA) and suppress the central nervous system,[24] resulting in hypnosis, anxiolysis, muscle relaxation, amnesia, and anticonvulsant activity.[25] Benzodiazepines lower the cerebral metabolic rate of oxygen consumption and decrease cerebral blood flow, but do so in a normal ratio. Midazolam has been shown to be safe and effective in sedating patients with head trauma.[26] As single agents, benzodiazepines do not possess analgesic properties; however, they are known to have an opioid-sparing effect related to modulation of the anticipatory pain response.[27]

Delirium is a side effect more commonly associated with the use of benzodiazepines compared to other

sedatives,[19,28] which is important because delirium has also been associated with higher mortality, longer lengths of hospital stay (including time in the ICU), and longer duration of mechanical ventilation.[29,30]

Midazolam

When used as a bolus, midazolam is rapid and short-acting, with an onset of 2 to 5 minutes, making it ideal for rapidly sedating acutely agitated patients.[7] It is a water-soluble benzodiazepine with a half-life of 3 to 12 hours and a large volume of distribution.[7,31] Its primary site of metabolism is the liver, where it oxidizes (via the cytochrome P450 enzyme system) to several water-soluble metabolites that are then renally cleared.[32] The only pharmacologically significant metabolite of midazolam is α1-hydroxymidazolam, an active metabolite with 20% less potency than midazolam and a half-life of approximately 1 hour.[33] Like its parent compound, α1-hydroxymidazolam is a potent central nervous system depressant and can accumulate significantly. Critically ill patients are particularly susceptible to midazolam accumulation and its products of metabolism because of their increased volume of distribution, lower albumin, and more frequent impairment of renal and hepatic function.[7,34] Midazolam should be used for less than 72 hours to avoid accumulation and prolonged sedation; longer use can lead to unpredictable awakenings and increased time to extubation.[7]

TABLE 35–2

PHARMACOLOGY OF SELECTED SEDATIVES

Drug	Onset (min)	Half-life (hours)	Active Metabolites	Special Considerations	IV Dose (ID or LD)	Continuous Infusion Dose
Midazolam	2–5	3–12	+	Accumulates in renal failure	LD: 0.01–0.05 mg/ kg q10 min	0.02–0.1 mg/kg/h
Lorazepam	5–20	10–20	–	Propylene glycol toxicity	ID: 0.01–0.1 q2–6h	0.01–0.1 mg/kg/h
Propofol	0.5–2	1.5–12	–	Elevated triglycerides, pain on injection, PRIS	10–30 mg titrated for rapid sedation	5–75 μg/kg/min
Dexmedeto-midine	2–20	2	–	Bradycardia, hyper/ hypotension, no respiratory depression	LD: 0–1 μg/kg over 10 min	0.2–1 μg/kg/h

ID: intermittent dose; IV: intravenous; LD: loading dose; PRIS: propofol infusion syndrome
Data sources: (1) Ostermann M, Keenan S, Seiferlin R, Sibbald W. Sedation in the intensive care unit: a systematic review. *JAMA* . 2000;283(11):1451–1459. (2) Jacobi J, Fraser GL, Coursin DB, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med*. 2002;30(1):119–141. (3) Shapiro BA, Warren J, Egol AB, et al. Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: an executive summary. *Crit Care Med*. 1995;23:1596–1600. (4) Gilliland HE, Prasad BK, Mirakhur RK, Fee JP. An investigation of the potential morphine sparing effect of midazolam. *Anaesthesia*. 1996;51:808–811. (5) Haefely W. The biological basis of benzodiazepine actions. *J Psychoactive Drugs*. 1983;15:19–39. (6) Arcangeli A, Antonelli M, Mignani V, Sandrone C. Sedation in PACU: the role of benzodiazepines. *Curr Drug Targets*. 2005;6:745–748. (7) Sanchez-Izquierdo-Riera JA, Caballero-Cubedo RE, Perez-Vela JL, Ambros-Checa A, Cantalapiedra-Santiago JA, Alted-Lopez E. Propofol versus midazolam: safety and efficacy for sedating the severe trauma patient. *Anesth Analg*. 1998;86:1219–1224. (8) Ghoneim MM, Mewaldt SP. Benzodiazepines and human memory: a review. *Anesthesiology*. 1990:172(5):926–938. (9) Pandharipande P, Pun B, Herr D, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS Randomized Controlled Trial. *JAMA*. 2007;298(22):2644–2653. (10) Spina S, Ensom M. Clinical pharmacokinetic monitoring of midazolam in critically ill patients. *Pharmacotherapy*. 2007;27(3):389–398. (11) Mandema JW, Tuk B, van Steveninck AL, Breimer DD, Cohen AF, Danhof M. Pharmacokinetic-pharmacodynamic modeling of the central nervous system effects of midazolam and its main metabolite alpha-hydroxymidazolam in healthy volunteers. *Clin Pharmacol Ther*. 1992;51:715–728. (12) Devlin J, Roberts R. Pharmacology of commonly used analgesics and sedatives in the ICU: benzodiazepines, propofol, and opioids. *Crit Care Clin*. 2009;25:431–449. (13) Arroliga AC, Shehab N, McCarthy K, Gonzales JP. Relationship of continuous infusion lorazepam to serum propylene glycol concentration in critically ill adults. *Crit Care Med*. 2004;32(8):1709–1714. (14) Ativan injection (lorazepam) [package insert]. Lake Forest, IL: Hospira Inc; 2012. (15) Newman L, McDonald J, Wallace P, Ledingham I. Propofol infusion for sedation in intensive care. *Anaesthesia*. 1987;42:929–937. (16) Dyck J, Ikeda K, Morita K, et al. The pharmacokinetics of propofol vs. age. *Anesthesiology*. 1991;75:A315. (17) Propofol [package insert]. Wilmington, DE: Astra Zenica; 2005. (18) Gerlach AT, Dasta JF. Dexmedetomidine: an updated review. *Ann Pharmacother*. 2007;41:245–254. (19) Gerlach AT, Dasta JF, Steinberg S, Martin LC, Cook CH. A new dosing protocol reduces dexmedetomidine-associated hypotension in critically ill surgical patients. *J Crit Care.* 2009;24:568–574. (20) Videira R, Ferreira R. Dexmedetomidine and asystole. *Anesthesiology*. 2004;101:1479. (21) Precedex [package insert]. Lake Forest, IL: Hospira Inc; 2011.

Erythromycin, itraconazole, diltiazem, and other drugs that are known to interfere with the cytochrome P3A4 can lead to a prolonged effect as well by interrupting midazolam metabolism.

Lorazepam

Lorazepam has a slower onset of action (5–20 minutes) than midazolam, making it less useful for sedating an acutely agitated patient. Additionally, its longer half-life (10–20 hours[7,32,34]) makes infusions less titratable. Therefore, lorazepam is often used as a sedative in intermittent boluses rather than a continuous infusion. If it is infused, intermittent boluses and a relatively constant infusion rate are recommended.[7]

Propylene glycol (PG) is used as a diluent to increase the solubility of lorazepam and diazepam. Either of the benzodiazepines can lead to PG toxicity, but toxicity has been reported most commonly in the ICU related to high-dose lorazepam infusions.[35] The presenting symptom of PG toxicity is usually a hyperosmolar gap metabolic acidosis. Toxicity can then progress to acute tubular necrosis and renal failure, lactic acidosis, intravascular hemolysis, cardiac arrhythmias, seizures, and central nervous system depression.[7,34,35] Toxic doses of PG can occur quickly when lorazepam is used for continuous sedation and in large doses approaching the maximum recommended dosage of 0.1 mg/kg/h.[7] The daily maximum dose of PG considered to be safe is 25 mg/kg. With each 2-mg vial of lorazepam (2 mg/mL) containing 664 mg of PG per milliliter of lorazepam, a heavily sedated, critically ill patient can easily receive more than the recommended daily amount, resulting in toxicity.[36] Patients with hepatic or renal insufficiency

are at an increased risk of PG accumulation because the liver metabolizes 55% and the remainder is excreted, unchanged, in urine.[35]

Unlike the other benzodiazepines commonly used in the ICU, lorazepam undergoes glucuronidation in the liver to inactive metabolites that are renally cleared. Both midazolam and diazepam have active metabolites that can accumulate in a critically ill patient with renal impairment. In patients with liver failure, metabolism of midazolam and, to a lesser degree, lorazepam are affected.[7]

Propofol

Propofol is a hydrophobic intravenous anesthetic in an emulsion of egg phospholipid and glycerol that has been used as a sedative in the ICU since the 1980s.[37,38] The mechanism of action occurs at several receptors, but its main mechanism of action is similar to that of benzodiazepines because it potentiates GABA activity. However, propofol has also been implicated in sodium channel blockade and the endocannabinoid system, making its mechanism of action quite unique.[39–41] The GABA activity is likely the most clinically significant compared to sodium channel blockade and endocannabinoid effects.

Propofol has a rapid onset, reaching peak effect in 90 to 100 seconds.[41] It has a short duration of action and is the recommended sedative when rapid awakening is desired.[7] This was demonstrated in a trial by Kress et al in which sedation was interrupted on a daily basis to allow patients to wake up. The patients receiving propofol showed no significant difference between the intervention and the control groups in the total dose of the drug, owing to its rapid offset.[42] Propofol's metabolism primarily occurs in the liver, where it is conjugated to inactive metabolites that are then renally cleared. In patients with renal or hepatic disease, propofol clearance is not significantly affected; however, in critically ill patients, propofol clearance is delayed compared to the general population.[43,44]

With propofol's conjugation to inactive metabolites, its use in patients with renal failure is not as concerning as with other sedatives that produce active metabolites; however, there are certain propofol side effects providers should be aware of. The most common side effect is a dose-related hypotension from a vasodilatory response.[45] This can be profound in patients who are hypovolemic, including those with trauma or sepsis. Unlike other sedatives, the lipid-based emulsion can support rapid bacterial growth, and multiple cases of bacterial sepsis related to propofol contamination have been reported[31]; therefore, strict aseptic technique should be employed when using propofol.[46] Depend-

ing on the manufacturers' formulation, a preservative is added to prevent bacterial growth, with ethylenediaminetetraacetic acid or sodium metabisulfite being the most common. In the ICU, once the propofol vial has been spiked, the infusion should be commenced and completed in 12 hours. At that time, any unused propofol and all tubing should be discarded.[45]

Because propofol is an emulsion, there are certain factors to remember when using it as a sedative. Propofol's formulation accounts for 1.1 kcal/mL and should be considered a source of calories from fat.[45] Hypertriglyceridemia is of concern with propofol infusions and occurs in up to 18% of those receiving it for continuous sedation. Hypertriglyceridemia is associated with high-dose infusions of propofol, hypertriglyceridemia at baseline, and parenteral nutrition lipid administration.[47] After 48 hours, triglycerides levels should be monitored.[7] Propofol has also been linked to pancreatitis. In a study of 159 patients sedated with a propofol infusion, Devlin and colleagues found that of the 18% of the patients that developed hypertriglyceridemia, 10% of those also developed pancreatitis.[47] Propofol's lipid nature also exhibits immunosuppressant effects by depressing neutrophil function.[48] However, the clinical significance of this is undetermined.

One rare complication of propofol use is a constellation of metabolic derangements and organ system failures that is referred to as propofol infusion syndrome (PRIS). It was first described in 1992 in a case series of five pediatric patients sedated in the ICU who died after developing increasing metabolic acidosis associated with bradyarrhythmias and progressive myocardial failure. The patients had been receiving high-dose propofol infusions at greater than 83 μg/kg/min for more than 48 hours.[49] PRIS is rare and has an unknown incidence. It is now known to occur more commonly in children, but can also occur in adults. Risk factors for PRIS are airway infection, severe head injury, propofol infusion (> 48 hours at a dose > 5 mg/kg/h), increased catecholamine and glucocorticoid serum levels, and low carbohydrate stores.[50] Its most prominent clinical characteristics, based on reviews of cases, are metabolic acidosis, cardiac dysfunction, hyperkalemia, hyperlipidemia, elevated creatinine kinase, rhabdomyolysis, myoglobinemia, myoglobinuria, and acute renal failure.[51,52] PRIS carries a very high mortality rate, estimated to be 30% in a retrospective review of the FDA's Med-Watch database of 1,139 patients who were suspected to have PRIS.[53] When there is prolonged need for sedation and propofol doses must be increased to maintain constant sedation, or if metabolic acidosis sets in during a propofol infusion, consider using an

alternative means of sedation and do not rule out a PRIS diagnosis if the clinical situation dictates.

PRIS treatment mainly involves supportive care. First and foremost, the propofol infusion must be stopped immediately. Hemodynamics should be supported. PRIS-associated bradycardia is often resistant to catecholamines and external pacing. Hemodialysis or hemofiltration is recommended to eliminate propofol and its potentially toxic metabolites.[54] Extracorporeal membrane oxygenation has assisted in the survival of several patients with PRIS[55–57] and may serve as a last-resort therapy.

Dexmedetomidine

Unlike the benzodiazepines and propofol that act on the GABA receptor, dexmedetomidine is a nonselective $\alpha 2$ agonist. It has 7- to 8-fold higher affinity than clonidine for the $\alpha 2$ adrenergic receptor and an $\alpha 1$ to $\alpha 2$ selectivity ratio of 1600:1.[57–59] The use of dexmedetomidine in the ICU has increased significantly. In 2001, 2% of patients received sedation via intravenous infusion of dexmedetomidine. This proportion increased to 7.2% by 2007.[60] Dexmedetomidine provides sedation and anxiolysis by interacting with receptors in the locus ceruleus, and analgesia through receptors in the locus ceruleus and spinal cord.[61] Two significant benefits of dexmedetomidine are its lack of respiratory depressant effect[61,62] and the ability to wake patients and have them follow commands while intubated and sedated.[61,63] In a phase III study, the most common adverse reactions associated with dexmedetomidine were hypotension (30%), hypertension (12%), nausea (11%), bradycardia (9%), and dry mouth (3%).[57] The most clinically significant side effects of hypotension and bradycardia are related to sympatholysis and more frequently occur during administration of the loading dose.[64–66] The sympatholytic effect of dexmedetomidine can be significant, progressing from bradycardia to asystole.[67,68] In patients with preexisting hypovolemia, it has the potential to cause pronounced hypotension.[69] Hypertension is usually seen with high or loading doses and is caused by peripheral vasoconstriction.[69,70]

For sedation in the ICU, the recommended dosage of dexmedetomidine is a 1 μg/kg loading dose over 10 minutes, followed by an infusion of 0.2 to 0.7 μg/kg/h. It is approved for sedation in the ICU for less than 24 hours.[69] In clinical practice and trials, dexmedetomidine is routinely started with or without a loading dose, infused as high as 1.5 μg/kg/h, and continued for up to several days.[60,62,71,72] Despite a longer duration to a goal level of sedation, many clinicians often forego the loading dose

to avoid the potential hemodynamic abnormalities of hypotension, hypertension, or bradycardia.[62,73] In 2009, Gerlach proposed a loading-dose-free protocol in which the infusion dose was based on the RASS score and titrations were made no more frequently than every 30 minutes. The protocol was effective and decreased the rate of hypotensive episodes from 68% to 16% compared to historical controls.[65] Several clinical trials[28,71,74] used maximum dosages in the range of 1.4 to 1.5 μg/kg/h. In these studies, dexmedetomidine was compared to propofol or benzodiazepines and was found to be safe and effective based on the studies' individual criteria. Where dexmedetomidine was found to be less effective was in a small subset of patients in whom the goal was to achieve a deep plane of sedation; there it did not perform as well as propofol or benzodiazepines.[74]

Clonidine is well known for its withdrawal syndrome, which is characterized by rebound hypertension, irrespective of the route of administration.[75] Because of dexmedetomidine's similar mechanism of action, it was originally approved only for short term (< 24 hours) sedation out of concern for similar withdrawal effects. Since its original approval, multiple trials have shown dexmedetomidine to be safe for sedation lasting greater than 24 hours (median duration of therapy ranged from 40 hours[74] to 5 days[28]).[71,76] In the trial by Shehabi et al,[76] 20 adult patients in a combined ICU received dexmedetomidine for a median time of 71 hours (range of 35 to 168 hours). Initially there was a 16% reduction in mean systolic blood pressure and 21% reduction in heart rate, which occurred over the first 4 hours, followed by insignificant changes thereafter. Following abrupt cessation, systolic blood pressure and heart rate were monitored for 24 hours and found to rise by 7% and 11%, respectively. This and other trials have not shown any evidence of a withdrawal syndrome associated with dexmedetomidine.[73,74,76]

Most studies have shown dexmedetomidine to be less commonly associated with delirium than benzodiazapines.[28,71,77] These studies all found significantly decreased rates of delirium or more delirium-free days when patients were sedated with dexmedetomidine compared to benzodiazepines or propofol. However, Ruokonen et al[74] found the contrary. They found a higher rate of delirium in the dexmedetomidine group (43.9%) compared to the propofol group (25%; $P = 0.035$). The authors reported that the dexmedetomidine group had more delirium assessments performed (106 vs 84) because of the interactisve nature of the dexmedetomidine sedation, but the overall rate of positive assessments were the same (17% vs 17.9%; $P > 0.05$).

HEAD INJURY

The mainstay of treating head-injured patients revolves around preventing and treating elevated intracranial pressure (ICP). When caring for these patients, sedation is frequently necessary to control ventilation, treat shivering, and prevent agitation, which can all contribute to transient elevations in ICP. Multiple sedatives can be employed in this population. Sanchez-Izquierdo-Riera et al[26] demonstrated the safety and efficacy of propofol and midazolam in severe trauma patients. Approximately 58% of the patients in their study sustained head trauma. They concluded that propofol and midazolam were both safe and noted no differences in ICP, cerebral perfusion pressure (CPP), or jugular venous saturation. The only difference noted was the time to wakefulness, which was significantly shorter in the propofol group. This is consistent with the SCCM recommendation that propofol be the drug of choice when rapid awakening is desired.[7] In addition to propofol's short duration of action, it has positive neurologic effects, including reducing ICP after traumatic brain injury and decreasing cerebral blood flow and metabolism.[78,79]

Kelly et al[78] compared a regimen of morphine alone to propofol with morphine to evaluate the propofol's safety. However, they also evaluated clinically relevant factors such as CPP, ICP, treatment-related adverse events, and neurologic outcome at 6 months. Despite the propofol arm having a higher incidence of poor prognostic indicators, including lower initial Glascow coma scale scores, older average age, and a higher rate of cistern compression on computed tomography scanning, the mean daily ICP and CPP were similar between the two groups, with the propofol arm having a lower ICP on day 3 of the infusion. At 6 months after injury, the propofol arm had more favorable neurologic outcomes (52.1% vs 47.4%) and a lower mortality rate (17.4% vs 21.1%). In a post hoc analysis, the authors compared the outcomes of high-dose propofol (> 100 μg/kg/min for > 48 hours) to low-dose propofol and found that, despite there being no difference in ICP or CPP between the two groups, there was a significant difference in the neurologic outcomes. At 6 months after injury, the high-dose group had 70% favorable outcomes (defined as a good neurologic recovery or moderate disability) compared to 38.5% in the low-dose group ($P < 0.05$). However, because of the risk of PRIS, high-dose propofol regimens are not recommended.[80]

Similarly, Chiu and colleagues[81] examined 104 head-injured patients who were either in a propofol or nonpropofol arm. They found that the mean ICP for the first 3 days was 17 mm Hg in the propofol group and 33 mm Hg in the nonpropofol group ($P = 0.17$). Over the first 5 days in the ICU, the mean CPP provided similar results as the ICP. The CPP was 71 mm Hg in the propofol arm and 43 mm Hg in the nonpropofol group ($P < 0.001$). The rate of survival was higher in the propofol arm (81.8% vs 46.7%, $P < 0.001$). These findings, in addition to other studies, contributed to joint guidelines published by the Brain Trauma Foundation and the American Association of Neurologic Surgeons for managing severe traumatic brain injury, which recommend propofol as the sedative of choice when managing ICP, but not in an attempt to improve mortality or 6 month outcome.[80]

DAILY INTERRUPTION OF SEDATION

Kress and colleagues showed that daily interruption of sedative infusions was associated with positive outcomes.[42] Patients treated with infusions of propofol with morphine or midazolam with morphine whose infusions were interrupted at the discretion of clinicians in the ICU were compared to those whose infusions were interrupted on a daily basis until the patient was able to answer three or more of four simple commands. The latter group demonstrated a significant reduction in the duration of mechanical ventilation (4.9 vs 7.3 days, $P = 0.004$), ICU length of stay (6.4 vs 9.9 days, $P = 0.02$), and number of diagnostic tests to assess mental status changes (9% vs 27%, $P = 0.02$), and no difference in self-extubations or other complications (4% vs 7%, $P = 0.88$). There was no difference between the propofol and midazolam groups, except for a lower total dose of midazolam and morphine. As a result of fewer ventilator days and a shorter ICU length of stay, daily sedation interruption has been linked to a lower rate of ICU complications related to a shorter length of stay.[82]

Daily interruption of sedation was also employed by Carson and colleagues.[83] In this study, sedation regimens of either a propofol infusion with morphine or intermittent lorazepam boluses with morphine were both interrupted on a daily basis. The propofol group showed a significantly shorter duration of mechanical ventilation (5.8 vs 8.4 days, $P = 0.04$). Overall, daily interruption of sedation has shown great benefit with little harm[42] and has been incorporated into the practice of many intensivists.[84] Despite daily interruptions of sedation being associated with increased levels of catecholamines, patients with coronary artery disease showed no evidence of increased ischemia during the

interruptions of sedation.[85] However, caution should be taken when interrupting sedation in certain patient populations, such as those with unstable cervical spine injuries in whom patient ventilator asynchrony could lead to coughing and potential exacerbation of neurologic injury.

RESTRAINTS

More than 70% of ICU patients may experience some degree of agitation during their ICU stays[86,87] that often coincides with mental status changes. As a result, patients may be unable to understand why certain therapies are ongoing, leading to patient-initiated treatment interference that can be self-injurious. The literature contains multiple reports of fatal self-extubations and removal of intravascular devices,[88,89] making the possibility of patient interference even more concerning. Before resorting to restraint use, clinicians should evaluate whether treatment of a physiologic perturbation (eg, hypoxia, hypercarbia, sepsis, or hypotension) would obviate the need for restraints.[88] After deciding restraints are necessary, the choice between employing pharmacologic or physical restraints must be made. Simple measures such as assuring patients are adequately sedated, as discussed above, can obviate the need for physically restraining a patient. When physical restraints are chosen, they should be the least invasive possible (hand mitts vs restraining all extremities to the bedframe), the need for the restraint selected should be continually evaluated every 8 hours, and complications from the restraint should be checked for every 4 hours. The restraints should be discontinued as soon as they are deemed unnecessary.[88]

SUMMARY

The increasing understanding of sedatives and their ramifications over the last 2 decades has made the sedation of critically ill patients more complex. We now have an improved understanding of delirium and which sedatives may increase its already high rate of occurrence in the trauma population. The importance of preventing delirium is also better understood as it has been shown to increase morbidity, mortality, and length of stay in the ICU, as well as worsening outcomes overall. Appropriate sedatives should be chosen with a thorough understanding of their side effect profile, and preparations must be made to deal with the possible consequences. A sedation scale should be employed to prevent the sequelae of oversedation. With the already high rates of posttraumatic stress disorder in the war wounded, maintaining the proper depth of sedation is vitally important to prevent additional posttraumatic stress related to ICU care.

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