

Pharmacological Treatment for the Prevention of Post-Anesthetic Shivering

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Abstract

This Capstone Project examines post anesthetic shivering (PAS), which is a relatively common manifestation following the administration of a general or regional anesthetic that can prolong the recovery time of patients stemming from hemodynamic instability. Many anesthesia professionals; including, student registered nurse anesthetists (SRNAs), lack a thorough understanding of PAS. The goal of this project was to increase the understanding among 43 SRNAs at Adventist University of Health Sciences, Nurse Anesthesia Program, regarding the etiology, risk factors, consequences, and pharmacological treatment options for PAS. The information was presented in the form of an educational-based presentation during the fall semester in a clinical conference. An informed consent was signed by each participant. A pre-test was administered, then a PowerPoint presentation on PAS was given, followed by a post-test. The pre- and post- test scores were analyzed using a paired t-test. Mean scores increased from 8.1 (pre-test) to 13.7 (post-test). This was a significant finding, with a p-value $< .001$. Based on these statistical findings, the presenters concluded that the PowerPoint presentation was an effective means for increasing the understanding and knowledge base of PAS.

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Pharmacological Treatment for the Prevention of Post-Anesthetic Shivering

Problem

Managing postoperative shivering remains a difficult task for all anesthesia providers, including Student Registered Nurse Anesthetists (SRNA). Initially it was thought that hypothermia was the cause for shivering; however, many patients shivered even though they were normo-thermic. As such, vigilance is warranted in treating post anesthetic shivering (PAS). The interventions that are used to prevent hypothermia only have a partial impact on the number of incidences. As SRNAs, it is important to have effective means of treating shivering, but also ways of preventing the incidence of shivering before it occurs. Prevention mainly entails averting preoperative hypothermia by actively rewarming the patient. Postoperative skin surface rewarming is a rapid way of obtaining the threshold shivering temperature while also raising the skin temperature and improving the comfort of the patient. However, this technique is less efficient than the use of certain drugs, such as meperidine, ondansetron or tramadol; these drugs reduce the shivering threshold temperature (Kose, Honca, Akinci, & Aypar, 2013). SRNAs need to be aware of alternative drugs used in the treatment of PAS, and be able to apply the appropriate pharmacological intervention when encountering PAS in the anesthetic management of patients.

Postoperative shivering is uncomfortable for the patient; it has detrimental effects on the body, such as an increase in circulating catecholamine's, heart rate, oxygen consumption, metabolic CO₂ production, and lactic acid levels. As a result, patients may experience increases in postoperative pain, cardiopulmonary complications, and intracranial pressure and interference with monitoring (Inoue, Shinjo, Kawagushi, Nakajima, & Furuya, 2011).

Shivering is a common occurrence after general and regional anesthesia; alone it can jeopardize both the recovery and the hemodynamic recovery of patients. Meperidine is the most frequently used pharmacological treatment for PAS; unfortunately, no standard of practice currently exists and the recommended options for PAS treatment are sometimes unknown to those caring for shivering patients, including SRNAs. The purpose of this project is to increase the knowledge base among SRNAs regarding the etiology, risk factors, consequences, and pharmacological options in the treatment of PAS by developing and disseminating an educational-based presentation.

Review of Literature

A large number of studies exist on the topic of PAS. A review of the literature showed that inadvertent perioperative hypothermia and postoperative shivering are associated with multiple factors including coagulopathy, an increased allogeneic transfusion requirement, surgical wound infection, prolonged hospitalization, delayed post anesthetic recovery, and morbid cardiac complications (Inoue, Shinjo, Kawagushi, Nakajima, & Furuya, 2011). Aggressive treatment of postoperative shivering is necessary to avoid such complications, which can be lethal if comorbidities exist. According to Song and Lee (2013) “PAS is common, and may be a result of intraoperative hypothermia. Another possible etiology is fever and chills secondary to activation of the inflammatory response and release of cytokines” (p.18).

Pharmacologic modalities are also used and could be just as effective as rewarming in the prevention and treatment of PAS. Adjusting the temperature to the providers’ comfort level could harm the patient as it may delay the rewarming period and cause other physiologic instabilities leading to a pharmacological intervention of PAS. Pharmacological interventions include the use of ondansetron, dexamethasone, tramadol, dexmedetomidine, ketamine, and

intrathecal fentanyl. Reducing the occurrence of PAS, it leads to better outcomes by avoiding physiologic instabilities and faster recovery for patients.

Post anesthetic shivering occurs due to impairment that general and regional anesthesia causes via the thermoregulation through multiple phases. Mohata and Singh (2013) states,

“Core hypothermia during general anesthesia develops with three characteristic phases. Initial core hypothermia results from core-to-peripheral redistribution of body heat when anesthesia inhibits tonic thermoregulatory vasoconstriction. Subsequently, heat loss exceeding metabolic heat production reduces core temperature in a slow, linear fashion. Finally, a core temperature plateau results when emergence of thermoregulatory vasoconstriction decreases cutaneous heat loss and constrains metabolic heat to the core thermal compartment” (p.442).

Theories about the cause of shivering have included pain, hypoxia, stress, hypocarbia and an overactive sympathetic system. However, researchers such as Sadegh (2000) have found “PAS was due to uninhibited spinal reflexes, it is thought that the spine recovers faster than the brain and manifests as shivering activity” (p.46). With so many conflicting theories more studies are needed to strengthen any one theory related to PAS.

Shivering can be described as tremors or fasciculation's that are seen in the jaw, face, head, and travels to the trunk and extremities that usually last longer than 15 seconds. Inoue et al. (2011) state, “The incidence of shivering has been reported to be about 36% to 85% after spinal anesthesia. In a recent meta-analysis, the average incidence of shivering was 52%” (p. 84.). Esmaeili (2000) explained that spinal anesthesia impairs the thermoregulation system by inhibiting tonic vasoconstriction, which plays a role in temperature regulation. Heat is internally

redistributed from the core to the peripheral compartment. The loss of thermoregulatory vasoconstriction below the blockage results in increased heat loss from body surfaces in excess of the metabolic heat production.

Post anesthesia shivering is uncomfortable for the patient and can result in very unfavorable physiological effects. In patients with multiple comorbidities, such as coronary artery disease, PAS can increase oxygen consumption. This mismatch between oxygen demand and consumption can lead to decompensation in ill patients, increasing their heart rates and cardiac output. If demand continues to exceed oxygen delivery, it will lead to a decrease in levels of mixed venous oxygen saturation. The last compensatory mechanism will result in metabolic acidosis.

In addition, PAS can cause an increase in pain from the surgical site and impede monitoring of vital signs in the postoperative period. When taking all of these effects into consideration, patients who cannot manage the oxygen depletion and cardiorespiratory work are more susceptible to deleterious outcomes. These patients may include, but are not limited to those experiencing anemia, respiratory compromised patients, and those that are at risk for myocardial infarction (Inoue, Shinjo, Kawagushi, Nakajima, & Furuya, 2011).

Identifying patients that are at risk for PAS can help healthcare workers provide treatment options for faster, more efficient care. Patients who are experiencing pain and whose core body temperature are below the threshold range show a greater risk at experiencing PAS. A major factor contributing to a decrease in core body temperature is radiant heat loss from the exposure of skin surfaces and abdominal viscera to the ambient environment. Other risk factors include the use of ambient irrigation solution in the peritoneal cavity, ambient intravenous fluid, and ventilation with dry anesthetic gases. Karaman et al. (2013) found that the length of surgery

and specifically laparoscopic surgery contributed to PAS since core hypothermia and vasoconstriction often occur before PAS.

Since a standard of practice is currently lacking in treating PAS. Prevention is the key to avoiding possible unfavorable consequences. In clinical practice, hypothermia is prevented via forced air warmers; however, when prevention is unsuccessful or when shivering is non-thermoregulatory in nature, healthcare providers must turn to pharmacological treatments such as meperidine, ondansetron, dexamethasone, tramadol, ketamine, and dexmedetomidine.

Meperidine (Demerol), is an opioid agonist analgesic that affects anticholinergic, serotonergic, and noradrenergic receptors. Meperidine was first used in the 1930s, and has become common in the treatment of pain and PAS. Meperidine mechanism of action exerts its effects by antagonizing the mu receptors, most specifically the kappa receptors, with an affinity ten times greater than morphine

In recent years, meperidine has come under intense scrutiny as medications with safer profiles have been produced. Many healthcare institutions have removed Meperidine from their formulary, limiting its use for healthcare providers. Its side effects include hallucinations, constipation, mydriasis, urinary retention, delirium, seizures, and reversible Parkinsonism. In the 1990s, monoamines oxidase inhibitors and serotonin reuptake inhibitors were used for the treatment of depression; when administered with meperidine, it could cause a lethal pharmacological effect known as serotonergic crisis (Song & Lee 2013). Normeperidine, the known metabolite of meperidine, has been linked to neurotoxicity and may cause many other negative effects such as seizures, myoclonus, anxiety, changes in mood, and hyper-reflexia. It has been studied extensively over the last 85 years. Song and Lee (2002) found that it prevents the uncoupling of thermoregulation by altering the body's perception of central body temperature

through peripheral vasoconstriction and central vasodilation, and that meperidine is a medication whose time has passed in routine pain management and whose use must be questioned in all instances.

Ondansetron (Zofran), a serotonin antagonist used as a prophylactic treatment for nausea, and vomiting is an effective treatment to prevent shivering. Eldaba (2012) did a study on the effects of ondansetron on post-anesthesia shivering. Ondansetron, which is a specific serotonin receptor antagonist, is widely used as an antiemetic drug. Serotonin receptors may also influence both heat production and heat loss pathways. In Eldaba's (2012) study, PAS was due to inhibition of the serotonin system, therefore, produced a dose-dependent reduction in shivering. The recommended dose of ondansetron for preventing postoperative nausea and vomiting is 4-8 mg in adult patients. When 8mg is used for prophylaxis, Eldaba (2012) noted that it can reduce shivering to 15%, and it has shown to be as effective as meperidine when given before the induction of anesthesia.

Dexmedetomidine (Precedex), is the same class of drug as clonidine an alpha-2 agonist, and is a new drug used for analgesia and sedation in the perioperative settings. A prophylactic single dose of dexmedetomidine was effective in treating established PAS and exert its effects by vasoconstriction and reducing the thresholds for shivering. According to Karaman (2013), who studied core temperature measurements, only 20% of patients in the Dexmedetomidine group experienced post anesthetic shivering after an abdominal hysterectomy when dexmedetomidine was infused at a rate of $0.4 \mu\text{g kg}^{-1} \text{ h}^{-1}$. In the study, Karaman found a 10% lower post anesthetic shivering in the dexmedetomidine group compared to the tramadol group. He attributed this difference to tramadol being administered at the end of surgery for postoperative

analgesia and to tramadol and dexmedetomidine acting synergistically.

Dexamethasone (Decadron), is a corticosteroid; that is a naturally produced hormone that is secreted by the adrenal glands. In the study done by Song and Lee (2013), The mechanism through which dexamethasone controls PAS by the central inhibition of prostaglandin synthesis, inhibition of endogenous opioid release, decreased serotonin turnover in the central nervous system, and changes in the permeability of the blood–brain barrier to serum proteins. Song and Lee's (2013), results indicate that dexamethasone 10 mg decreased PAS, pain, and postoperative nausea. A single dose of dexamethasone given preoperatively decreased the incidence and severity of PAS and the need for rescue drugs after surgery.

Tramadol (Ultram), is an atypical opioid that acts centrally by inhibiting the reuptake of 5-hydroxy-tryptamine-3 and noradrenaline. Tramadol is not available in the United States for intravenous use; however, it is widely used in other countries. Mohta and colleagues (2009) found tramadol in doses of 1, 2, and 3 mg/kg to be effective for the prophylaxis of post anesthetic shivering in adult patients undergoing surgical procedures under general anesthesia. Used during wound closure, tramadol can provide both an anti-shivering effect and analgesia in the postoperative period.

Fentanyl (Sublimaze), a fast-acting narcotic analgesic and sedative, has a rapid onset and shorter duration of action. When it is administered, the unionized component is rapidly transferred into the spinal cord. A small dosage of fentanyl administered directly into the cerebrospinal fluid has been found to be effective in minimizing discomfort during and after cesarean section without increasing serious adverse effects. Kose (2013) has “suggested that intrathecal fentanyl could decrease both the incidence and severity of shivering during spinal

anesthesia for transurethral resection of prostate” (p. 51). Kose continues to say that “the reduction of shivering may be attributable to the effect of fentanyl on the thermo-regulator and spinal affect afferent thermal inputs at the spinal cord” (p.51). Fentanyl, a drug most commonly used in anesthesia and when given intrathecally, can decrease the amount of shivering.

Ketamine (Ketalar), is a competitive NMDA receptor antagonist. Ketamine also has a local anesthetic action and works on kappa opioid agonist receptors. Ketamine plays a role in thermoregulation at various levels. Shakya, Chaturvedi, and Sah (2015) state that “ketamine is believed to control shivering by non-shivering thermogenesis, either by action on the hypothalamus or by the β -adrenergic effect of norepinephrine” (p.467). However, the exact mechanism of ketamine is not clear.

In conclusion, the widespread use of meperidine is dwindling because of its controversial and vast negative side effects. Meperidine is still an appropriate treatment option, but many factors affect the ability to use meperidine in the clinical setting such as the availability, and the numerous negative contraindications. There are many different therapeutic alternatives that are appropriate to use, with less side effects. Although, tramadol is not currently available in the United States, the other drugs studied are readily available in the clinical setting.

Project Description

The goal of this project was to provide an educational lecture that included a PowerPoint presentation (Appendix C) on the etiology, risk factors, consequences, and pharmacological interventions of PAS. A convenience sample of 43 SRNAs enrolled at Adventist University of Health Sciences (ADU) Nurse Anesthesia Program (NAP) was selected. Submission to the ADU Scientific Review Committee (SRC) and Institutional Review Board (IRB) was performed and approved. The Informed consent (Appendix A) of all participating SRNAs was obtained prior to

administering the pre-test. An identical pre- and post- test (Appendix B) were administered. The pre-test was used to assess the existing understanding of PAS. After the lecture, the post-test was administered to determine if there had been any change in the SRNAs understanding of PAS. The intent of this capstone project was to increase the SRNAs understanding regarding PAS because, if prevention fails or shivering occurs in patients with a normal core temperature, pharmacological intervention is necessary. The intention was that the participating SRNAs would have a more in-depth understanding of PAS, thus preparing SRNAs to safely use alternatives pharmacological treatments for PAS.

The capstone project was delivered on October 15, 2015 to both ADU NAP cohorts consisting of 43 participants (graduating classes of 2016 and 2017). The project included an educational lecture with a presentation to serve as a visual aid to enhance learning. The pre- and post- test were returned anonymously and SRNAs were instructed to refrain from including any identifiers. The pre- and post- tests were numbered to correlate for comparison because, the projects success was determined by analyzing the pre- and post- test.

Evaluation

A convenience sample of 43 SRNAs (NAP class of 2016 and 2017), quantitative study design with a pre- and post- test was administered. The evaluation plan was aimed towards determining if the SRNAs in the NAP at ADU had benefited from the presented material. The test assessed the etiology, risk factors, consequences, and pharmacological treatment options for PAS in a multiple choice format. The independent treatment variable included the presentation of an educational-based presentation (Appendix C). A pre- and post-test was given to evaluate the effectiveness of the information presented. A significant variance between the pre- and post- test scores was anticipated from the presenters, with the post-test scores showing a greater

improvement. This analysis enabled the presenters to determine if the presentation was successful. A paired t-test was used to analyze the pre- and post- test scores. An improvement in scores between the pre- and post- test, indicates that the SRNAs had acquired key concepts and increased knowledge base PAS. The objective of this project was to provide SRNAs with evidence-based information to be utilized in the prevention of PAS and avoid complications that accompany the onset of shivering.

Results and Conclusions

The results showed an increase between the pre-and post- test with a mean score increase of approximately 8.1957 (pre-test) to 13.7826 (post-test), (Table 2). This was a significant finding, with a p-value < .001. The pre- and post- test administered were identical (Appendix B). The presenters concluded that the lecture increased subjects' understanding of PAS. The outcomes that were achieved was an increased understanding of PAS, which could translate to improved outcomes for patients. Overall, the presentation provided an increase in the understanding of PAS that the SRNAs can utilize in future clinical decisions.

Table 1

Paired Samples Test									
		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	PreTest - PostTest	-5.58696	2.86298	.59697	-6.82500	-4.34891	-9.359	22	.000

Table 2

Paired Samples Statistics					
		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	PreTest	8.1957	23	2.91446	.60771
	PostTest	13.7826	23	1.83294	.38220

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Appendix A

ADU NAP CAPSTONE PROJECT – INFORMED CONSENT

Our names are Sarah Reed & Mohammed Brini and we are MSNA students in the Nurse Anesthesia Program (NAP) at Adventist University of Health Sciences (ADU). We are doing a Capstone Project called *Pharmacological Treatment for the Prevention of Post-Anesthetic Shivering*. This project is being supervised by Dr. Steve Fowler. We would like to invite you to participate in this project. The main purpose of this form is to provide information about the project so you can make a decision about whether you want to participate.

WHAT IS THE PROJECT ABOUT?

The purpose of this project is to increase understanding among Student Registered Nurse Anesthetists regarding the etiology, risk factors, consequences, and pharmacological treatment options in the treatment of post-anesthesia shivering through the development and dissemination of an evidence based lecture.

WHAT DOES PARTICIPATION IN THIS PROJECT INVOLVE?

If you decide to participate in this project, you will be asked to complete an anonymous pre-assessment, attend a classroom presentation, and then complete an anonymous post-assessment. The assessment will address your understanding of post-anesthesia shivering and understanding about the pharmacologic treatment modalities available to prevent it. Your participation by attendance at the presentation and completion of the survey is anticipated to take approximately 1 hour.

WHY ARE YOU BEING ASKED TO PARTICIPATE?

You have been invited to participate as part of a convenience sample of students currently enrolled in the ADU NAP. Participation in this project is voluntary. If you choose not to participate or to withdraw from the project, you may do so at any time.

WHAT ARE THE RISKS INVOLVED IN THIS PROJECT?

Although no project is completely risk-free, we don't anticipate that you will be harmed or distressed by participating in this project.

ARE THERE ANY BENEFITS TO PARTICIPATION?

We don't expect any direct benefits to you from participation in this project. The possible indirect benefit of participation in the project is the opportunity to gain additional understanding about the risks associated with the current treatment modalities for post-anesthesia shivering as well as providing you with the with enough tools to be utilized in the prevention of post-anesthesia shivering and avoid complications that accompany the onset of shivering.

HOW WILL THE INVESTIGATORS PROTECT PARTICIPANTS' CONFIDENTIALITY?

The results of the project will be published, but your name or identity will not be revealed. To maintain confidentiality of assessments, the investigators will conduct this project in such a way to ensure that information is submitted without participants' identification. You will be given a pre-numbered pre-assessment that will be matched to a post-assessment with the same number as a tool to evaluate the presentation outcome. You are not required to write your name or any identification information on either assessment. Thus, the investigators will not have access to any participants' identities.

WILL IT COST ANYTHING OR WILL I GET PAID TO PARTICIPATE IN THE PROJECT?

Your participation will cost approximately 1 hour of your time, but will require no monetary cost on your part. You will not be paid to participate.

VOLUNTARY CONSENT

By signing this form, you are saying that you have read this form, you understand the risks and benefits of this project, and you know what you are being asked to do. The investigators will be happy to answer any questions you have about the project. If you have any questions, please feel free to contact Sarah Reed at sarah.reed@my.adu.edu or Mohammed Brini at mohammed.brini@my.adu.edu. If you have concerns about the project process or the investigators, please contact the Nurse Anesthesia Program at (407) 303-9331.

Participant Signature

Date

Participant Name (PRINTED LEGIBLY)

Appendix B

Pharmacological Treatment for the Prevention of Post-Anesthetic Shivering
Survey Questions

Pre- and Post- Test

1. Post-Anesthetic shivering is believed to occur in approximately how many patients recovering from general or regional anesthesia?
 - a) <1%
 - b) 1-4%
 - c) 5-64%
 - d) >65%
2. Which of the following statements are true about PAS?
 - a) It is described as spontaneous, uncontrollable muscular shaking.
 - b) It involves skeletal muscular contraction with increases metabolic heat production.
 - c) The exact cause of PAS is not known.
 - d) All of the above.
3. Select the following statement that is not a consequence of post anesthetic shivering?
 - a) Increased minute ventilation
 - b) Oxygen consumption increases up to 600%
 - c) Nausea and vomiting
 - d) Increased post operative pain
4. Non-thermoregulatory shivering is caused by?
 - a) Cutaneous vasoconstriction
 - b) Cutaneous vasodilation
 - c) Controlled intra-operative patient cooling
 - d) Unsuccessful perioperative patient warming
5. What is the major cause of post anesthetic shivering?
 - a) Benzodiazepines
 - b) Hypothermia
 - c) Anti-cholinergics
 - d) Pain
6. Select the factor that is associated with increased risk for patients experiencing PAS?
 - a) Orthopedic surgery
 - b) Hypothermia
 - c) Male gender
 - d) Young age
7. The drug of choice by many healthcare providers for the treatment of PAS is Meperidine, which drug when combined with Meperidine can cause a lethal reaction?

- a) Anti Cholinergic
 - b) Barbiturates
 - c) Mono-amine oxidase inhibitors
 - d) Neuromuscular blockers
8. Normeperidine the metabolite for Meperidine is a neurotoxin and has what major side effects?
- a) Seizures
 - b) Hyperreflexia
 - c) Anxiety
 - d) All of the above
9. What other drugs are effective alternatives for PAS?
- a) Atropine, Doxapram, Tramadol, Ondansetron
 - b) Ondansetron, Tramadol, Dexmedetomidine, Dexamethasone, Ketamine
 - c) Clonidine, Atropine, Tramadol, Doxapram
 - d) Ondansetron, Nalbuphine, Clonidine, Tramadol
10. Which drugs have been found to be equally as effective to Meperidine in numerous studies in preventing PAS?
- a) Tramadol
 - b) Clonidine
 - c) Atropine
 - d) Doxapram

Appendix C

Pharmacological Treatment for the Prevention of Post-Anesthetic Shivering

SARAH REED RN, BSN, SRNA
MOHAMMED BRINI RN, BSN, SRNA

Clinical Scenario

A student registered nurse anesthetist (SRNA) took part in delivering anesthesia during a Whipple procedure under the lead of a new graduate certified registered nurse anesthetist (CRNA). The patient history was significant for several comorbidities including coronary artery disease (CAD), stage II congestive heart failure (CHF), anemia, and emphysema. By the end of the 5 hour long surgery, the patient had an estimated blood loss of 2 liters and was transfused with 2 units of packed red blood cells. The patient was emerged with no problems and was fairly stable to be transferred to recovery.

Clinical Scenario

The SRNA accompanied the CRNA during the transfer of the patient and brought the CRNA's attention to the patient's shivering. The CRNA who was a recent graduate made the comment that the shivering was due to the low temperature in the operating room and that it will subside after the patient is covered with warm blankets once in the recovery area. When the patient was connected to the monitor, it was noted that the patient's was tachycardic with an oxygen saturation of 92% and worsening shivering. As the CRNA was leaving to get drugs to treat the patient's symptoms the patient became agitated and went into supraventricular tachycardia with a heart rate in the 200s. The attending anesthesiologist was notified for help. However, by the time the CRNA came back with the drugs, the patient had already converted to a lethal rhythm and was being resuscitated. Twenty minutes went by and the patient was declared dead as he could not be resuscitated considering his comorbidities.

Issue at Hand

- Management of PAS remains a difficult task for providers
- Shivering manifested even in normothermic patients
- A standard of care does not currently exist and the recommended options for PAS treatment are sometimes unknown to many of those caring for shivering patients including anesthesia providers
- Conventional hypothermia prevention measures only have partial impacts on the number of incidences

- Effective means to treating shivering
- **Prevent** the incidence of shivering before it occurs

Purpose

Increase knowledge among SRNAs regarding

- Etiology
- risk factors
- Consequences
- pharmacological treatment options of PAS

Etiology of Shivering

- Shivering is defined as a detectable fasciculation or tremor of the face, jaw, head, trunk, or extremities lasting longer than 15 seconds
- The incidence of shivering has been reported to be about 36-85% after spinal anesthesia
- A recent meta-analysis had the average incidence of shivering of 52%
- The exact mechanism of shivering during spinal anesthesia is not known
 - Heat is internally redistributed from the core to the peripheral compartment
 - The loss of thermoregulatory vasoconstriction below the blockage results in increased heat loss from body surfaces in excess of metabolic heat production
 - There is altered thermoregulation characterized by a 0.5° C decrease in vasoconstriction and a slight increase in the sweating threshold

Etiology of Shivering

- As of the mid 70's shivering has been an extensively documented phenomenon, unfortunately the cause remains controversial among researchers
- Most research agree the majority of PAS occur due to impairment that general and regional anesthesia cause to the thermoregulation via multiple mechanisms
- Core hypothermia during general anesthesia develops with 3 characteristic phases
 - Core-to-peripheral redistribution of body heat when anesthesia inhibits tonic thermoregulatory vasoconstriction
 - Heat loss exceeding metabolic heat production reduces core temperature in a slow, linear fashion
 - A core temperature plateau results when emergence of thermoregulatory vasoconstriction decreases cutaneous heat loss and constrains metabolic heat to the core thermal compartment

Etiology of Shivering

- Thermal inputs are integrated at the level of the anterior hypothalamus
- compares peripheral information with a threshold value, or the set-point
 - Temperatures higher than this set point will trigger responses to cool the body
 - Temperatures lower than this set point will activate reflexes to warm the body
- Shivering is a response to hypothermia, body temperature should normally be maintained within the range of 36.5–37.5 °C
- Regional anesthesia also decreases this threshold by 0.5 °C, triggering vasoconstriction and shivering above the level of block
 - This reduction in threshold is proportional to the number of spinal segments blocked, advanced age and high-level spinal blockade

Why is shivering manifested in some normothermic patients?!

Other Theories

- Many other theories have included pain, hypoxia, stress, hypocarbia and an overactive sympathetic system
- Fever and chills secondary to activation of the inflammatory response and release of cytokines
- Uninhibited spinal reflexes
 - It is thought that the spine recovers faster than the brain and manifests as shivering activity
- many identified pain as the main cause

Risk Factors



Identified to help surveillance of susceptible patients



- Orthopedic surgery
- Young age
- Hypothermia
- Pain
- Duration of surgery
- Radiant heat loss from the exposure of skin surfaces and abdominal viscera to the ambient environment
- Use of ambient irrigation solution in the peritoneal cavity
- Ambient intravenous fluid
- Ventilation with dry anesthetic gases

Risk Factors

How about laparoscopic surgery?

- Hypothermia is a common event during laparoscopic surgery
- The contact of carbon dioxide, which is usually delivered at room temperature 20–21 °C and at relatively low humidity, with the peritoneal surface can cause hypothermia
- The risk of intraoperative hypothermia is increased especially when the duration of the laparoscopic operation is long (>3 h)

Consequences

Post-anesthetic shivering

- Shivering on emergence reported in up to 60% of patients recovering from general anesthesia
- Common manifestation following the administration of a general or regional anesthetic
- Detrimental effects remain underestimated
 - Hemodynamic instability
 - ↑ circulating catecholamine
 - ↑ heart rate
 - ↑ metabolic demand → O_2 consumption of up to 500%
 - ↑ metabolic CO_2 production
 - ↑ lactic acid levels
 - ↑ postoperative pain → patients report cold sensation associated with shivering to be less bearable than surgical pain
 - ↑ intracranial pressure → Neurosurgical patients
 - cardiopulmonary complications
 - interference with monitoring
 - prolonged recovery

Traditional Pharmacologic Treatment



Meperidine



Meperidine

- Synthetic opioid analgesic
- The only narcotic with antishivering properties
- The most frequently used pharmacological treatment for PAS
- Affects anticholinergic, serotonergic, and noradrenergic receptors
- 1st used in the 1930s and became popular for the treatment of pain

Meperidine MOA for PAS

- Theorized
- Agonist to both Mu but more specifically Kappa receptors
- "Meperidine, which binds both mu and kappa opioid receptors, is reportedly more effective in treating shivering than are equianalgesic doses of morphine (a nearly pure mu-receptor agonist). Furthermore, butorphanol, a kappa-receptor agonist/antagonist, treats shivering better than does fentanyl, which mostly binds mu receptors. These data indicate that much of meperidine's special antishivering activity may be mediated by its kappa activity"
- It uncouples thermoregulation by altering the bodies perception of central body temperature through peripheral vasoconstriction and central vasodilation

Meperidine Side Effects

- Restricted in some hospital settings due to its detrimental side effects

• Dry mouth	• QT-interval prolongation
• Dry eyes	• Dysphoria
• Dizziness	• Hypotension
• Sweating, flushing, warmth of face/neck/upper thorax	• Mental clouding
• Seizures	• Restlessness
• Tachycardia (structure similar to atropine)	• Respiratory arrest
• Angina	• Urinary retention
• Agitation	• Visual disturbances
• Severe cardiac arrhythmia	• Nausea
• ST-segment elevation	• Nervousness
	• Palpitation

Meperidine Side Effects

The coadministration of monoamine oxidase inhibitors and serotonin reuptake inhibitors with meperidine causes a **lethal** pharmacological effect known as serotonergic crisis

Normeperidine the known metabolite of meperidine has been linked to being neurotoxic and causing many other negative affects such as seizures, myoclonus, anxiety, changes in mood, and hyperreflexia

"Meperidine is a medication whose time has passed in routine pain management and whose use must be questioned in all instances." (Latta and colleagues, 2002)

With hospital policy's and government warnings placed on meperidine it is imperative that healthcare providers understand ways of managing patients with other pharmacological treatments

Literature Review

Alternative Treatments

Karaman, S., Gumusen, I., Ceylan, M. A., Karaman, Y., Cetin, E. N., Derbent, A., & Ergenoglu, A. M. (2013). Dexmedetomidine infusion prevents postoperative shivering in patients undergoing gynecologic laparoscopic surgery. *Turkish Journal of Medical Sciences*, 43, 232-237. <http://dx.doi.org/10.3906/sag-1204-80>

- Controlled, randomized study
- 60 patients undergoing gynecologic laparoscopic surgery
- 2 groups of 30
- Perioperative tympanic temperatures were not different between the groups
- PAS
- 14 patients in NS group
- 3 patients in dexmedetomidine

Intraoperative dexmedetomidine infusion reduces postoperative shivering in patients undergoing gynecologic laparoscopy

Sadegh, A., Tazehkand, N. F., & Eslami, B. (2012). Intrathecal fentanyl for prevention of shivering in spinal anesthesia in cesarean section. *Medical Journal of Islamic Republic of Iran*, 26(2), 85-89. Retrieved from <http://web.b.ebscohost.com/resource.adu.edu/ehost/pdfviewer/pdfviewer?sid=44f31b98-87c-45f5-ac05-2aa531dc3f53%40sessionmgr111&vid=5&hid=121>

- Double-blind randomized controlled study
- 80 ASA I women elective cesarean section under spinal anesthesia
- 2 groups of 40
- Shivering significantly lower in study group
- 10% in study group
- 75% in control group
- Intrathecal bupivacaine combined with fentanyl is associated with a lower incidence and severity of shivering

Song, Y., & Lee, C. (2013). Effects of ramosestron and dexamethasone on postoperative nausea, vomiting, pain, and shivering in female patients undergoing thyroid surgery. *Journal of Anesthesia*, 27, 29-34. <http://dx.doi.org/10.1007/s00540-012-1473>

- Randomized, controlled study
- 123 female patients undergoing thyroid surgery
- 3 equally divided groups
- No significant difference in the overall incidence of shivering between dexamethasone and ramosestron.
- The severity of shivering was significantly lower in group ramosestron than group dexamethasone.
- Ramosestron 0.3 mg was more efficacious than dexamethasone 10 mg as monotherapy for POS.
- Cost may favor dexamethasone.

Mohta, M., Kumari, N., Tyagi, A., Sethi, A. K., Agarwal, D., & Singh, M. (2009). Tramadol for prevention of postanesthetic shivering: A randomised double-blind comparison with pethidine. *Journal of the Association of Anaesthetists of Great Britain and Ireland*, 64, 141-146. <http://dx.doi.org/10.1111/j.1365-2044.2008.05711.x>

- Randomized double-blind study
- 165 ASA I and II patients in 5 equal groups of 33
- Control group shivering $p < 0.005$, tramadol and pethidine (Meperidine) groups shivering $p > 0.005$
- All three doses of tramadol were effective and comparable to pethidine in preventing postanesthetic shivering
- Tramadol 2 mg/kg best combination of antishivering and analgesic efficacy without excessive sedation

Eldaba, A. A., & Amr, Y. M. (2012). Premedication with granisetron reduces shivering during spinal anaesthesia in children. *Anaesthesia Intensive Care*, 40, 150-153. Retrieved from <http://web.b.ebscohost.com/resource.adu.edu/ehost/pdfviewer/pdfviewer?vid=8&sid=44f31b98-87c-45f5-ac05-2aa531dc3f53%40sessionmgr111&hid=121>

- 80 children ASA I and II ages 2-5 in 2 groups
- No PAS in study group
- 6 PAS control group

Granisetron is an effective agent to prevent shivering after spinal anesthesia in children ages 2-5

Inoue, S., Shinjo, T., Kawaguchi, M., Nakajima, Y., & Furuya, H. (2011). Amino acid infusions started after development of intraoperative core hypothermia do not affect rewarming but reduce the incidence of postoperative shivering during major abdominal surgery: A randomized trial. *Journal of Anesthesia*, 25, 850-854. <http://dx.doi.org/10.1007/s00540-011-1230-4>

- Randomized trial
- 22 patients in 2 groups of 11
- Tympanic temperature at extubation were similar between the 2 groups
- POS was significantly lower in amino acid (AA) group
- AA infusion failed to accelerate rewarming. However, AA infusions reduced the incidence of PAS

Kose, E. A., Horca, M., Dal, D., Akinci, S. B., & Aypar, U. (2013). Prophylactic ketamine to prevent shivering in parturients undergoing Cesarean delivery during spinal anesthesia. *Journal of Clinical Anesthesia*, 25, 275-280. <http://dx.doi.org/10.1016/j.jclane.2012.11.014>

- Compare dose and safety of Ketamine in preventing PAS
- Prospective, randomized, double-blinded, placebo-controlled study
- 120 ASA I and II female patients for Cesarean delivery during spinal anesthesia.
- 3 groups of 30
- Prophylactic IV ketamine 0.25 mg/kg was as effective as IV ketamine 0.5 mg/kg

Other Literature Review Findings

PAS can lead to several undesirable effects

- coagulopathy
- increased allogeneic transfusion requirement
- surgical wound infection
- delayed postanesthetic recovery
- prolonged hospitalization
- morbid cardiac complications

All of this could result in an **unhealthy recovery** or even **death** in some instances

Alternative Treatments

- Ondansetron
- Dexmedetomidine
- Dexamethasone
- Tramadol
- Intrathecal Fentanyl
- Ketamine
- Amino Acid infusion

Ondansetron

A 5-HT₃ antagonist

Used as a mainstay prophylactic treatment for nausea and vomiting

MOA theorized to be related to the inhibition of serotonin reuptake on the preoptic anterior hypothalamic region

5-HT₃ receptors may also influence both heat production and heat loss pathways

The recommended dose of Ondansetron for prevention of POV is 4-8 mg in adult patients, interestingly when 8mg is used for prophylaxis it can reduce the shivering to 15% and has shown to be as effective as meperidine when given **before** the induction of anesthesia

Dexmedetomidine

Alpha-2 agonist

Analgesia and sedation in perioperative settings or in intensive care units

A prophylactic single dose of dexmedetomidine found to be effective for PAS

- Vasoconstriction and reducing the thresholds for shivering

Bradycardia and hypotension is often seen with alpha-2 agonists and should be avoided in these patients

Also effective for nonthermoregulatory PAS that is facilitated by surgical pain

Dexamethasone

- Corticosteroid that is a naturally produced hormone secreted by the adrenal glands
- A single dose of dexamethasone 10 mg given preoperatively decreased the incidence and severity of PAS
- MOA for PAS is not understood

Tramadol

Atypical opioid that acts centrally by inhibiting the reuptake of 5-hydroxy-tryptamine-3 and noradrenaline

Not currently available in the United States for intravenous use but is widely used in other countries

Shown to be far superior than meperidine in treating PAS

Tramadol used in doses of 1, 2 and 3 mg/kg at the time of wound closure could provide both antishivering effects as well as analgesia in the postoperative period

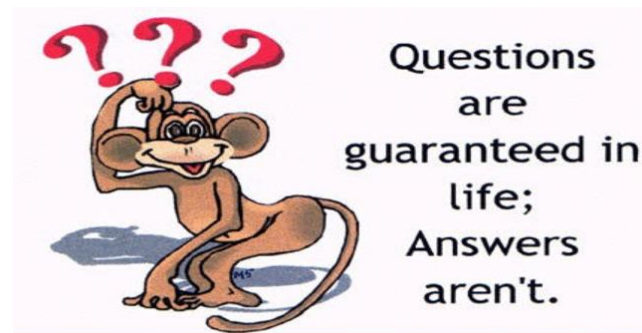
MOA not understood

Intrathecal Fentanyl

- Fentanyl is a highly ionized, lipophilic μ -receptor agonist. When it is administered intrathecally, the unionized component is rapidly transferred into the spinal cord
- The reduction of shivering maybe attributable to the effect of fentanyl on the thermo-regulator and spinal affect afferent thermal inputs at the spinal cord

Ketamine

- Ketamine causes sympathetic stimulation and vasoconstriction in patients at risk of hypothermia
- Ketamine is a competitive NMDA receptor antagonist, plays a role in thermoregulation at various levels
- Ketamine has other pharmacological properties such as
 - blocking uptake in the descending inhibitory monoaminergic pain pathways
 - Interacting with muscarinic receptors
 - Having a local anesthetic action
 - Being a kappa opioid agonist
- Ketamine is believed to control shivering by nonshivering thermogenesis, either by action on the hypothalamus or by the β -adrenergic effect of norepinephrine
- The exact mechanism of ketamine is not clear



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