

Prevention of Shivering During Therapeutic Temperature Modulation: The Columbia Anti-Shivering Protocol

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Abstract

Background As the practice of aggressive temperature control has become more commonplace, new clinical problems are arising, of which shivering is the most common. Treatment for shivering while avoiding the negative consequences of many anti-shivering therapies is often difficult. We have developed a stepwise protocol that emphasizes use of the least sedating regimen to achieve adequate shiver control.

Methods All patients treated with temperature modulating devices in the neurological intensive care unit were prospectively entered into a database. Baseline demographic information, daily temperature goals, best daily GCS, and type and cumulative dose of anti-shivering agents were recorded.

Results We collected 213 patients who underwent 1388 patient days of temperature modulation. Eighty-nine patients underwent hypothermia and 124 patients underwent induced normothermia. In 18% of patients and 33% of the total patient days only none-sedating baseline interventions were needed. The first agent used was most commonly dexmedetomidine at 50% of the time, followed

by an opiate and increased doses of propofol. Younger patients, men, and decreased BSA were factors associated with increased number of anti-shivering interventions.

Conclusions A significant proportion of patients undergoing temperature modulation can be effectively treated for shivering without over-sedation and paralysis. Patients at higher risk for needing more interventions are younger men with decreased BSA.

Keywords Hypothermia · Normothermia · Shivering · Dexmedetomidine · Meperidine

Introduction

Over the past several years, there has been an increasing use of advanced temperature modulating devices to achieve both therapeutic hypothermia and normothermia as a treatment for out of hospital cardiac arrest, refractory fever in the acutely brain injured patient, and raised intracranial pressure. Each device works by promoting conductive heat loss either by surface or intravascular cooling and maintains a tightly regulated temperature ($\pm 0.1^{\circ}\text{C}$) thru a feedback mechanism linked to a continuous core body temperature measurement.

These technological advances have made it feasible to achieve and maintain normothermia and hypothermia for a prolonged period. As the practice of aggressive fever control with these devices becomes more commonplace, new, unanticipated clinical problems are arising, of which shivering is the most common [1]. The shivering response is part of the centrally mediated thermoregulatory defense mechanism that can have a significant detrimental impact on systemic oxygen consumption, brain tissue oxygenation, and intracranial pressure. The overall metabolic consequences

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of shivering may eliminate many of the clinical benefits of temperature control [2–4]. Moreover, many of the anti-shivering therapies are associated with prolonged sedation, which may result in prolonged obscuration of the neurological exam and prolonged length of stay in the Neuro ICU.

In this study, we report our use of a stepwise protocol that emphasizes utilization of the least sedating regimen to achieve adequate shiver control.

Methods

Patient Selection and Data Collection

Beginning in January 2006, all patients treated with a temperature modulating device in our Neurological Intensive Care Unit (NICU) have been prospectively entered into our therapeutic temperature modulating (TTM) database. Baseline data collection includes demographics, as well as admission clinical and laboratory data. Once TTM is initiated, data collection includes daily temperature goal, minimum and maximum temperature best GCS score, routine daily chemistries, a tabulated SIRS score, type and cumulative dose of each vasoactive and sedative infusion. Scoring of infectious complications using standard criteria for pneumonia, urinary tract infection, meningitis/ventriculitis, bloodstream infection, and *Clostridium difficile* infection as well as antibiotic use are recorded daily. Each patient is also linked to a high resolution data acquisition system (BedmasterEX, Excel Medical Electronics, Jupiter, FL) to acquire digital data every 5 s from General Electric (GE) Solar 8000i monitors. The conduct of this study has been approved by the Columbia University Institutional Review Board.

Therapeutic Temperature Modulation

Decisions regarding method and duration of cooling are at the discretion of the attending neurointensivist (NB, JC, KL, SM). Established indications for TTM at our

institution include: cardiac arrest, raised intracranial pressure, and refractory fever in the setting of acute brain injury. Target temperatures for normothermia are between 36 and 37°C; target temperatures for hypothermia range between 33 and 35.5°C. TTM is performed with either intravascular cooling methods (Celsius Control System, Innercool Therapies, Inc, San Diego, CA; Cool Guard, Zoll Therapeutics, San Francisco, CA) or external cooling (Arctic Sun Cooling System; Medivance Inc, Louisville, Colo). Each device is regulated to a core body temperature measured either by a bladder thermistor (Bardex; C. R. Bard Inc, Covington, GA) or esophageal temperature probe (Lifesound, Novamed, Elmsford, NY).

Anti-Shivering Algorithm

During the cooling period, shivering is scored hourly using the Bedside Shivering Assessment Scale by the NICU nursing staff. The goal for each patient undergoing TTM was to achieve no to minimal shivering, as defined by the BSAS score ≤ 1 . Our stepwise protocol for shivering control is shown in Table 1. At baseline (Step 0), we initiate a series of interventions prior to the initiation of cooling designed to minimize shivering during the induction phase. These measures are then continued empirically throughout the entire cooling period. The initial intervention (Step 1) of either an opiate or dexmedetomidine is made for any patient demonstrating moderate to severe shivering (BSAS score 2–3) despite all baseline interventions. The choice between which agent to use first is based upon additional needs for the particular patient. For example, opiates are considered first in patients with either poorly controlled pain or baseline bradycardia, and likewise, dexmedetomidine in patients with poorly controlled agitation. If the initial intervention is not successful the next step is the combination of dexmedetomidine and an opiate (Step 2). The goal for both steps 1 and 2 of the protocol is to maximize the use of one agent prior to proceeding to the second agent; therefore patients graduating between Steps

Table 1 The Columbia Anti-Shivering Protocol

Step		Intervention	Dose
0	Baseline	Acetaminophen	650–1000 mg Q 4–6 h
		Buspirone	30 mg Q 8 h
		Magnesium sulfate	0.5–1 mg/h IV Goal (3–4 mg/dl)
		Skin counterwarming	43°C/MAX Temp
1	Mild sedation	Dexmedetomidine	0.2–1.5 mcg/kg/h
		or	Fentanyl starting dose 25 mcg/h
		Opioid	Meperidine 50–100 mg IM or IV
2	Moderate sedation	Dexmedetomidine and Opioid	Doses as above
3	Deep sedation	Propofol	50–75 mcg/kg/min
4	Neuromuscular blockade	Vecuronium	0.1 mg/kg IV

1 and 2 have a synergistic anti-shivering effect of an opiate and dexmedetomidine. Deep sedation with propofol (50–75 mcg/kg/min) is achieved in those patients failing to achieve adequate shiver control (BSAS ≤ 1) (Step 3). As many time patients are already on a lower dose of propofol for sedation only increases in the initial dose of propofol or high levels of propofol were considered as shivering interventions. Neuromuscular blockade with boluses of a paralytic is reserved for hypothermic patients not able to achieve control with deep sedation (Step 4). Our preference for neuromuscular blockade is to use vecuronium (0.15 mg/kg IV bolus).

Statistical Analysis

To examine use of anti-shivering interventions univariate analysis categorizing the type of medications used according to the sum total number of interventions was performed. A multivariate multinomial regression model was created to determine factors associated with the number of anti-shivering interventions. To examine potential differences between hypothermia and normothermia treatments all analysis was repeated stratifying across goal temperature (hypothermia versus normothermia). Data analysis was performed with standard statistical software (version 9.2, SAS Institute, Inc.) and significance was set at $P < 0.05$ (Table 2).

Results

Data was collected for 213 patients who underwent 1388 patient days of TTM therapy from January 2006 to March 2010. Eighty-nine patients were started on hypothermia therapy, accounted for 871 TTM patient-days in total, 517 days of which were hypothermia days. Hundred and twenty-four patients were started on normothermia, accounting for 848 TTM patient days of normothermia. Patients started on hypothermia who were transitioned to normothermia contributed another 251 patient days accounting for a total of 1099 normothermia days.

The mean age was 59 (SD 17), mean BMI was 28 kg/m² (SD 6.5), mean BSA was 1.9 m² (SD 0.3). 47% were men. The median daily best GCS was 7 (IQR 5–10). 35% of patients were diagnosed with subarachnoid hemorrhage; intracerebral hemorrhage and cardiac arrest diagnosis were of equal prevalence at 23%; 13% had ischemic strokes and 7% had traumatic brain injury (Table 3).

Analysis of all patients showed that in 18% of patients and 33% of the total number of patient days, no additional anti-shivering medications besides those in Step 0 were used. Beyond the Step 0 medications, 29% of patients received one agent, 35% received two agents, 15%

Table 2 Population characteristics

Age (mean, SD)	59 ± 17
Male (N, %)	100 (47)
BMI (mean, SD)	28 ± 6.5
BSA (mean, SD)	1.9 ± 0.3
Best GCS (median, IQR)	7 (5–10)
Subarachnoid hemorrhage	75 (35)
Cardiac arrest	48 (23)
Intracerebral hemorrhage	48 (23)
Stroke (N, %)	27 (13)
Traumatic brain injury	15 (7)
Intravascular device (N, %)	24 (11)
Surface device (N, %)	189 (89)
Hypothermia (patients)	89 (42)
Hypothermia (patient days)	289 (20)
Normothermia (patient days)	1099 (80)

received three agents, and 2.4% required four agents. According to our protocol 50% of the time the first agent added was dexmedetomidine; 36% of the time opiates were added, 9% of the time propofol was increased, 5.1% of the time paralytics were added. The second agent added was most commonly an opiate and the third agent added was propofol (Table 4).

Analysis of patients started on hypothermia treatment showed that 25% of patients and 38% of the total number of patient days, no additional shivering interventions were used. 26% needed one additional intervention, 31% needed two additional interventions, 13% needed three additional interventions, and 4.5% needed all four interventions. Similarly, the most commonly added first agent was dexmedetomidine, 43% of the time, the next most commonly added agent was an opiates, followed by propofol and paralytics.

Analysis of patients during normothermia treatment showed similar results. 14% of patients and 32% of the time, patients received only the Step 0 interventions. 35%

Table 3 Maximum number of interventions for patients during TTM

All patients	Hypothermia		Normothermia		
	Interventions	N (%)	Interventions	N (%)	
0	39 (18)	0	22 (25)	0	17 (14)
1	61 (29)	1	23 (26)	1	38 (31)
2	74 (35)	2	28 (31)	2	46 (37)
3	34 (15)	3	12 (13)	3	22 (18)
4	5 (2.4)	4	4 (4.5)	4	1 (1)
Total	213	Total	89	Total	124

Table 4 Daily number of interventions characterized by medication

Interventions	Days (N, %)	Dexmed (%)	Opioids (%)	Propofol (%)	Paralytics (%)
TTM					
0	453 (33)				
1	470 (34)	50	36	9	5.1
2	364 (26)	71	84	29	17
3	96 (6.9)	90	92	83	34
4	5 (0.36)	100	100	100	100
Total	1388				
Hypothermia					
0	103 (36)				
1	84 (29)	36	38	12	14
2	72 (25)	57	69	31	43
3	29 (10)	26	90	83	56
4	1 (0.4)	100	100	100	100
Total	289				
Normothermia					
0	350 (32)				
1	386 (35)	53	36	8	3
2	292 (27)	74	87	28	10
3	67 (6)	97	94	84	25
4	4 (0.4)	100	100	100	100
Total	1099				

of the time one agent was added, dexmedetomidine being the most common, 27% of the time patients needed two agents, 6.1% needed 3 agents and less than 1% received all four interventions.

Average doses of medication used are shown in Table 5.

Analysis of all patients showed age, gender, and BSA were significant factors in predicting the number of anti-shivering interventions used. Young men with lower BSA were more likely to require additional interventions. Patients with better GCS were more likely to be in Step 1 compared to Step 0, but this relationship did not hold true for increasing interventions (Table 6).

Discussion

Shivering management is essential for effective TTM. In order to standardize shivering treatment during TTM, we

Table 5 Medication doses

Medication	Median dose (IQR)
Magnesium sulfate (G/h)	0.5 (0.3–1)
Dexmedetomidine (mcg/kg/h)	0.43 (0.18–0.69)
Meperidine (mg/24 h)	125 (55–250)
Fentanyl (mcg/h)	47 (24–83)
Propofol (mg/h)	101 (42–186)
Vecuronium (mg/24 h)	13 (10–20)

have developed a stepwise management strategy to treat shivering while minimizing side effects of shivering management: sedation, hemodynamic effects, neuromuscular blockade.

Table 6 Multinomial regression model

Interventions		β	OR	95%CI	P value
1	Age	−0.18	0.83	0.76–0.92	<0.001
	Male	0.36	2.1	1.5–2.9	<0.001
	BSA	−0.75	0.47	0.24–0.92	0.028
	GCS	0.08	1.1	1.0–1.1	<0.001
2	Age	−0.40	0.67	0.60–0.74	<0.001
	Male	0.50	2.7	1.8–4.0	<0.001
	BSA	−0.75	0.12	0.06–0.27	<0.001
	GCS	0.01	1	0.95–1.1	0.85
3	Age	−0.46	0.63	0.54–0.74	<0.001
	Male	0.76	4.6	2.5–8.6	<0.001
	BSA	−1.5	0.23	0.07–0.75	0.015
	GCS	−0.05	0.96	0.88–1.0	0.291
4	Age	−0.63	0.54	0.32–0.89	0.017
	Male	1.3	13	1.0–177	0.048
	BSA	−2.7	0.07	0–7.1	0.256
	GCS	−0.03	0.97	0.70–1.3	0.869

Controlled for age (per 10 years), gender, BSA, GCS

With our protocol, we have found that 18% of all TTM patients (33% of patient days) undergoing TTM do not need additional anti-shivering interventions beyond skin counterwarming, acetaminophen, buspirone and intravenous magnesium.

Each baseline intervention has specific anti shivering properties without leading to additional sedation. Because mean skin temperature contributes approximately 20% to the input the hypothalamus receives about body temperature, the shivering threshold can be manipulated by skin counterwarming [5, 6]. Acetaminophen acts by inhibiting cyclooxygenase-mediated prostaglandin synthesis to lower the hypothalamic set point [7–9]. Buspirone is thought to act on the 5-HT_{1A} receptor to lower the shivering threshold, and has a synergistic effect when added to other anti-shivering interventions. Magnesium sulfate infusion has been shown to be effective in increasing the comfort and decreasing the time to goal temperature. Its effect on peripheral vasodilation is thought to be the mechanism of action [10].

In our analysis 50% of the time dexmedetomidine was the first anti-shivering agent added, followed by opiates, and <10% of the time high dose propofol. Dexmedetomidine is a central alpha-2 receptor agonist which has effective anti-shivering properties on both the vasoconstriction and shivering thresholds. The main side effect is bradycardia and hypotension, while the considerable advantage is the lack of respiratory depression [11]. Both μ - and κ -opioid receptor agonists impair thermoregulatory control. Meperidine has been shown to lower the shivering threshold by its effect on the alpha 2B adrenoceptor subtype [12, 13] and works synergistically with both buspirone and dexmedetomidine to lower the shivering threshold [11, 14]. An important side effect to consider is the lowering of the seizure threshold. The other commonly used opiate in our NICU is Fentanyl. It has less selective anti-shivering properties, and its primary mechanism of shiver control may be its related sedative impact on brain-injured patients. Propofol is frequently used in the ICU for sedation. In addition to sedative and amnestic actions it mildly reduces the vasoconstriction and shivering thresholds [15]. Hypotension, negative cardiac ionotropy, sedation, and propofol infusion syndrome are limiting factors in the use of propofol for shivering. Because propofol is so frequently used in our NICU for sedation only increases in propofol levels from baseline or when baseline levels were not available, only high levels of propofol (50–70mcg/kg/min) were considered shivering interventions.

We consider the use of paralytics as the last step because of the considerable side effects including loss of the neurologic exam and increased incidence of prolonged weakness associated with critical illness [16]. In addition, patients who are paralyzed are required to have adequate

sedation. On the other hand, it is important to remember that paralytics are the quickest method of ceasing the shivering response and can help in achieving goal temperature quicker.

Other interventions aimed at decreasing shivering exist. Dantrolene has little effect on the central shivering threshold but works to decrease shivering by peripheral actions on muscle by reducing gain [17]. Ketamine and ondansetron have both been shown to decrease shivering mainly by lowering the shivering threshold [18, 19]. We have not included these medications in our analysis as we do not use them routinely for shivering.

Factors identified which impacted the use of anti-shivering were age, gender, BSA, and GCS. We suspect the association with age, gender, and BSA are associated with muscle mass. Given a decrease in muscle mass with age and lower muscle mass in women shivering will be easier to control in older women with low muscle mass compared to young men with higher muscle mass. The association with GCS most likely has to do with the brain's ability to modulate core body temperature. In patients with devastating brain injury and loss of the brain's ability to thermo-regulate the shivering response is dampened. The relationship with GCS is complicated in that many of the interventions cause sedation and will impact the patient's clinical state.

Our analysis of shivering control is limited in its scope due to the observational study design. It is a study of group practice over a span of 4 years, and though designed as a stepwise guideline, there were no strict rules. No active intervention was performed to assess any single treatment or multiple treatments' effect on shivering. Although the bedside shivering assessment scale was recorded a more continuous real-time measure may be needed to accurately measure shivering and its response to anti-shivering treatments. Because of the complex clinical needs of patients anti-shivering medications were often given for sedation and pain as well as shivering. They are many times interchangeable and isolating one effect from the other is difficult. This is especially true with propofol as it is the most frequently used sedative for patients in our NICU.

Further studies on the effect of shivering on outcomes and additionally the effect of anti-shivering medications on outcome are needed. Outcomes important to include would be clinical outcomes, but also time to goal temperature, hemodynamic effects and metabolic effects. Fortunately, some medications used for shivering have proposed neuro-protective effects and are being studied as therapeutic interventions in brained injured patients [20]. Others are used for dual effects of anti-shivering properties and rapid temperature modulation by blocking the vasoconstrictive effects or sedation.

In summary, we have described our rationale for the Columbia Shivering Protocol and described our adherence. A significant proportion of patients undergoing TTM can be treated effectively for shivering without over-sedation and paralysis during both hypothermia and normothermia treatments. Factors associated with increased number of anti-shivering interventions were younger patients, men and decreased BSA.

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