Chapter 14
Special ICU Populations: Opioids in Neurocritical Care

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Overview of Sedation and Analgesia Practices in Neurocritical Care

As with other critically ill patients, brain-injured patients require sedation and analgesia for multiple purposes including, but not limited to, the facilitation of mechanical ventilation, treatment of pain associated with procedures and routine ICU care, and for minimizing anxiety. In accordance with the most recent Society of Critical Care Medicine (SCCM) Pain, Agitation/Sedation, Delirium, Immobility and Sleep Disruption (PADIS) guidelines, the practice of using light sedation targets has generally been adopted in the neurocritical care population, including incorporation of analgosedation and general avoidance of benzodiazepine sedatives in favor of non-benzodiazepine options such as propofol and dexmedetomidine [1–3]. However, because the landmark studies that paved the way for these recommendations largely excluded patients with primary neurologic injuries, the impact of these sedation practices and corresponding outcomes in patients with brain injury remains poorly understood [4–7].

In addition to their general uses that are common for all critically ill patients, sedation and analgesia are often required in neurocritical care to minimize the impact of routine ICU care on secondary brain injury. For example, common scenarios encountered in the ICU—such as coughing or gagging on endotracheal tubes, tracheal suctioning, or episodes of acute pain or anxiety—can precipitate acute

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elevations of intracranial pressure (ICP) to critical levels in patients with poor intracranial compliance. Alternatively, the hemodynamic side effects of sedatives and analgesics, such as bradycardia and hypotension, may decrease cerebral perfusion and negate any advantages of their use [8, 9].

On the other hand, the requirements of sedation and analgesia must also be balanced with the need to detect minute changes in neurological examination which indicate new or worsening intracranial processes that potentially require rapid intervention. Brain-injured patients require frequent neurologic assessments, and the desire to minimize sedation (which can interfere with these assessments) presents a unique challenge in this ICU population. Fear of masking a patient's subtle signs of neurologic deterioration with sedating agents may also lead to undertreatment of pain, thus creating an ever conflicting need for balancing patient comfort with quality neurologic assessment.

On the opposite end of this spectrum, deep sedation with pharmacologic coma must at times be employed in the treatment of certain pathologic states [9]. Indeed, notable exceptions to the application of light sedation in the neurocritical care setting include the treatment of intracranial hypertension, status epilepticus, and use of continuous neuromuscular blockade for refractory intracranial hypertension, acute respiratory distress syndrome (ARDS), and management of shivering in targeted temperature management (TTM). With the exception of status epilepticus, optimization of analgesia with the use of opiate infusions is considered a standard component of the regimen employed for deep sedation, in addition to use of hypnotic sedatives such as propofol or midazolam. Deep sedation should generally be reserved for use when a clear indication exists and where short-term benefits to the brain are deemed to outweigh the long-term risks.

Assessment of Pain in Patients with Acute Brain Injury

Assessment of pain in patients in neurocritical care represents a particular challenge, since both impairments of consciousness and aphasia can confound standardized assessment tools [10]. Indeed, damage to cortical networks involved in pain perception after brain injury may significantly alter the need for pain control. However, the fact that such patients generally continue to exhibit physiological responses (such as tachycardia, elevated blood pressure, and increased ICP) to painful stimuli highlights the need for tools that can accurately assess pain in brain-injured patients. The Behavioral Pain Scale (BPS) and Critical Care Pain Observation Tool (CPOT) have the highest validity and reliability in patients without brain injury who are unable to self-report pain [1, 11, 12]. Based on small validation studies, their use in neurocritical care is endorsed by both SCCM and the Neurocritical Care Society (NCS) [1, 13]. Larger scale validation and potential refinement of the scales for optimal use in patients with neurologic injuries is needed; however, both the BPS and CPOT seem to be useful tools to systematically evaluate pain in brain-injured patients [14–17].

In survivors of brain injury who develop chronic disorders of consciousness—including persistent vegetative state (VS, also termed unresponsive wakeful syndrome, UWS) and minimally conscious states (MCS)—the inability to communicate and uncertainty about the capacity to consciously perceive pain makes pain assessment extremely challenging [18, 19]. Neuroimaging studies in patients with MCS suggest that cortical responses may be preserved and probably permit the processing and perception of pain; however, similar studies in VS/UWS patients have demonstrated severe impairment in function and connectivity of these pathways [19–21]. Nevertheless, there exists the possibility that a subset of patients with VS/UWS may also retain cortical processing and potentially the ability perceive pain [19, 22]. Thus, a reliable scale to assess for potential pain/nociception responses in these patients is undoubtedly important to providing compassionate care.

The Nociception Coma Scale (NCS) was developed for use in patients with prolonged coma and severe disorders of consciousness. After initial validation, the NCS was further refined by removing the visual response subcategory, which was found to be unchanged in response to noxious stimuli, giving way to the newer NCS-Revised (NSC-R). Similar to the CPOT and BPS-NI (BPS–Non-Intubated), the NCS-R assesses behaviors in categories related to facial expression, motor movements, and vocal responses (Table 14.1) [12, 23, 24]. Importantly, the maximum potential score in VS/UWS patients is lower than in MCS due to the intrinsic limitations of their lower level of consciousness. The NCS-R has since been validated in several small studies, demonstrating a reliable increase in score when patients are exposed to painful stimuli as compared to non-noxious stimuli [18, 24, 25]. Although it is still not possible to know whether the detection of nociceptive responses correlates to subjective pain sensation in an individual patient, the development of the NCS-R represents an important step in objective assessment and quantification in this setting.

Overview of Cerebrovascular Physiology and Hemodynamics

The brain has high energy demands and receives approximately 20% of the cardiac output. Under normal circumstances, cerebral blood flow (CBF) is tightly matched to cerebral metabolic demands, and increases as the cerebral metabolic rate of oxygen consumption ($CMRO_2$) trigger increases in CBF. However, after acute brain injury, perfusion may not be adequate to meet cerebral metabolic demands. In such instances, secondary brain injury occurs [26, 27].

CBF depends linearly on the cerebral perfusion pressure (CPP) and inversely on the cerebrovascular resistance (CVR). Thus, changes in either CPP or CVR can have profound impacts on CBF. In brain-injured patients, CPP equals the difference between mean arterial pressure (MAP) and ICP. Increases in ICP can therefore deleteriously reduce CPP and lead to ischemia. Increases in systemic partial pressure of CO_2 (pCO_2), which most often occur due to reductions in respiratory drive, can lead to pH-dependent vasodilatation of cerebral arterioles. Normally, hypercapnia leads to increases in CBF by decreasing CVR. However, in brain-injured patients, the increased

Table 14.1 Comparison of the Nociception Coma Scale-Revised with other critical care behavioral pain assessment scales

Scoring Domains	Behavioral Pain Assessment Tools					
	BPS-NI		CPOT		NCS-R	
Facial expression	**1**	Relaxed	**0**	Relaxed	**0**	None
	2	Partially tightened	**1**	Tense	**1**	Oral reflexive movement/ startle response
	3	Fully tightened	**2**	Grimacing	**2**	Grimace
	4	Grimacing			**3**	Cry
Motor movements	**1**	No movement of upper limbs	**0**	No movements/ neutral position	**0**	None/flaccid
	2	Partially bent	**1**	Protection	**1**	Abnormal posturing
	3	Fully bent with finger flexion	**2**	Restlessness/ agitation	**2**	Flexion withdrawal
	4	Permanently retracted			**3**	Localization
Verbal	**1**	Vocalization	**0**	Normal vocalization	**0**	None
	2	Moaning ≤3 min	**1**	Sighing, moaning	**1**	Groaning
	3	Moaning >3 min	**2**	Crying out, sobbing	**2**	Vocalization
	4	Verbal complaint or breath holding			**3**	Verbalization (unintelligible)
Muscle tension (CPOT only)			**0**	Relaxed		
			1	Tense, rigid		
			2	Very tense or rigid		
Pain score range	**3–12**		**0–8**		**0–9**	
Threshold score for presence of significant pain/ nociception	≥6		≥3		Unknown ≥4 in MCS or ≥3 in VS/UWS in the validation study; ≥2 in a subsequent study	

Adapted from [12, 23–25]

BPS-NI Behavioral Pain Scale – non-intubated, *CPOT* Critical Care Pain Observation Tool, *MCS* minimally conscious state, *NCS-R* Nociception Coma Scale-Revised, *VS/UWS* vegetative state/ unresponsive wakeful syndrome

cerebral blood volume that occurs after hypercapnia-induced vasodilation can markedly increase ICP, leading to decreased CPP and reductions in CBF. Hyperventilation can similarly decrease ICP through pH-dependent vasoconstriction. While this increases CPP, it will also lead to marked increases in CVR and ultimately decreased CBF and ischemia. For these reasons, maintaining pCO_2 consistently within normal range is a major goal when caring for brain-injured patients [26, 27].

Table 14.2 Comparison of properties of opioids and sedative agents impacting cerebral physiologic parameters

	Mechanism of Action	$CMRO_2$	ICP	CPP and MAP	Comments
Opioids (fentanyl, morphine)	μ-opioid receptor agonist	↔	↔ / ↑	↔ / ↓	Bolus opiates may transiently ↑ICP in response to ↓ MAP Prevent/reduce elevations in ICP by treating pain and blunting response to noxious stimuli
Propofol	$GABA_A$ agonist	↓↓	↓↓	↓/↓↓	Therapy for status epilepticus; typically the agent of choice for sedation in elevated ICP unless hemodynamic instability (use midazolam)
Benzodiazepines (midazolam bolus/ infusion)	$GABA_A$ agonists	↓↓	↓	↓	Therapy for intracranial hypertension and status epilepticus (alternative to propofol)
Dexmedetomidine	α_2-adrenergic agonist	↔ / ↓	↔	↓/↓↓	Used for sedation in a similar fashion as other ICU populations
Ketamine	NMDA-receptor antagonist	↓	↔ / ↓	↔ / ↑	Emerging therapy for refractory status epilepticus (high dose)
Barbiturates (pentobarbital, thiopental)	$GABA_A$ agonists	↓↓↓	↓↓↓	↓↓↓	Last-line therapy for refractory intracranial hypertension and status epilepticus

References: [8, 9, 28–34]
$CMRO_2$ cerebral metabolic rate of oxygen, CPP cerebral perfusion pressure, *ICP* intracranial pressure, *MAP* mean arterial pressure

Changes in cerebral perfusion pressure can also directly alter cerebrovascular tone through pressure-dependent cerebral autoregulation pathways. Reductions in CPP lead to arteriolar vasodilation, while increases in CPP lead to vasoconstriction. Cerebral autoregulation thus serves to maintain near constant levels of CBF in the face of wide fluctuations in CPP [26, 27].

Sedative medications used in neurocritical care can markedly alter cerebral metabolic demand, ICP, respiratory CO_2 production, and MAP. These changes can induce profound alterations in cerebral hemodynamics, and it is important to know the effects of these different medications on cerebrovascular physiology (Table 14.2).

Bolus Dosing of Opioids and ICP

A 2011 systematic review of randomized controlled trials of sedation in patients with severe traumatic brain injury (TBI) found a negative, though transient, impact of bolus opioids (administered over ≤5 minutes) on cerebral hemodynamics [28].

In this review, four small randomized studies compared the use of IV bolus doses of morphine 0.07–2 mg/kg, fentanyl 2–10 mcg/kg, sufentanil 0.37–1 mcg/kg, and alfentanil 100 mcg/kg administered over 1–6 minutes. Three of the four studies found that moderate to high opioid boluses resulted in significant increases in ICP from baseline (range of maximum increase, 3–9 mm Hg) [35–37]. The mechanism for ICP elevations after bolus opioid administration in these studies is largely thought to be the result of a cerebral autoregulatory response to a decrease in MAP, where cerebral vasodilation occurs in order to restore cerebral perfusion.

In contrast, a fourth study by Lauer and colleagues showed that slower bolus infusion of opioids (fentanyl, morphine, or sufentanil over 5 minutes, titrated to a maximal 5% decrease in MAP) resulted in no significant increases in ICP in any group [38]. Another study by Werner and colleagues not included in the systematic review found that ICP was unchanged after administration of a sufentanil 3 mcg/kg bolus when MAP was maintained with a norepinephrine infusion, but was significantly higher in the group of patients who became hypotensive despite vasopressor administration [39]. Overall, these studies suggest that a reduction in MAP leads to ICP elevation after rapid opioid boluses, rather than an intrinsic drug-related mechanism being the underlying contributor.

None of the above studies found significant differences between specific agents and change in ICP or MAP. However, higher doses, which resulted in greater decreases in MAP, were shown to produce greater increases in ICP [28, 35–38].

In summary, although bolus doses of opioids can potentially increase ICP, these elevations seem to be driven by decreases in MAP. Thus, the effect of opioids on ICP can be mitigated by moderating the opioid bolus administration rate in order to minimize systemic hypotension. Given the class effect of opioids to produce respiratory depression, maintaining minute ventilation to prevent elevations of $PaCO_2$ would also be an additional important consideration, as hypercarbia would also be expected to increase ICP through cerebral vasodilation.

General Approach to Selection of Analgesic Regimens

In patients requiring close neurologic monitoring due to high risk or concern for impending neurologic deterioration, short-acting agents may be ideal. In this setting, the use of small, frequent bolus doses of IV fentanyl is common. However, due to its high lipophilicity, fentanyl administered as repeated bolus doses or as a continuous infusion can result in accumulation and a prolonged duration of effect. Remifentanil represents an enticing option for analgesia in the neurocritical care setting, as its ultra-short half-life allows rapid awakening for neurologic exams when the infusion is paused. This was demonstrated in a multi-center study that compared an analgesia-based sedation protocol using remifentanil and propofol to a hypnotic-based sedation protocol using either fentanyl or morphine in addition to propofol. Sedation was titrated to a deep sedation goal in all patients. Ultimately, all groups required similar propofol doses during the first three study days

(approximately 30–40 mcg/kg/min). However, the study demonstrated that when sedation was paused for examinations, time to neurological assessment was significantly shorter with remifentanil, occurring on average 18 and 25 minutes sooner compared to the fentanyl and morphine arms, respectively; they found no differences between groups in duration of mechanical ventilation or adverse events [2]. Despite the advantage in ability to perform more timely neurologic assessments with remifentanil, its widespread use in the ICU setting is currently curtailed by its cost in relation to other available agents such as fentanyl.

Morphine remains a commonly used agent worldwide; however, its use continues to decline in neurocritical care due to its multiple undesirable properties as compared to other agents—these include a relatively longer half-life, predisposition to accumulation in renal failure due to its renally cleared active metabolite (morphine-6-glucuronide), and elevated risk of adverse hemodynamic effects due to impact on histamine release. However, as detailed below, morphine has a specific place in therapy in the treatment of paroxysmal sympathetic hyperactivity (commonly known as "storming"), where it is considered the IV opiate of choice.

Bolus doses of an IV opioid agent can be repeated as needed based on assessments of pain (numeric rating scale, BPS, CPOT), while maintaining light sedation and limiting hemodynamic responses to noxious stimuli such as endotracheal suctioning, which may cause or exacerbate elevations in ICP. When bolus administration is insufficient, a continuous infusion of fentanyl or remifentanil may be initiated and titrated to similar goals, or in the case of a requirement for deep sedation, to a minimal pain score (e.g., BPS 3–5/12), with additional titration of a sedative agent beyond this [8, 9].

Use of Opioids in Specific Neurocritical Care Disease States

Sedation and Shivering Management in Targeted Temperature Management

Collectively termed targeted temperature management, TTM, the use of induced hypothermia (targeting a body temperature of 32 °C to <36 °C) and controlled normothermia (36–37 °C) for neuroprotection after cardiac arrest is a field of expanding research in the modern era of critical care, as mounting evidence supports improvement in patient outcomes [40–44].

Outside of cardiac arrest-associated brain injury, fever has long been recognized as a contributor to secondary brain injury in varying primary pathologies, including ischemic and hemorrhagic stroke, subarachnoid hemorrhage, and traumatic brain injury [45–51]. Because of this, treatment of fever is considered a universal measure in the management of brain-injured patients along with standard airway, breathing, circulation assessment, according to the Emergency Neurological Life Support (ENLS) treatment algorithm for elevated ICP, and remains a staple of care for neurocritically ill patients during their ICU stay [50, 52].

Thermoregulatory Responses to Hypothermia and Fever in TTM

Core body temperature is normally tightly regulated by the hypothalamus and maintained between 36.5–37.5 °C. Below this temperature, peripheral vasoconstriction is activated to reduce heat loss in addition to eliciting behavioral responses to conserve heat. Shivering—involuntary oscillatory muscle movements which produce heat to increase core body temperature—commences at approximately 1 °C below the vasoconstriction threshold, activated at approximately 35.5 °C (Fig. 14.1) [53]. The shivering response ceases below temperatures of approximately 33.5 °C [51].

Fever, defined as an increase in core body temperature above normal which is triggered by a change in the hypothalamic set point, occurs commonly after acute brain injury. During fever, normal thermoregulatory responses (vasoconstriction and shivering) are also shifted to a higher value to maintain the elevated temperature. Thus, when TTM is used to actively lower core body temperature in a febrile patient, feedback pathways to the hypothalamus trigger these counter-regulatory mechanisms to induce shivering in an attempt to elevate core temperature back to the hypothalamic set point (Fig. 14.2) [50, 51]. For this reason, TTM for active fever control is often met with higher rates of shivering than therapeutic hypothermia after cardiac arrest [50, 51]. Shivering in the setting of both therapeutic hypothermia and controlled normothermia is associated with negative impacts on the patient, including increased metabolic rate and energy expenditure, oxygen consumption, and production of carbon dioxide as well as decreases in brain tissue oxygen levels [44, 54, 55].

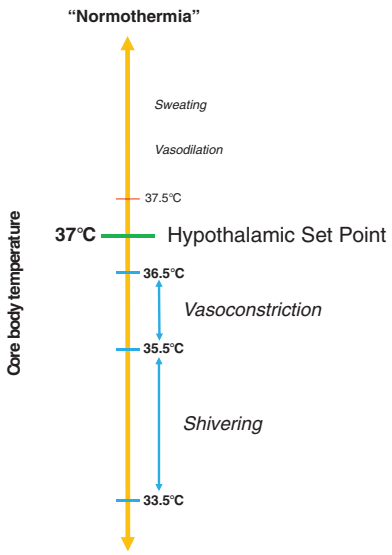

Fig. 14.1 Normal thermoregulatory responses to lowering core body temperature in hypothermia

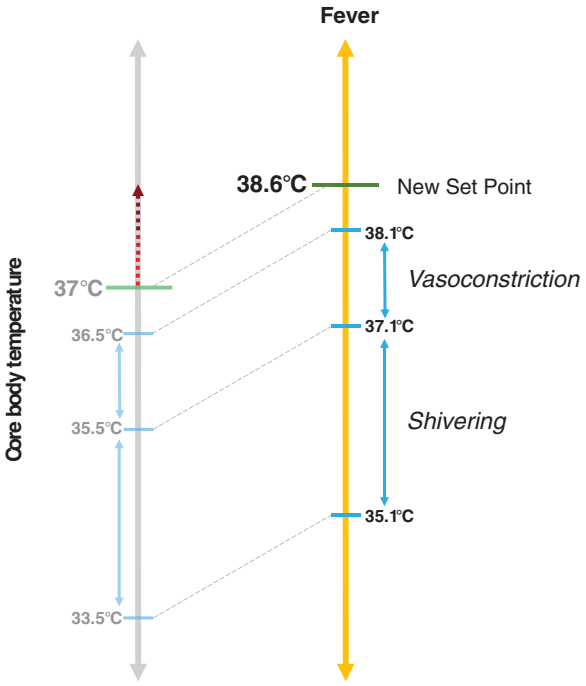

Fig. 14.2 Representation of thermoregulatory responses in fever; in this example where a patient's hypothalamic set point is raised to 38.6 °C, the normal counter-regulatory responses are also shifted upward, demonstrating the elevated risk of shivering when TTM is implemented even to maintain body temperatures in the normothermia range

Table 14.3 The Bedside Shivering Assessment Scale (BSAS)

Score	Interpretation	Definition
0	None	No shivering noted on palpation of the masseter, neck, or chest wall
1	Mild	Localized to the neck and/or thorax only
2	Moderate	Involves gross movement of the upper extremities (in addition to neck and thorax)
3	Severe	Involves gross movements of the trunk and upper and lower extremities

Adapted from [55]

The Bedside Shivering Assessment Scale (BSAS) is a widely used tool for shivering assessment (Table 14.3) [44, 55]. The BSAS was validated in neurocritical care patients with the assessment of the shivering score and indirect calorimetry to assess the metabolic impact of shivering severity. The authors found high inter-rater reliability of the scoring tool and demonstrated that each increased level of the BSAS score (0–3) was associated with an incremental rise and independent association with higher energy expenditure (Fig. 14.3) [55].

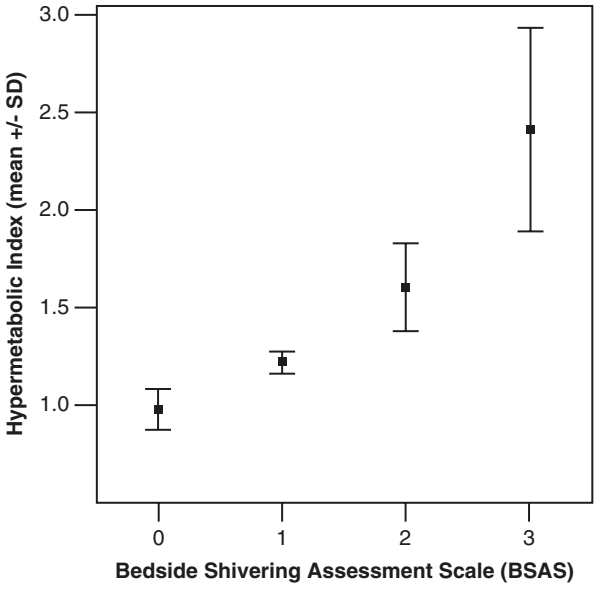

Fig. 14.3 Each increasing level of the BSAS score was found to be associated with a significant increase in each of the metabolic parameter outcomes, including hypermetabolic index (HMI), resting energy expenditure (REE), oxygen consumption, and carbon dioxide production. The BSAS was found to have the most significant association with the HMI, pictured here. The HMI was derived by dividing the REE (kcal/day) by the expected energy expenditure (calculated by Harris-Benedict equation × 1.2–1.3 to account for patient acuity) [55].

Younger age, male sex, higher body mass, and the presence of hypomagnesemia are factors consistently shown to increase the risk of shivering with TTM [51, 55, 56]. This may be considered when weighing the risk and benefit of inducing controlled normothermia in the febrile patient with acute brain injury.

Management of Shivering

In patients managed with therapeutic hypothermia after cardiac arrest, shivering must be aggressively controlled during the induction phase where body temperature is actively being lowered, as shivering can significantly prolong the time to reach goal temperature. In theory, if a lower temperature of 33 °C (TTM_{33}) is selected, then the shivering response is expected to abate once the patient reaches goal temperature, and will re-emerge upon re-warming when approaching normothermia. Conversely, patients managed with a target temperature of 36 °C (TTM_{36}) may be at risk for shivering for the entire duration of their hypothermia phase until rewarming [51]. Despite these theoretical concerns, however, there were no differences seen in the rate or severity of shivering between hypothermia doses in the recent TTM-trial, which compared outcomes after cardiac arrest in patients randomized to 24 hours of TTM at either 33° or 36 °C [42]. When utilizing normothermia for fever control, treatment of shivering is also necessary in order to obtain maximal benefit from implementation of TTM.

A number of pharmacologic and non-pharmacologic interventions have demonstrated beneficial effects in lowering of the vasoconstrictive and shivering thresholds (Table 14.4) [69]. This excludes the consideration of neuromuscular blocking agents, which exert direct actions on skeletal muscle to inhibit shivering.

Table 14.4 Selected therapies for the prevention and treatment of shivering in TTM

	Anti-Shivering Mechanism	Dosing	Reduction in Shivering Threshold
Opioids			
Meperidine (pethidine)	μ- and κ-opioid receptor agonist Central α_{2b}-receptor agonist	25–100 mg IV	1.2–2.3 °C
Tramadol	μ-receptor agonist Partial inhibition of norepinephrine and 5-HT uptake	125–250 mg IV[a]	0.6–0.9 °C
Other pure μ-opioid receptor agonists (fentanyl, alfentanil)	Activation of μ-opioid receptors	--	--
Dexmedetomidine	Central α_2-adrenergic agonist	0.2–1.5 mcg/kg/hr	0.7–2.4 °C
Buspirone	5-HT_{1A} partial agonist	30–60 mg	0.7–1 °C Synergistic effect in combination with meperidine
Propofol	General anesthetic ($GABA_A$ agonist)—vasodilator, blunts thermoregulatory responses	50–75 mcg/kg/min	1.3–2 °C
Skin counter-warming	Increases skin surface temperature (responsible for 20% of input to hypothalamic thermoregulatory center)	Forced air warming blanket (max temperature 43 °C)	1 °C for every 4 °C ↑ in skin temperature Synergistic effect in combination with meperidine
Magnesium sulfate	Cutaneous vasodilation and muscle relaxation	2–4 grams IV bolus or Infusion, 0.5–1 g/hr titrated to serum level 3–4 mg/dl	Minimal; improves rate of cooling, and has shown to improve patient comfort during induction

References [57–68]

[a]IV formulation not available in the United States

Meperidine is considered the most effective agent for the treatment of shivering, which is postulated to result from its effect on κ-opioid receptors as well as α_{2b}-receptors, potentially explaining its augmented anti-shivering activity as compared to other opioids [70–73]. Other pure μ-opioid receptor agonists also appear to be beneficial in the treatment of shivering, though to a lesser extent [70].

For most pharmacologic interventions, the impact on lowering of the shivering threshold is dose-dependent. For this reason, the use of combinations of therapies with synergistic effects is desirable to limit adverse effects related to individual medications, while optimizing efficacy. In particular, this has been demonstrated

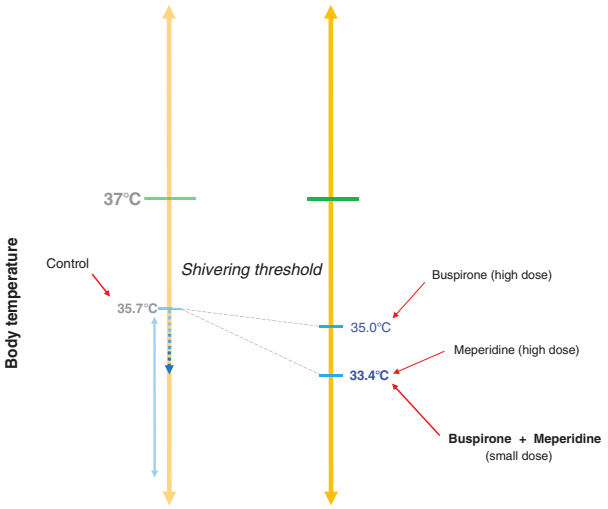

Fig. 14.4 This figure uses an example to demonstrate the use of anti-shivering medications to significantly lower the threshold temperature at which shivering occurs, highlighting the use of synergistic medication combinations. This example uses the reported change in shivering threshold demonstrated in one study (described in detail in the text), which found the combination of buspirone + meperidine to be synergistic in lowering the shivering threshold as compared to larger doses of either agent alone [57]

with the use of meperidine in combination with buspirone, as well as with the combined use of skin counter-warming (Fig. 14.4) [57, 58]. These findings are important, as they permit usage of lower doses of meperidine. Of particular concern in the brain-injured or post-cardiac arrest patient is the potential for accumulation of the neurotoxic active metabolite, normeperidine, which has impaired clearance in renal failure, and the potential increased risk of seizures due to lowering of the seizure threshold.

As an example of the synergistic potential with the use of combination of therapies, Mokhtarani and colleagues assessed the combination of meperidine with buspirone for the treatment of shivering (Fig. 14.4) [57]. This study was conducted in eight healthy volunteers treated with induction of hypothermia via administration of IV fluids (Lactated Ringer's solution) cooled to 4 °C. Each volunteer received each of four interventions on four separate days: (1) no therapy (control group), (2) high dose buspirone (60 mg), (3) high dose meperidine (0.8 mcg/mL), and (4) small-dose combination of buspirone 30 mg + meperidine 0.4 mcg/mL. Compared to the control group which had a baseline shivering threshold of 35.7 ± 0.2 °C, the combination of lower doses of buspirone plus meperidine lowered the shivering threshold by 2.3 °C (group 4), as compared to larger doses of either buspirone alone (group 2, shivering threshold lowered by 0.7 °C) or large dose meperidine (group 3, shivering threshold lowered by 2.3 °C). In this example, the combination produced a comparable lowering of the shivering threshold

to that of large dose meperidine (shivering threshold lowered by 2.3 °C in both groups), with synergy demonstrated as the actual threshold in the small-dose combination group was significantly less than predicted for an additive response ($p = 0.0006$) [57].

Unfortunately, most of the evidence regarding efficacy of shivering therapies is derived from studies in healthy volunteers or in the post-anesthesia care environment [72]. The Columbia Anti-Shivering Protocol was the first comprehensive algorithm studied for the prevention and treatment of shivering in TTM and incorporated a multitude of therapies with varied mechanisms of actions and combinations effective for the treatment of shivering. These include antipyretics (namely acetaminophen), 5-HT agonists (buspirone), opioid agonists (meperidine and fentanyl), central α_2-agonists (dexmedetomidine), and propofol [74]. The protocol incorporates systematic assessment for the presence of shivering using the BSAS and recommends a stepwise approach for management (Table 14.5). Agents with the least sedating potential are preferred to reduce impact on neurologic examination. Synergistic combinations of less-sedating therapies are utilized first, with stepwise addition of more potent sedatives, and ultimately neuromuscular blockade. The Columbia Shivering Protocol is applicable regardless of mechanical ventilation status (with limitations on use of specific therapies such as propofol and paralytic agents in non-intubated patients) [44, 74, 75]. It remains the only systematically studied shivering protocol for use during TTM in the ICU and has been widely adapted for use for both normothermia and hypothermia [75].

Table 14.5 The Columbia Anti-Shivering Protocol

Step		Intervention	Dose
0	Baseline	Acetaminophen Buspirone Magnesium sulfate Skin counterwarming	650–1000 mg q4–6h 30 mg q8h 0.5–1 g/hr infusion (goal 3–4 mg/dL) Maximum 43 °C
1	Mild sedation	Dexmedetomidine *or* Opioid	0.2–1.5 mcg/kg/hr Fentanyl infusion[a] (25 mcg/hr+) Meperidine 50–100 mg IM/IV
2	Moderate sedation	Dexmedetomidine *plus* opioid	As above
3	Deep sedation	Propofol[a]	50–75 mcg/kg/min[a]
4	Neuromuscular blockade	Vecuronium[a]	0.1 mg/kg IV bolus[a]

The Columbia anti-shivering protocol included implementation of hourly assessments for shivering (using the Bedside Shivering Assessment Scale, BSAS) by the bedside nurse, with a target BSAS of 0–1. Prior to initiation of cooling, each of the Step 0 interventions are implemented for shivering prevention, and continued for the duration of TTM. If a BSAS of ≥2 is reported, then a Step 1 intervention is initiated. After maximizing a Step 1 intervention with failure to achieve a BSAS ≤1, the provider then proceeds to Step 2, and so on

Adapted from [74]

[a]Note: Patients receiving fentanyl or propofol infusions and neuromuscular blockade must be mechanically ventilated.

In publishing the results from implementation of the shivering protocol in their Neuro ICU over a period of approximately 4 years, a total of 213 patients were observed over a total of 289 hypothermia days and 1099 normothermia days; 124 of the 213 patients were initiated on TTM for normothermia goals only [74]. In total, 18% of all TTM patients (and 33% of patient days) received no intervention for the treatment of shivering. Beyond Step 0, the authors reported that 29% of patients required one agent, 35% received two agents, 15% received three, and 2.4% received four agents for the treatment of shivering. Thirty-six percent of Step 1 interventions included opioid administration, though these were not subdivided to account for the volume of use of meperidine as compared to fentanyl. However, dosages were recorded during the course of the study, with a median meperidine dose of 125 mg/24 hours, and fentanyl at a median dose of 47 mcg/hour [74].

Specific considerations for approach to the use of neuromuscular-blocking agents (NMBA) during therapeutic hypothermia are discussed below in relation to the use of sedation and analgesia during TTM after cardiac arrest.

Altered Metabolism and Pharmacodynamics of Medications in Hypothermia

Hypothermia is known to have a profound impact on the pharmacokinetic (PK) parameters of medications and largely results in higher serum levels due to reduced hepatic clearance. This is the result of both reduced hepatic blood flow and impaired metabolism of many drugs by cytochrome P450, in which the temperature-dependent enzymatic process is slowed and consequently reduces systemic drug clearance [76]. Additionally, impaired hepatic or renal function, either chronic or new-onset after cardiac arrest, further compounds this effect.

Few comprehensive pharmacokinetic studies have been performed to quantify the effects of hypothermia on medication clearance, with even fewer conducted in critically ill patients after cardiac arrest; however, estimates of the reduction in clearance in hypothermia are available (Table 14.6). One review analyzing existing PK studies in hypothermia prior to 2007 found that systemic clearance of drugs metabolized by CYP450 was overall reduced by 7–22% per degree below 37 °C, though the variation between patients in studies is understandingly wide, as many factors in an individual patient and setting can affect the PK parameters of specific drugs [76].

Sedation Practices in TTM and Considerations for Neuroprognostication

During hypothermia, sedation is routinely used primarily to prevent and treat shivering, ensure ventilator compliance, as well as to adequately prevent awareness in case use of neuromuscular blocking agents is required [83]. However, increasing recognition of the impact of hypothermia on prolonging the duration of action of sedative agents has called to question the influence these drugs may have on clinical

Table 14.6 Altered pharmacokinetic properties of common opioids used in therapeutic hypothermia

	Specific PK Changes Observed in $TTM_{32–34}$	Metabolism	Active Metabolites	Comments
Opioids				
Fentanyl	Cl_{total} ↓ 20–45%	Hepatic (CYP 3A4)	n/a	Risk for accumulation and prolonged effect with high doses
Morphine	Cl_{total} ↓ 29% t ½ ↑ 1.6-fold	Hepatic (glucuronidation)	Yes—renally cleared	Least optimal opiate in TTM, especially in hepatic and renal impairment
Remifentanil	Cl_{total} ↓ 27% *(↓6.7% per °C)*[a] Rewarming $C_{Δ33–37}$ ↑16%	Plasma and tissue esterases	n/a	Optimal agent where available—least variable PK

References [76–82]

Cl_{total} total clearance, *PK* pharmacokinetics, *PRN* as needed, *Rewarming $C_{Δ33–37}$* Δ in serum concentration observed during rewarming period (from 33 → 37 °C), *t ½* half-life, *$TTM_{32–34}$* target temperature management with goal temperature between 32 and 34 °C

[a]Reduced clearance per each 1 °C below 37 °C

decision making after the completion of TTM [83, 84]. The underestimation of lingering sedation action and resultant late awakening can confound patient examination and neuroprognostic testing when performed too early after rewarming. Indeed, if not accounted for by the clinician, the most dire consequence of this would be resultant withdrawal of care in patients deemed to have a "poor prognosis" who may otherwise have been able to make a meaningful recovery [82, 83, 85, 86]. Nearly all components of the neurologic exam may be affected by sedative medications—including pupillary light reflex, corneal reflex, and motor responses. Electroencephalography (EEG) background rhythm is also known to be sensitive to residual sedative effects. Specific assessments which alternatively do not seem to be impacted by medications include brain imaging (loss of gray-white matter differentiation on head computed tomography, CT), interpretation of absent N20 potentials on somatosensory-evoked potentials (SSEPs), and serum biomarker levels such as neuron-specific enolase (NSE) [86–89].

Supporting this notion is a post-hoc analysis of the TTM-trial which assessed for factors related to time to awakening when comparing the TTM_{33} and TTM_{36} groups, with the aim of correlating this to long-term outcome in patients [90]. In this international multicenter study, sites were required to initiate sedation with TTM, but the specific regimens were left to local practice and provider decision. While no differences in cumulative analgesia or sedation doses were found within 48 hours between the study groups, randomization to the TTM_{33} arm was found to be an independent predictor of late awakening. As no differences in good neurologic outcome or prognostic factors were identified, the main hypothesis of the study authors was that the

delay in awakening in the TTM_{33} group may have been related to delayed drug clearance occurring with deeper hypothermia [90].

Additionally, a recent study by May and colleagues aimed to address the issue of appropriate level of sedation needed in TTM [91]. At their center, patients were preemptively initiated on a predefined basal sedation dose prior to cooling to 33 °C, and shivering during TTM was instead treated largely with intermittent bolus doses of neuromuscular blocking agents (NMBA) rather than escalation of sedation doses. A total of 166 patients underwent TTM_{33}, and received fentanyl at a median dose of 25 mcg/hr. in addition to propofol at a median dose of 20 mcg/kg/min; a minority of patients (<15%) received alternative sedation, such as low-dose midazolam infusion. Ninety-five percent of patients were reported to experience shivering, and a median of five doses of NMBA were administered in the 24-hour cooling period. In their cohort, awakening occurred at a median of 3 hours after the end of rewarming, with extubation at a median of 28 hours after rewarming, in surviving patients. While this study has no comparator group, it suggests that implementing sedation doses sufficient to prevent awareness with NMB administration, but not unnecessarily deep so as to require an exaggerated period of time to clear after rewarming, is a safe and effective strategy. This is highlighted by comparison to the sedation doses reported in the TTM-trial, where patients received fentanyl and propofol at much higher doses (median ~175 mcg/hr and ~45 mcg/kg/min, respectively) [90]. While lower rates of shivering were reported in the TTM-trial (approximately 30% in both arms), awakening in the TTM_{33} group occurred at a median on day 4, which was likely a day later compared to the May study patients using estimated similar definitions [90, 92].

Lastly, a single-center PK study assessed the time to clearance after discontinuation of fentanyl in 23 patients after cardiac arrest treated with TTM_{36}. Patients received an average fentanyl dose of 119 mcg/hr for 24 hours of TTM, with a PK analysis showing that 68% of patients (15/22) would not have cleared at 24 hours, and 5/22 (23%) would have required >48 hours to achieve 95% clearance after discontinuation. These authors' findings emphasize the prolonged duration of effect these patients can experience and which may potentially interfere with prognostication assessments occurring soon after rewarming [91].

Cumulatively, these studies illustrate the impact of hypothermia on reduced clearance of analgesia and sedative agents, which is known to be proportional to the degree of hypothermia. While the precise cooling target to best optimize outcomes after cardiac arrest is still of considerable debate, the prolongation of effect when employing TTM_{33} as compared to TTM_{36} must be considered, since the lower target temperature has been shown to potentially result in longer time to awakening, especially when higher doses of analgesia and sedative agents are used [90]. The clinician must carefully consider the selection of agents and titration strategy to effectively prevent and treat shivering in patients undergoing TTM regardless of the temperature target.

Upon completion of the rewarming period, after the risk of shivering has abated, clinical assessment with minimization or discontinuation of sedation as soon as possible is important in order to allow for optimal prognostication conditions in patients

who do not regain consciousness. Postponement of impacted prognostic assessments normally recommended at the 72-hour post-resuscitation point is highly recommended in patients receiving significant sedation and analgesia doses, as reasonable, in order to permit prolonged observation; consideration should be given to ordering non-impacted testing (SSEPs, brain imaging, NSE levels) first [88].

Paroxysmal Sympathetic Hyperactivity (PSH)

Pathophysiology and Clinical Presentation of PSH

Paroxysmal sympathetic hyperactivity (PSH) is a syndrome encountered in patients with various forms of severe acute neurologic injury who exhibit a constellation of symptoms with autonomic and motor features. This condition has historically been associated with severe TBI, which was noted to be the etiology of 79.4% of cases in a 2010 review. This was followed by hypoxic brain injury in 9.7%, hemorrhagic or ischemic stroke in 5.4% of cases, and the remaining associated with conditions such as hydrocephalus, tumor, and CNS infection [93].

This review also noted that over 30 terms have been used to describe PSH including "dysautonomia," "diencephalic seizures," and "sympathetic" or "autonomic storming" [93]. In 2014 a consensus group formed to address the definition and diagnosis of the syndrome and recommended the uniform term "paroxysmal sympathetic hyperactivity," and also created the first version of a unified diagnostic tool, which they termed the PSH Assessment Measure [94].

The pathophysiology of the condition is poorly understood, but impaired descending inhibitory control of excitatory spinal circuits, which then permits unregulated sympathetic outflow, is a commonly proposed mechanism [95]. Patients with PSH may display a number of autonomic features, including tachycardia, hypertension, tachypnea, fever, diaphoresis, and decerebrate posturing. Triggering of symptomatic episodes by both noxious and non-noxious stimuli also appears to be an important defining feature of PSH [95, 96]. Episodes may last several minutes to hours and recur several times per day [97–100]. Symptoms typically begin to manifest around one week after injury, often once sedation is weaned, and may persist for weeks to months, including into the rehabilitation period [101–103]. The degree of sympathetic overactivity and frequency of episodes varies widely across affected patients. Over time, episodes become less frequent and less pronounced in severity.

Pharmacologic Treatment of PSH

Numerous medications are used to treat PSH, but there is minimal strong evidence to guide therapy. The most common therapeutic classes employed in clinical practice include opioids, non-selective β-antagonists, α_2 agonists (e.g., clonidine),

Table 14.7 Selected opioids commonly used in the treatment of PSH

Medication	Mechanism in PSH	Suggested Initial Doses	Comments
Morphine	μ-opioid receptor agonists, modulate pain transmission and perception Target allodynia	IV: 2–4 mg q1–2h prn PO: 15–30 mg q4–6h[a]	IV morphine is the prototypical opiate studied in PSH (opiate of choice) Doses up to 10 mg IV have been used for treatment of PSH Histamine release with IV morphine is advantageous in PSH (BP and HR-lowering)
Fentanyl		25–100 mcg IV q1–2h prn	
Oxycodone		10–20 mg PO q4–6h[a]	

References [93, 104–106]
[a]Initial maintenance dosing based on current opiate requirements

GABA agonists (e.g., benzodiazepines and baclofen), and additional agents such as bromocriptine and gabapentin. Despite the preponderance of low quality evidence for therapeutic interventions in PSH, the majority of data support the use of opioids and β-blockers as the backbone of therapy. Beyond this, building a regimen may be guided by the patient's predominant symptoms and comorbidities, and by combining agents with varying mechanisms of action [93, 104–106].

The initial approach to treatment is two-fold. First, rapid-acting IV agents should be utilized to abort acute episodes. These agents may include morphine, β-blockers, or benzodiazepines, with trials necessary to establish the effective agent and dose. Second, maintenance medications should also be initiated with the goal of reducing the number and severity of paroxysms, while balancing efficacy with minimal adverse effects (Table 14.7).

Opioids, as well as nonselective β-blockers such as propranolol and labetalol, are typically considered first-line therapies for both the abortive and maintenance treatment of PSH, serving to combat the allodynic response that is thought to be central to the pathophysiology of PSH and the resultant sympathetic response. IV morphine is the prototypical agent used for treatment of PSH, and is particularly effective to abort symptomatic episodes, though other opiates may also be useful. Morphine can additionally be given on a scheduled basis orally or converted to an equivalent dosage of oxycodone or other preferred opiate [93, 104–107].

Once acceptable control of PSH has been achieved with pharmacotherapy, as indicated by the frequency, duration, and severity of episodes requiring abortive treatment, then therapeutic doses may be maintained for a period of time. Beyond this, attempts may be made to begin weaning agents carefully, while paying close attention to recrudescence of symptoms.

Conclusion

Opioid use in the neurocritical care population is similar in many ways to the general critical care population as it relates to sedation and treatment of pain. Specific disease states which rely on specific use of opioids include the prevention or

treatment of shivering in TTM and the treatment of paroxysmal sympathetic hyperactivity. Influence of these medications on the assessment of the neurologic examination and neuroprognostication in acute brain injury require careful consideration by the critical care clinician.

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