

CONTROLLED THERMOREGULATION FOR THE NEURO-ICU

ANTI-SHIVERING PROTOCOL:

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ANTI-SHIVERING PROTOCOL:

I. Background Controlling Thermoregulatory Defenses Against Hypothermia:

a. Overview:

One of the key elements in therapeutic induced hypothermia is to defeat the counteracting physiologic thermoregulatory responses. The reason for controlling these thermoregulatory defenses is not only to speed up the process and have more control on therapeutic hypothermia but also because these responses may have potential harmful implications.^[1] Mammal organisms have several independent and redundant systems to maintain the core temperature. The primary defenses against hypothermia are vasoconstriction and shivering. These responses can modify the blood flow in the fingertips by about 10 fold.

b. Behavioral compensation:

The behavioral related compensatory mechanisms in response to the induction of hypothermia are not as important clinically as other compensatory mechanisms. Some of these behavioral mechanisms are related to the search of warmth and shelter. In the ICU we have control over the patient's environment. Hypothermia generates discomfort, which in turn will trigger the formerly mentioned behavioral responses. Mild sedation is recommended to control the hypothermia related discomfort.^[1]

c. Vasoconstriction:

Vasoconstriction is one of the initial physiological responses to counteract hypothermia. The trigger for vasoconstriction is up to one degree higher than the shivering threshold.^[1] Vasoconstriction occurs many times during the day as we move to colder environments and is controlled by the autonomic system. This mechanism does not have any expense in terms of energy or fluid loss. The normal threshold for vasoconstriction is 36.5 C. Vasoconstriction of 100 μ m arterioles cause AV shunt especially on toes and fingertips. To estimate the degree of vasoconstriction we have to subtract the temperature at the fingertips from the temperature at the forearms.^[1] Any difference of temperature will represent some degree of vasoconstriction. The end effect of vasoconstriction is reducing heat loss. When shunt occurs from vasoconstriction, the temperature of the whole extremity cools down. Peripheral temperature can fluctuate by many degrees Celsius at difference from core temperature, which is not allowed to fluctuate more than a few tenths of a degree Celsius.^[1] This peripheral temperature variation depends on the temperature of the environment, conduction-convection of heat within the organism, and the efficiency of the autonomic system to induce vasoconstriction. The core to peripheral tissue temperature can range from + 4 C to -4

C. Each degree change in the peripheral compartment dissipates or absorbs 29 kcal. Changes in acid-base, sepsis, medications (e.g., magnesium sulfate), spinal shock, and neurological disorders, among others can affect these autonomic mechanisms against hypothermia.

d. Shivering:

Shivering is part of the physiologic homeostatic mechanisms to maintain temperature and is triggered when the behavioral and vasoconstriction mechanisms fail. The normal threshold for shivering is 35.5 C. Most humans shiver at temperatures < 36 C. Elderly have at least 1 degree C lower shivering threshold than younger patients. ^[2] All mammals are programmed to shiver when body temperature drops below a threshold, an automatic and subconscious function, but shivering ceases at temperatures < 34 C. The CNS controls the shivering mechanisms. Research on rodents has demonstrated that specialized cutaneous thermoreceptors carry the temperature information to the neurons of the lateral parabrachial nucleus of the brain, which in turn sends the temperature information to the preoptic area (hypothalamus). ^[3] Skin cooling increases in sympathetic thermogenesis in brown adipose tissue, in metabolism and in heart rate. Those responses are reversed by inhibition of neurons in the median preoptic nucleus. Glutaminergic stimulation of the median preoptic nucleus neurons evokes thermogenic, metabolic and cardiac responses very similar to the cold-defensive responses to skin cooling. Antagonizing GABA receptors in the medial preoptic area, which is thought to contain neurons providing thermoregulatory output to effectors, blocked these cold-defensive responses. ^[3] These last group of neurons trigger shivering, which is the involuntary contractions of the skeletal muscles produce warmth, raising the body temperature. The brain temperature centers constantly supervise the temperature and establish when the shivering should start.

Non-shivering thermogenesis occurs in the brown adipose tissue and has minimal effect on the metabolic rate. Transient shivering causes 4-5 fold increase in the metabolic rate. More sustained shivering increases the metabolic rate by 2 fold. Shivering increased the metabolic rate and increases the adrenergic response. A reduction of 0.7 C increases norepinephrine concentration by 400% and oxygen consumption by approximately 30%. ^[1] Hypothermia is associated with vasoconstriction and hypertension.

The process of shivering involves first the pectoralis muscles, and then it extends to the limb muscles.

The process of shivering is detrimental since it counteracts cooling induction, consumes energy, may contribute to increased intracranial pressure, increased energy expenditure and brain oxygen consumption. [4] Shivering results in large increases in resting energy expenditure, and in the systemic rate of oxygen consumption. These findings have previously been validated with the use of indirect calorimetry.

Low serum magnesium is independently associated with shivering. [4]

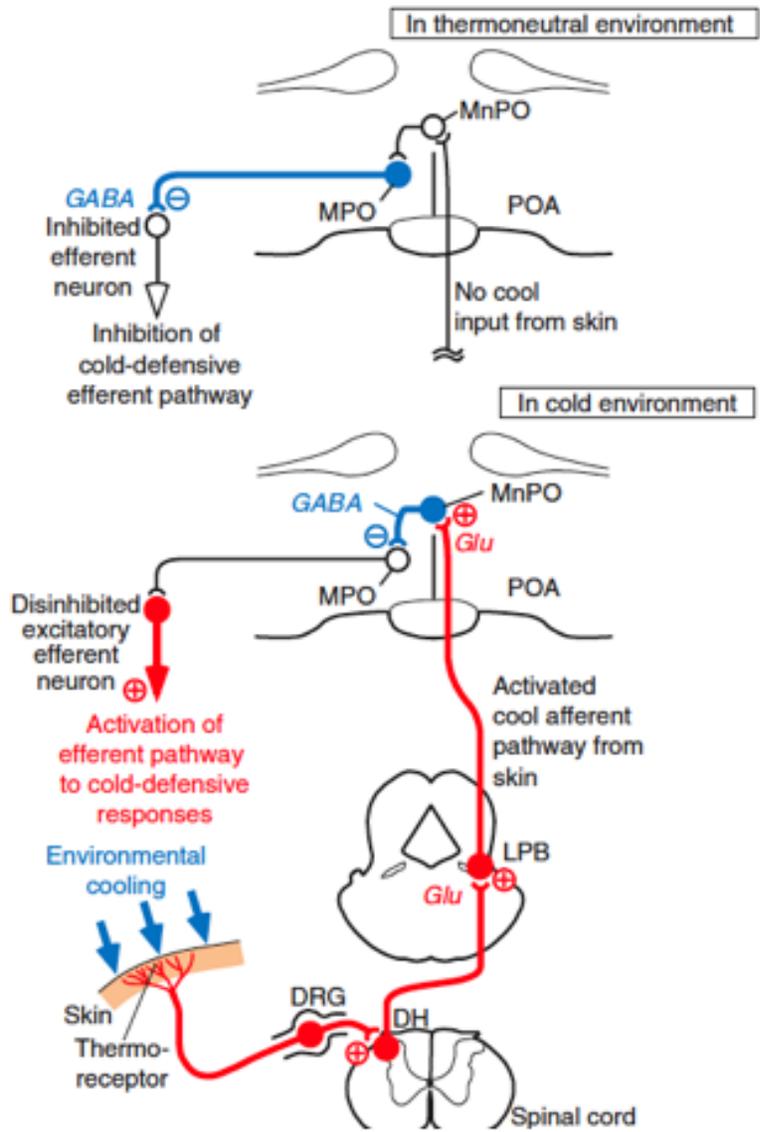


Figure 1. Model of the mechanism for cold-defensive responses to thermo-sensory signals from the skin [3]

Table 1: The Bedside Shivering Assessment Scale (Modified scale from Badjatai et al Stroke 2008;39:3242-3247) (4)

Score	Term	Description
0	None	No shivering noted on palpation of the masseter, neck or chest wall and no electrophysiological evidence of shivering (using EKG)
1	Subclinical	Electrophysiological evidence of shivering (using EKG), without clinical evidence of shivering
2	Mild	Shivering localized to the neck and/or thorax only
3	Moderate	Shivering involves gross movement of the upper extremities (in addition to neck and thorax)
4	Severe	Shivering involves gross movements of the trunk, upper and lower extremities

Table 2: Magnesium Sulfate Titration*

- Obtain baseline serum magnesium level and every 4-6 hrs while on treatment
- Drip initiation
 - If serum Mg level < 2.0, give 2 gram IV bolus over 1 hr followed by initial maintenance infusion of 0.5 g/hr
 - If serum Mg level \geq 2.0, initiate magnesium infusion at rate of 0.5 g/hr
- Goal serum magnesium level 3.0-3.5 mg/dL
- Titrate magnesium drip per table

Serum Magnesium Level	Intervention
2.0-2.5 mg/dL	Increase drip by 0.5 g/h
2.5-3.0 mg/dL	Increase drip by 0.25 g/h
3.0-3.5 mg/dL	Continue current drip rate
3.5-4.0 mg/dL	Decrease drip by 0.25 g/h
>4.0 mg/dL	Hold drip, contact H.O., recheck Mg level in 4 hours and resume drip at rate 0.5 g/h less than previous rate

*Caution if renal insufficiency

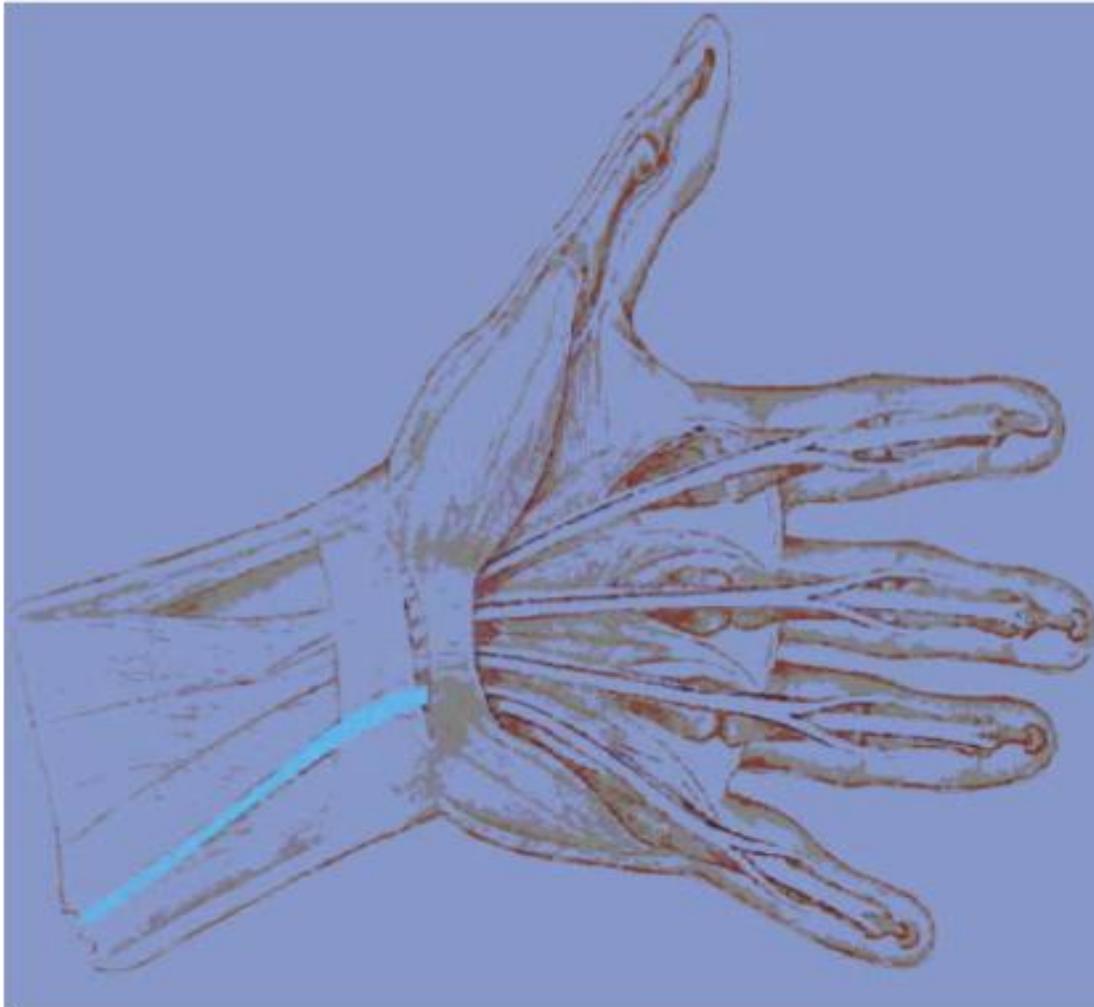
Table 3: Level of neuromuscular blockade as assessed with train-of-four testing

Based on Foster et al and Viby-Mogensen (5)

No. of twitches	Approximate percentage of receptors blocked
0	100%
1	90%
2	75-80%
3	75%
4	0%

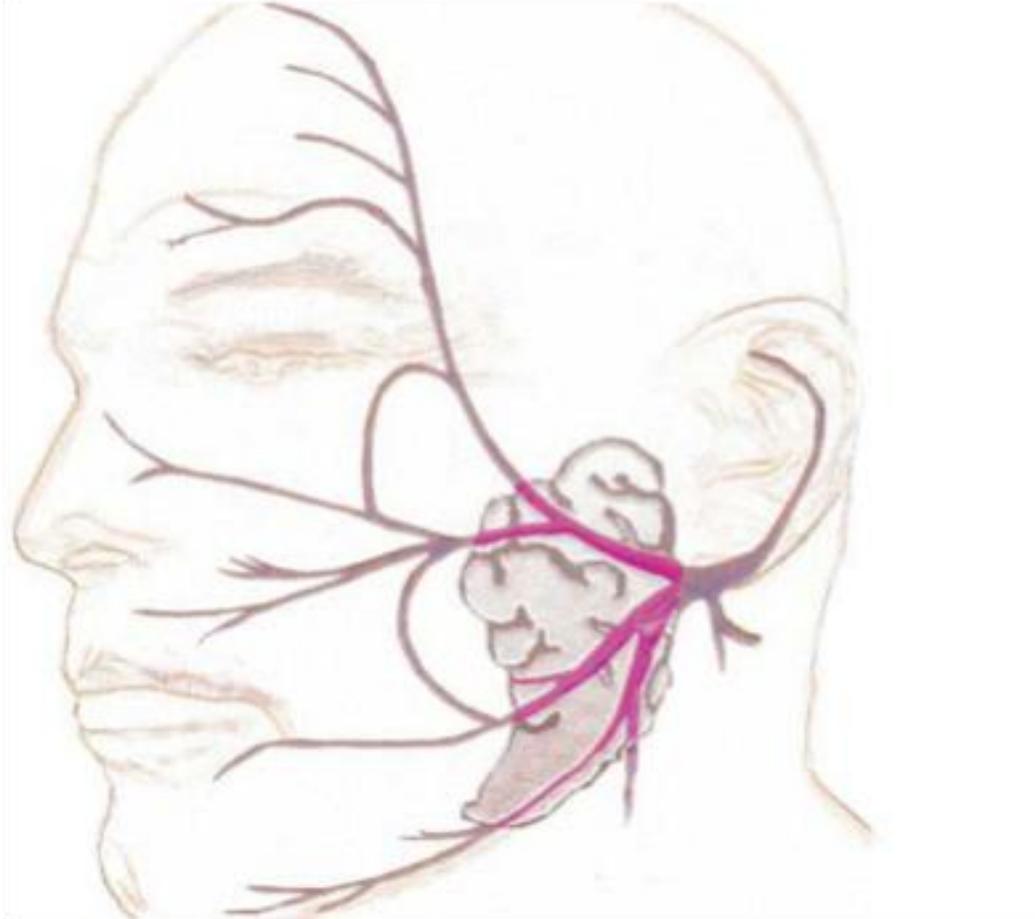
Electrode Placement for Neuromuscular Blockade:

Figure 2A (Ulnar Nerve Placement): [6]



Orient the nerve stimulator so the positive electrode is more proximal and the negative more distal. Use at least 20 mA of current.

Figure 2B Facial Nerve Placement: [6]



Orient the nerve stimulator so the positive electrode is more proximal to the neck and the negative more distal. Use at least 20 mA of current.

General Objectives:

- **Rapid suppression of shivering (induction):**
 - Pharmacological induction to avoid shivering during the transition of normothermia to hypothermia after initiation of controlled hypothermia.
 - Induction for controlled hypothermia could be aided by rapid cooling to the target hypothermic temperature.
 - Use the most effective therapeutic combination during the induction phase.

- **Aggressive suppression of shivering in those patients with hyperthermia or fever (step wise escalating approach):**
 - If shivering recurs, the anti-shivering treatments will be re-started in a stepwise manner.
 - The shivering scale will be used in the titration of the anti-shivering treatments. It will aid in choosing a more or less aggressive stepwise titration of the anti-shivering therapy.
 - Treatments that induce sedation or paralysis are reserved for the end.

- **Weaning challenge in a reverse step wise fashion (based on safety and invasiveness):**
 - Once induction phase is completed, the patient is weaned from the anti-shivering treatments in the reverse order of initiation. The most sedating or harmful therapy is weaned first and the less invasive anti-shivering treatments are weaned at the end.
 - Challenge the patient to remove the anti-shivering therapy every 6 hrs.
 - Use reverse stepwise process in weaning the anti-shivering treatments.

- **Prevent delays in reaching controlled therapeutic hypothermia goals and increase synergy with cooling devices.**
 - By effectively suppressing the shivering process we are aiding the therapeutic temperature control.

- **Prevent detrimental effects of shivering:**
 - Shivering has detrimental effects on the patient's physiology, including detrimental effects on systemic energy and brain oxygen consumption.

ANTI-SHIVERING ALGORITHM

Induction:

(At the start of controlled hypothermia)

Use the combination of therapies 1, 2, 3 and 4

Add therapy 5 and/or 6 if patient intubated

Maintenance:

(After temperature goal is reached)

Step 1: Bair Hugger is started first and always kept on during temperature modulation therapy

Step 2: If still shivering, add treatments 2 and 3 together

Step 3: Add treatment 4 and titrate up until shivering is suppressed

Step 4: If still shivering, start neuromuscular blockade. Use nerve stimulator to titrate neuromuscular blockade. Target 1 contraction from train of 4.

Step-down/Discontinuation:

(In reverse order, starting with the therapies initiated at the end first)

Patients on induced barbiturate coma do not need anti-shivering treatment until they are weaned from this therapy.

1. Bair Hugger Therapy:

Use upper chest warming blanket to warm upper chest neck and face
Consider using Bair Hugger designed for upper chest of adult patient
Keep Bair Hugger at all times.

2. Buspirone:

Start with 10 mg PO/NG TID

Monitor for sedation, EPS, tardive dyskinesia, akathisia, dystonia, hostility, serotonin syndrome

3. Magnesium Sulfate:

If serum Mg < 2.0, load with 2 g magnesium sulfate IV over 1 hour, then initiate maintenance infusion at 0.5 g/hr

If serum Mg \geq 2.0, start maintenance infusion at 0.5 g/hr and titrate up or down by 0.25 g/hr q4hrs until goal of 3-3.5 mg/dL is achieved

Monitor Chem10 q4-6hrs

4. Meperidine (Demerol):

Load with 25 mg IV

Maintenance 25-100 mg IV q4hrs prn

Caution: meperidine can increase ICP in patients with intracranial HTN

5. Dexmedetomidine (Precedex):

Initiate maintenance infusion 0.2-0.7 mcg/kg/hr

Use this treatment only if prior ones fail and only in intubated patients

Propofol can be used as an alternative

6. Neuromuscular Blockers:

Rocuronium

Load with 600-1200 mcg/kg IV

Maintenance infusion 10-12 mcg/kg/min

Use this treatment only if the prior ones fail and only in intubated patients

Cisatracurium can be used as an alternative in hepatic failure

Medications used in Anti-shivering Protocol

Medication	Dosing	Rationale	Side Effects	Metabolism & Monitoring
Buspirone (Buspar®)	Oral Dose: 10-30 mg orally q8h	5HT _{1A} partial agonist Binds to dopamine D ₂ receptors Reduces shivering threshold	Dizziness, sedation, nausea, headache	Metabolism: Hepatic CYP 450 3A4 Monitor: Sedation Adjustment: Renal and hepatic impairment
Dexmedetomidine (Precedex®)	IV Maintenance: 0.2 - 0.7 mcg/kg /hr continuous infusion	Central α-2 agonist Reduces the vasoconstriction and shivering thresholds	↓ BP, ↓ HR, sedation	Metabolism: Hepatic CYP 450 2A6 Monitor: Sedation, vital signs Adjustment: Renal and hepatic impairment
Magnesium Sulfate	IV Load: 2 g bolus if serum Mg < 2 IV Maintenance: Initiate at 0.5 g/h and titrate to achieve serum Mg level 3-3.5 mg/dL	NMDA receptor antagonist Peripheral vasodilator exerts negative feedback control on hypothalamus Physiologic Ca channel blocker Reduces shivering threshold	Flushing, ↓ BP, N/V, diarrhea	Metabolism: Urine excretion Monitor: Chem10 q6h, vital signs Adjustment: Avoid if severe renal failure
Meperidine (Demerol®)	IV Dose: 12.5-75 mg IV q2-4 h prn (0.5-1 mg/kg/dose)	Agonist at μ and κ opioid receptors Agonist at α-2 _B receptors NMDA receptor antagonist Reduces shivering threshold	Sedation, ↓ BP, N/V, respiratory depression, seizures	Metabolism: Hepatic CYP 450 2B6, 2C19, 3A4 Renal excretion Monitor: Sedation, vital signs, Chem10 per day Adjustment: Avoid use in renal impairment
Propofol (Diprivan®)	IV Load: 0.25-1 mg/kg IV x 1 IV Maintenance: 20-80 mcg /kg /min continuous infusion	NMDA receptor antagonist	Sedation, ↓ HR, ↓ BP, respiratory depression	Metabolism: Hepatic CYP 450 2B6 Monitor: Cardiac monitor, O ₂ sat, ABG Serum TG 2x/wk Adjustment: Caution if hepatic dysfunction
Rocuronium Bromide (Zemuron®)	IV Load: 600-1200 mcg/kg IV x1	Nondepolarizing neuromuscular blocking agent	Ventilatory failure, muscle weakness,	Metabolism: Deacetylated in the liver

	<p><u>IV Maintenance:</u> 10-12 mcg/kg/min continuous infusion</p>	with a rapid to intermediate duration	↓ BP, apnea	<p>Biliary & renal elimination Monitor: Monitor neuromuscular blockade with nerve stimulator Adjustment: Caution if neuromuscular disorders, pulmonary HTN</p>
Cisatracurium (Nimbex®)	<p><u>IV Load:</u> 150-200 mcg /kg</p> <p><u>IV Maintenance:</u> 1-3 mcg/kg/min continuous infusion</p>	Nondepolarizing neuromuscular blocking agent with intermediate duration	Ventilatory failure, muscle weakness, apnea, seizures	<p>Metabolism: 80% Hoffman elimination; rest hepatic with metabolites eliminated primarily by urine, feces (<4%) Monitor: Monitor neuromuscular blockade with nerve stimulator Adjustment: Caution if renal impairment</p>

References:

1. Sessler, D., *Defeating Thermoregulatory Defenses Against Hypothermia*, in *Therapeutic Hypothermia*, S. Mayer and D. Sessler, Editors. 2005, Taylor & Francis Group: Boca Raton, FL. p. 229-263.
2. Kurz, A., et al., *The Threshold for Thermoregulatory Vasoconstriction during Nitrous Oxide/Isoflurane Anesthesia is Lower in Elderly Than in Young Patients*. *Anesthesiology*, 1993. 79(3): p. 465-469.
3. Nakamura, K. and S.F. Morrison, *Preoptic mechanism for cold-defensive responses to skin cooling*. *The Journal of Physiology*, 2008. 586(10): p. 2611-2620.
4. Badjatia, N., et al., *Metabolic impact of shivering during therapeutic temperature modulation: the Bedside Shivering Assessment Scale*. *Stroke*, 2008. 39(12): p. 3242-7.
5. Foster, J., S. Kish, and C. Keenan, *National practice with assessment and monitoring of neuromuscular blockade*. *Crit Care Nurs Q.*, 2002. 25: p. 27-40.
6. Corso L, *Train-of-four results and observed muscle movement in children during continuous neuromuscular blockade*. *Crit Care Nurse*, 2008. 28(3): p. 30-8; quiz 39.
7. Badjatia N. *Hyperthermia and fever control in brain injury*. *Crit Care Med* 2009;37(7):S250-257.
8. Badjatia N, Kowalski RG, Schmidt JM, et al. *Predictors and clinical implications of shivering during therapeutic normothermia*. *Neurocrit Care* 2007;6:186-191.
9. Bicer C, Esmaoglu A, Akin A, Boyaci A. *Dexmedetomidine and meperidine prevent postanaesthetic shivering*. *European Journal of Anaesthesiology* 2006;23:149-153.
10. De Georgia MA, Krieger DW, Abou-Chebl A, et al. *Cooling for Acute Ischemic Brain Damage (COOL AID): A feasibility trial of endovascular cooling*. *Neurology* 2004;63:312-317.
11. De Witte J and Sessler DI. *Perioperative Shivering: Physiology and Pharmacology*. *Anesthesiology* 2002;96:467-484.
12. Doufas AG, Lin C-M, Suleman M-I. *Dexmedetomidine and Meperidine Additively Reduce the Shivering Threshold in Humans*. *Stroke* 2003;34:1218-1223.
13. Elvan EG, OC B, Uzun S, et al. *Dexmedetomidine and postoperative shivering in patients undergoing elective abdominal hysterectomy*. *European Journal of Anaesthesiology* 2008;25:357-364.
14. Kollmar R, Schellinger PD, Steigleder T, et al. *Ice-Cold Saline for the Induction of Mild Hypothermia in Patients with Acute Ischemic Stroke: A Pilot Study*. *Stroke* 2009;40:1907-1909.
15. Lenhardt R, Orhan-Sungur M, Komatsu R, et al. *Suppression of Shivering during Hypothermia Using a Novel Drug Combination in Healthy Volunteers*. *Anesthesiology* 2009; 111: 110-5.
16. Mokhtarani M, Mahgoub AN, Morioka N, et al. *Bupirone and Meperidine Synergistically Reduce the Shivering Threshold*. *Anesth Analg* 2001;93:1233-9.
17. Wadhwa A, Sengupta P, Durrani J, et al. *Magnesium sulphate only slightly reduces the shivering threshold in humans*. *British Journal of Anaesthesia*;2005;94(6):756-762.