A prospective randomized clinical trial evaluating the effect of convective pre-warming on intra-operative thermoregulatory capabilities in patients enrolled in the TIGER anesthesia perioperative protocol

PI: Claire Spradling, BS[1]
Medical Student

Co-PI: Terri Monk, MD[2]
Professor

Co-I: Kristen Richter, CRNA[2]

Co-I: Kay Smith, RN[2]

Co-I: Adam Zino, MPH[2]

[1]University of Missouri School of Medicine

[2]Department of Anesthesiology and Perioperative Medicine

University of Missouri

Columbia, MO 65201

NCT03876808

Contact: Claire Spradling, BS

University of Missouri School of Medicine

1001 University Ave Apt 102

Columbia, MO 65201

Telephone: (314) 541-7858

Email: cssqn8@health.missouri.edu

Summary

This prospective randomized clinical trial will assess the effect of pre-operative convective warming on intra-operative thermoregulation in patients undergoing gastrointestinal or genitourinary surgical procedures with the TIGER* anesthesia perioperative protocol.

*See addendum 1

Objectives:

Primary Endpoint:

1. Change in core temperature between induction of anesthesia and end of skin preparation (but before turning on the operating room forced-air warmer) as measured by a temperature-sensing Foley catheter

Secondary Endpoints:

1. Change in skin temperature between arrival to the holding area and departure to the operating room
2. Intraoperative temperatures
3. Skin temperature on arrival to the PACU (post-anesthesia care unit)
4. Differences in temperature changes between elderly (≥ 65 years) and younger patients

Clinical Hypotheses:

Primary Hypothesis:

We hypothesize that patients who are convectively warmed at 43°C for at least 60 minutes pre-operatively will have a higher core body temperature during the intraoperative period as measured by a temperature-sensing Foley catheter

Exploratory Hypothesis:

Patients who are convectively warmed prior to surgery will have

1. Temperatures that are significantly increased
    a. At departure from the preoperative holding area

   b. In the OR after surgical preparation
   c. On arrival to the PACU
2. Older (age ≥ 65 years) patients will demonstrate a greater change in mean intraoperative temperature compared to younger patients

Background & Rationale:

By the year 2030 the geriatric presence in the United States, defined as any adult >65 years of age, is estimated to reach around 20% of the entire population.[1] Thus, understanding medical concepts as they relate to the elderly is becoming increasingly important. One such concept is that of hypothermia - a core body temperature < 36°C - for which age >65 has been found to be an independent risk factor.[2] This complication is especially prevalent intra-operatively due to use of general anesthetics, cool ambient operating room (OR) temperatures, and impaired thermal regulation in the elderly.[3]

The human body employs numerous mechanisms to maintain thermal homeostasis including: behavioral means of thermoregulation, sweating, pre-capillary vasodilation, non-shivering and shivering means of heat production, and arteriovenous shunt vasoconstriction.[4] The first, and arguably most important, regulatory response to occur is that of vasoconstriction, which normally results in redistribution of blood from the relatively cool periphery to the warmer core compartment in order to confine metabolic heat to the central tissues.[2,5] Patients undergoing general anesthesia experience reduced vasoconstriction due to decreased cold response thresholds while patients undergoing epidural anesthesia experience sympathetic blocks resulting in blunted vasoconstrictive responses.[2,5] All patients experience the afore mentioned side effects of anesthetics, however it has been proven that the elderly are more susceptible to hypothermia due to lower vasoconstriction thresholds - determined by a temperature gradient of 4°C between the periphery and core.

First explored by *Kurz et al.*[6] in 1993, it was found that use of nitrous oxide and isoflurane anesthesia lead to an approximately 1.2°C lower vasoconstriction threshold of 33.9±0.6 in the elderly versus 35.1±0.3 in the young ($p < .01$). This subject was again looked at in a 1997 study wherein the vasoconstriction threshold during nitrous oxide and sevoflurane was observed to be decreased by approximately 0.8°C in the elderly at 35.0±0.8 versus 35.8±0.3 in the young ($p < .01$).[7] This is relevant because intraoperative hypothermia has long been known to lead to adverse outcomes such as increased incidence of myocardial ischemia, arrhythmias, coagulopathic states, and wound infections.[4] In a 2014 retrospective cohort study by *Billeter et al.*[2] patients experiencing core temperatures <35°C had a four times increase in mortality with complication rates increasing two fold and incidence of stroke increasing six fold. To counter this thermoregulatory failure in patients, numerous methods of warming have been practiced over time to augment the normal body response.

One method used to decrease intraoperative hypothermia is warming patients before surgery via skin surface warmers. Numerous studies have found that even brief periods of pre-warming can improve intraoperative temperatures significantly for as long as 75-90 minutes after induction.[8,9] In procedures lasting less than 90 minutes, *Horn et al.*[10] found that as little as 10 minutes of pre-warming decreased incidence of intraoperative hypothermia from 69% to just 13% while *Torossian et al.*[11] decreased the incidence from 60% to 38% in his study using a self-warming blanket for 30 minutes pre-operatively. Studies have also shown that longer pre-warming of 45-60 minutes can prevent hypothermia for up to 2 hours after induction.[12]

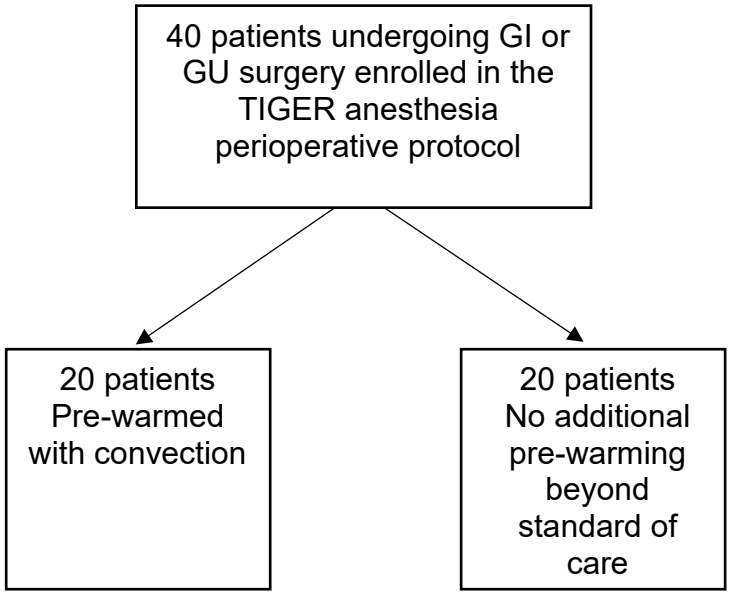
While significant research has been performed on the effects of warming patients before they undergo surgical procedures, scant evidence demonstrates the effect of pre-warming in the elderly. In one article specifically looking at pre-warming in the elderly (mean age ~72-73) it was found that, after pre-warming for 20 minutes, there was no significant change in incidence of hypothermia but there

was a significant difference in severity of hypothermia when it did occur.[13] This study focused only on men undergoing transurethral resection of the prostate however, and suffers from lack of generalizability. With the proportion of the geriatric population continuing to expand, and the potential adverse effects resulting from their increased susceptibility to intraoperative hypothermia, it is of the utmost importance to look into methods to counter this dilemma and expand the database on the topic.

Study Design:

This will be a prospective randomized clinical trial performed at a single academic hospital. Due to the nature of the trial, the anesthesiologists and subjects will not be blinded to their group assignment, but the postoperative assessments will be. All subjects will receive standardized pre-operative preparations, induction, and intraoperative infusions, as dictated by the TIGER anesthesia perioperative protocol.

In addition to these measures, one group will undergo convective warming during the preoperative preparations, completed for a minimum of 60 minutes prior to entering the operating room, while the other group will undergo standard of care, which includes providing each patient with a warming gown that is not turned on as well as blankets and sheets with more blankets provided on patient request.



Study Procedures:

I. Patient population: 40 patients undergoing gastrointestinal or genitourinary surgeries, who are enrolled in the TIGER anesthesia perioperative protocol

II. Inclusion criteria:

a. ASA I-IV
b. Other inclusion criteria as delineated in the TIGER anesthesia perioperative protocol

III. Exclusion criteria:

a. Inability to obtain written informed consent
b. Inability to obtain Foley catheter temperature recordings
c. Family history of malignant hyperthermia
d. Preoperative temperature > 38° C
e. Other exclusion criteria as delineated in the TIGER anesthesia perioperative protocol

IV. Randomization: On the day of surgery, patients will be randomized to one of two groups:

1. Warming group: This group will undergo pre-warming at a temperature of 43° C or a minimum of 60 minutes beginning upon arrival to the pre-operative room continuing until they are taken to the operating room. This will be achieved with blankets as well as the use of a Bair Hugger® heating gown.
2. Standard of care group: this group will receive the standard of care during the preoperative period, which includes providing the patient with blankets and sheets, as well as additional blankets upon request. They will also wear a Bair Hugger® heating gown, but it will not be used for preheating prior to surgery.

V. Randomization will be stratified for the type of surgery (gastrointestinal versus genitourinary) in an effort to reduce confounding.

VI. Blinding: Due to the nature of this study, the anesthesiologist, nursing staff, operating room staff, and the subject will know to which group the subject has been assigned.

VII. Anesthetic management as outlined in the enhanced recovery protocol.

VIII. Postoperative pain management as outlined in the enhanced recovery protocol.

IX. Perioperative assessments

a. Duration of pre-warming prior to surgery
b. Temperature change from arrival in the pre-operative holding area to leaving for the operating room as measured by a skin-temperature thermometer.
c. Temperature change, as measured by a Foley catheter sensor inserted, after induction of anesthesia to the end of surgical skin preparation.
d. Temperature as measured with a Foley catheter sensor throughout the operative procedure.
e. Temperature change between leaving the operating room and arrival in the Post Anesthesia Care Unit (PACU).
f. Duration of hospital stay, estimated blood loss, transfusion requirements, and postoperative complications

X. Sample size and statistical consideration:

a. This is a pilot study and, if pre-warming is successful at preventing intraoperative hypothermia, data from this study will be used to develop larger studies. We plan to enroll 20 patients per group for a total sample size of 40 subjects to obtain pilot data.
b. Data will be analyzed using chi-square and t-tests as appropriate with $p < 0.05$ considered significant.

Risks:

I. No adverse effects are currently expected through participation in this study other than possible sweating and discomfort in patients in the pre-warming group heated for more than one hour.
   a. Patients in the pre-warming group will be warned of the potential for sweating or discomfort due to warmth during informed consent at the pre-operative clinic visit. If they feel uncomfortable during the pre-warming process, staff will turn down the warmers from 43C to 38C; if symptoms persist staff will turn the warmers off.
   b. If significant adverse events other than sweating or discomfort occur, the gown will be turned off, standard of care for the event provided, and the investigators will be notified
II. All identifiable information will be kept in a secure location and will not be given to anyone unaffiliated with the University Hospital except as required by law.
   a. Despite efforts to maintain confidentiality, a small risk associated with breach of confidentiality is still present
III. There are no anticipated financial risks to patients.

Benefits:

Direct Benefit -

- In the pre-warming group, patient's may feel warmer pre- and post-operatively. Patients may also have higher temperatures throughout the day of surgery which may contribute to decreased incidence of hypothermia and it's adverse effects.

Indirect Benefit -

- Patients may benefit from taking part in this research to the extent that they are contributing to medical knowledge. The information learned from this study may benefit other patients with risk of low body temperatures during surgery in the future.

Costs:

Patients will be required to pay for any treatment considered standard of care for the procedure under which they will be going. Bair Hugger® gowns are included in standard of care measures (each patient is provided with one pre-operatively whether or not they are used) and thus using them throughout the morning, prior to surgery, does not increase cost.

Ethical Considerations:

I. Patient Expectations:
    a. This study is not double-blinded and thus patients in the experimental arm may expect improved outcomes due to participation.
    b. Expectations of improved outcomes will be managed in the pre-operative clinic setting during the informed consent process.
    c. Patients will be explicitly told that this trial measures temperatures and only a few post-operative clinical outcomes, thus they may not experience a tangible benefit.

II. Patient Comfort:
    a. Increasing pre-operative temperatures with convective heating methods may compromise patient comfort and cause sweating to occur;[14] this will be clearly explained to all patients agreeing to participate in the study during the informed consent process.
        i. If patients in the experimental arm begin to feel uncomfortable, the staff will lower the temperature of the

heating gown from 43°C to 38°C; if discomfort persists at 38°C, staff can turn the heating gown off

b. Patient comfort may be compromised by use of Foley catheter temperature sensors; this will be mitigated by insertion of catheters post-induction.
    i. Inserting Foley catheters is routine care for all of the surgeries studied in this trial and thus should not be exposing patients to the potential of more harm than is inherent in the process of surgery

III. Confidentiality:
    a. Investigators will have access to patient information and records.
    b. All paper files will be de-identified
    c. All computerized information will be de-identified and kept in files on password-secured computers in the University of Missouri Department of Anesthesiology
    d. A code key with identifiable information will be kept in a separate secure location

IV. Informed Consent:
    a. Informed consent will be obtained from all participating patients in the pre-operative clinic setting.
    b. This study is excluding vulnerable patients comprising of prisoners, minors, and those with mental disability in order to maintain the integrity of the informed consent process.

V. Managing Adverse Events:
    a. No adverse effects are currently expected through participation in this study other than possible sweating and discomfort in patients heated more than one hour.[14]
    b. If any adverse events should arise due to pre-warming measures, they will be documented in the patient's chart, disclosed to the PI, and observed in study results.

c. If any serious adverse events occur due to pre-warming measures, that interfere with or require discontinuation of said measures, patient's will be treated with the standard of care for the event and it will be disclosed to the PI immediately for review of safety.

VI. Retention of Records:

a. Paper patient records will be retained in a locked cabinet for no more than 7 years after completion of the study.
b. For retention of computerized patient records, within 1 year of completion of the study they will be printed and held in a locked cabinet for no more than 7 years after completion of the study.

VII. Gender Considerations:

a. This intervention is expected to affect both male and female patients and is not currently intended for use in only one sex.

References:

1. Centers for Disease Control and Prevention. The State of Aging and Health in America 2013. Atlanta, GA: Centers for Disease Control and Prevention, US Dept of Health and Human Services; 2013.
2. Billeter, Adrian T., et al. "Unintentional Perioperative Hypothermia Is Associated with Severe Complications and High Mortality in Elective Operations." *Surgery*, vol. 156, no. 5, 2014, pp. 1245–1252., doi:10.1016/j.surg.2014.04.024.
3. Frank SM, Beattie C, Christopherson R, et al. Epidural versus general anesthesia, ambient operating room temperatire and patient age as predictors of inadvertent hypothermia. Anesthesiology 1992; 77: 252-257.
4. Sessler, Daniel I. "Chapter 8: Preoperative Thermoregulation." *Geriatric Anesthesia*, 2nd ed., Springer, New York, NY, 2008, pp. 107–118.
5. Glosten B, Hynson J, Sessler DI, McGuire J. Preanesthetic skin-surface warming reduces redistribution hypothermia caused by epidural block. Anesth Analg. 1993; 77: 488-93.

6. Kurz A, Plattner O, Sessler DI, et al. The threshold for thermoregulatory vasoconstriction during nitrous oxide/isoflurane anesthesia is lower in elderly than young patients. Anesthesiology 1993; 79: 465-469
7. Ozaki, Makoto, et al. “The Threshold for Thermoregulatory Vasoconstriction During Nitrous Oxide/Sevoflurane Anesthesia Is Reduced in the Elderly.” *Anesthesia & Analgesia*, vol. 84, no. 5, 1997, pp. 1029–1033., doi:10.1213/00000539-199705000-00014.
8. Kim JY, Shinn H, Oh YJ, Hong YW, Kwak HJ, Kwak YL. The effect of skin surface warming during anesthesia preparation on preventing redistribution hypothermia in the early operative period of off-pump coronary artery bypass surgery. Eur J Cardiothoracic Surg. 2006; 29: 343-7.
9. Perl, T, et al. *Efficacy of a Novel Prewiring System in the Prevention of Preoperative Hypothermia. A Prospective, Randomized, Multi Center Study*. Edizioni Minerva Medica, Apr. 2014, www.minervamedica.it/en/journals/minerva-anestesiologica/article.php?cod=R02Y2014N04A0436. Accessed 2 June 2017.
10. Horn EP, Bein B, Bohm R, Steinfath M, Sahili N, Hocker J. The effect of short time periods of pre-operative warming in the prevention of peri-operative hypothermia. Anesthesia. 2012; 67: 612-7.
11. Torossian, Alexander, et al. “Active Perioperative Patient Warming Using a Self-Warming Blanket (BARRIER EasyWarm) Is Superior to Passive Thermal Insulation: a Multinational, Multicenter, Randomized Trial.” *Journal of Clinical Anesthesia*, vol. 34, 2016, pp. 547–554., doi:10.1016/j.jclinane.2016.06.030. Accessed 1 June 2017.
12. Vanni, Simone Maria Dâ€™Angelo, et al. “Preoperative Combined with Intraoperative Skin-Surface Warming Avoids Hypothermia Caused by General Anesthesia and Surgery.” *Journal of Clinical Anesthesia*, vol. 15, no. 2, 2003, pp. 119–125., doi:10.1016/s0952-8180(02)00512-3. Accessed 1 June 2017.

13. Jo, Youn Yi, et al. "Effect of preoperative forced-air warming on hypothermia in elderly patients undergoing transurethral resection of the prostate." *Urology journal* 12.5 (2015): 2366-2370.
14. Sessler DI, Schroeder M, Merrifield B, Matsukawa T, Cheng C. Optimal duration and temperature of pre-warming. Anesthesiology 1995; 82: 674-81.