Title of Project:

The Optimal Warming Strategy to Reduce Perioperative Hypothermia: A Prospective Randomized Non-Blinded Clinical Trial

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A Objectives/Purpose

This study design will answer 3 questions:

1. Is a conductive warming system (CW, HotDog Warming System, Augustine Medical, Eden Prairie, MN) similarly effective in preventing intraoperative hypothermia compared to conventional forced air warming (FAW, Bair Warming System, 3M, Maplewood, MN)?

2. Does active preoperative warming (using either FAW or CW) combined with intra-operative warming reduce intra-operative hypothermia when compared to only intraoperative active warming (using either FAW or CW)?

3. Is active preoperative warming combined with intraoperative warming using CW the current superior perioperative warming strategy?

B Hypotheses

Whit regards to the 3 respective research questions we hypothesize that:

1. Active warming with CW will be non-inferior in preventing hypothermia when compared to active warming with FAW.

2. Active preoperative warming with CW or FAW will lead to a reduction in intraoperative hypothermia when compared with only intraoperative warming with CW or FAW.

3. Active preoperative warming combined with intraoperative warming using CW is a superior strategy compared to only intra-operative warming with the CW, intraoperative warming with FAW only, or pre-operative and intra-operative warming with FAW.

C ***Background***

General and regional anesthesia can induce redistribution of core body heat and alter thermoregulation causing unintended intraoperative hypothermia. Intraoperative hypothermia is associated with several adverse effects such as: coagulopathies, increased risk of infection, cardiac arrhythmias and increased hospital length stay [1]. Maintaining a patient's temperature >36 degrees during surgery is thus essential in reducing these complications [1].

Current guidelines for maintaining intraoperative normothermia recommend the use of active intra-operative warming devices during longer surgical procedures [2]. Active warming using forced air (Bair Hugger, 3M, Maplewood, MN) has been the predominant method for intra-operative warming. Recently, it has been suggested that forced air warming is associated with an increase in perioperative surgical infections through the disruption of operating room laminar air flow and an overall warmer perioperative environment [3, 4]. These claims have never been substantiated with robust evidence [5], but have led to an increased focus on active warming technologies that do not use forced air. A new warming system has been introduced that uses an electric resistive-polymer blanket to actively warm patients (HotDog Patient Warming System, Augustine Medical, Eden Prairie, MN). This active warming system appears to be comparable in heat transfer to forced air warming [6, 7] and received initial approval from the Food and Drug Administration through a 510k pathway in 2005 [8]. The significant clinical uptake of this system warrants more systematic evaluation of its effectiveness in preventing intraoperative hypothermia.

Outside a focus on technological alternatives for forced air warming there has been a recent interest in warming strategies extending beyond the operating room. Studies are evaluating whether active preoperative warming before surgery [9], in addition to active warming during surgery, may be more effective in reducing hypothermia during surgery than intraoperative warming alone. Active preoperative warming has recently been shown to potentially reduce core hypothermia by increasing peripheral tissue temperature and decreasing the core-to-peripheral gradient [10].

The aim of the present study is to address key questions in perioperative warming strategies in anesthesiology: **1.** is the HotDog active warming system equally effective in preventing intraoperative hypothermia compared to FAW?; **2.** does active preoperative warming combined with intra-operative warming (using either FAW or CW) reduce intra-operative hypothermia when compared to only intraoperative active warming (using either FAW or CW); and **3.** is active preoperative warming combined with intraoperative warming using CW the current clinically superior perioperative warming strategy?

D Significance of the research

Intraoperative hypothermia has been associated with adverse outcomes after surgery. Active warming

using either forced air or resistive heating can be used to prevent intraoperative hypothermia. Active warming using either forced air or resistive heating can be applied only during the intraoperative period or during both the preoperative period and the intraoperative period. The present research will compare active forced air warming to resistive heating and will also compare preoperative warming combined with intraoperative to intraoperative warming only. The results of the research are expected to provide important evidence on what the most effective clinical active warming strategy is. This is significant, because active warming is used widely to prevent intraoperative hypothermia during longer surgical procedures.

E Study Design

Prospective randomized non-blinded study

F Research Plan

1 Subjects

a Number of Subjects:

We will enroll 184 participants (46 per group).

b Exclusion and Inclusion criteria:

Inclusion criteria:

- Subjects undergoing elective abdominal, gynecologic, breast surgery, plastic/reconstructive or urologic surgery under general anesthesia
- Surgery projected to last longer than 1.5 hours, but no longer than 4 hours

Exclusion criteria:

- Cardiac surgery
- Vascular surgery
- Pregnancy
- Age < 18 years
- Imprisonment
- Inability to provide written informed consent
- Inability to speak and/or read English

c Recruitment Methods:

Potentially eligible subjects will be identified by screening the surgical schedule at Cooper Hospital (main operating room, One Cooper Plaza). The patients will be approached in person at the time of arrival to the hospital.

2 Research Methods and Procedures

Devices

CW

CW consists of four primary, FDA (510k) Approved components:

- Warming Blankets,
- Warming Pads (Mattresses),
- Connecting Cables, and a
- Temperature Controller

Cooper University Hospital has access to multiple models of both the warming blankets and the warming pads (mattresses) to accommodate varying body size, height, and/or weight of patients. Each model is part of the FDA (510k) approved CW.

FAW

FAW consists of the following, FDA (510k) approved, components:

- Portable Forced-Air Temperature Management Units,
- Disposable Bair Hugger Forced-Air Blankets

Cooper University Hospital has access to multiple models of the Bair warming blankets to accommodate varying body size, height, and/or weight of patients. Each model is part of the FDA (510k) approved FAW.

Randomization and Study Arms

Using a computer generated randomization list enrolled subjects will be allocated to one of four warming strategies (Table 1) in a 1:1:1:1 ratio. We will use a block randomization for scheduled surgical stratum (1.5 h – 2.5 h and 2.5 – 4 h) and type of surgery (abdominal, gynecologic, breast surgery, plastic/reconstructive, urologic surgery) to ensure equal distribution of likely confounding variables.

Table 1. Study groups

Group	Pre-Warming	Pre-Warming Protocol Description	Intra-operative Warming
1	CW	Pre-warmed with the HotDog warming blanket for up to 30 min, 43 ° C setting	CW (HotDog System pad+warming blankets – upper or lower body)
2	Pre-warmed with FAW	Pre-warmed with Bair System (forced air). for up to 30 min, 43 ° C	FAW (Bair System - upper or lower body)
3	No Active Pre-Warming (NAPW) (warm cotton blankets allowed)	Pre-warmed with warm cotton blankets on request by the patient. If the patient does not wish to have a warm blanked placed over them, such blanket will not be used.	CW (HotDog System pad+warming blankets – upper or lower)
4	NAPW (warm cotton blankets allowed)	Pre-warmed with warm cotton blankets on request by the patient. If the patient does not wish to have a	FAW (Bair System upper or lower body)

		warm blanked placed over them, such blanket will not be used.	

Warming plan in **Group 1**: Subject will be pre-warmed with the CW. Subjects will have a HotDog warming blanket placed on their lower body in the preoperative area. The warming blanket will be connected to the temperature controller via a connection cable. The warming blanket will be set to 43° C (or 109.4° F) and will be used for at least 30 minutes prior to the subject being transferred to the operating room. We will not delay surgical cases to achieve the full 30 minutes, but we expect that with typical preoperative waiting times we will easily achieve at least 30 minutes of preoperative warming. Prior studies on preoperative warming have followed a similar preoperative warming period and approach [10]. Once in the operating room, the subject will be placed on the operating table which will have a HotDog warming pad (mattress) already on it. The underbody pad will be pre-heated to 39° C, which is the maximum allowable setting for the pad (pre-set by the manufacturer). The operation room staff will place a HotDog warming blanket over the subject after induction, which will be an upper or lower body type depending on the type of surgery set to 43 °C (or 109.4° F).

Warming plan in **Group 2:** Subjects will be pre-warmed by placing a disposable Bair Hugger Forced-Air lower body blanket on them in the preoperative area. The blanket is connected to the Portable Forced-Air Temperature Management Unit. The blanket will be set to 43° C (or 109.4° F) for at least 30 minutes prior to the subject being transferred to the operating room. We will not delay surgical cases to achieve the full 30 minutes, but we expect that with typical preoperative waiting times we will easily achieve at least 30 minutes of preoperative warming. Once the subject is in the operating room, an upper or lower body Bair Hugger blanket (depending on the type of surgery) will be applied after induction of anesthesia. The blanket will be set to 43° C (or 109.4° F).

Warming plan in **Group 3**: Subjects will be given a pre-warmed regular blanket that will cover their body in the preoperative area. Subjects may decline the warm blanket if they do not want it. Once in the operating room, the subject will be placed on the operating table which will have a HotDog warming pad (mattress) already on it. The underbody pad will be pre-heated to 39° C, which is the maximum allowable setting for the pad (pre-set by the manufacturer). The operation room staff will place a HotDog warming blanket over the subject after induction, which will be an upper or lower body type depending on the type of surgery set to 43 °C (or 109.4° F).

Warming plan in **Group 4**: Subjects will be given a pre-warmed regular blanket that will cover their body in the preoperative area. Subjects may decline the warm blanket if they do not want it. Once the subject is in the operating room, an upper or lower body Bair Hugger blanket (depending on the type of surgery) will be applied after induction of anesthesia. The blanket will be set to 43 °C (or 109.4 °F)

For all groups the operating room ambient temperature will be continuously recorded throughout the case with a portable digital thermometer.

Measurements & Data Collection

Preoperative measurements: Subject characteristics including age, sex, height weight, and surgical procedure will be collected. Subject temperature at arrival in the holding area will be measured using an oral thermometer. The duration of use of the pre-warming device will be recorded. Subject temperature just prior to leaving for the operating room will be measured using an oral thermometer.

Intraoperative measurements: An esophageal temperature probe will be used to measure subject

temperature very minute after intubation of the subject. The minute temperature data will be downloaded from the EPIC anesthesia record. The operating room temperature will be recorded every half hour.

Postoperative measurements: Subject temperature will be measured using an oral thermometer upon arrival in the post-anesthesia care unit (PACU). On postoperative day 1 we will ask subjects for their satisfaction with the warming strategy (appendix..) From the electronic medical record we will collect if unexpected intraoperative bleeding occurred, if unexpected perioperative blood transfusion occurred, if unexpected perioperative cardiac arrhythmia occurred, if unexpected myocardial ischemia or infarction occurred within 12 hours of surgery, and the length of stay in the hospital. Subjects will receive a phone call at 30 days after the day of surgery to ensure they have not been re-admitted in another facility or have been treated for any of the complications listed in the protocol.

Study outcomes

For hypothesis 1: 'Active warming with CW will be non-inferior in preventing hypothermia when compared to active warming with FAW' the intraoperative hypothermia magnitude will be the primary outcome. Hypothermia will be defined as a core temperature <36 °C and quantified as the intraoperative area under the curve (AUC) < 36 °C (units °C*hr). We will accept the hypothesis if we encounter a difference ≤ 1.0 °C*hr between the combined prewarming + intraoperative warming and the intraoperative warming only CW groups vs. the combined prewarming + intraoperative warming and the intraoperative warming only FAW groups. Secondary outcomes will be the lowest temperature measured intraoperatively, the percentage of the time of the case spent hypothermic, the absolute incidence of hypothermia, and the thermal comfort score.

For hypothesis 2: 'Active preoperative warming with CW or FAW will lead to a reduction in intraoperative hypothermia when compared with only intraoperative warming with CW or FAW' the intraoperative AUC <36 °C will be the primary outcome. We will accept the hypothesis if we encounter a statistically significant smaller AUC between the combined CW/FAW prewarming & intraoperative warming groups vs. the combined CW/FAW intraoperative warming only groups. Secondary outcomes will be the percent of case spent hypothermic, the lowest temperature measured intraoperatively, the absolute incidence of hypothermia, and the thermal comfort score.

For hypothesis 3: 'Active preoperative warming combined with intraoperative warming using CW is a clinically superior strategy compared to only intra-operative warming with the CW, only intraoperative warming with FAW, or pre-operative and intra-operative warming with FAW' the intraoperative AUC <36 °C will be the primary outcome. We will accept the hypothesis if we encounter a statistically significant smaller AUC in the active preoperative warming combined with intraoperative warming using CW group vs. only intra-operative warming with the CW, only intraoperative warming with FAW, and pre-operative and intra-operative warming with FAW. Secondary outcomes will be the percent of case spent hypothermic, the lowest temperature measured intraoperatively, the absolute incidence of hypothermia, the thermal comfort score, and the average ambient temperature in the operating room.

3 Data Analysis Plan, Statistical Tests, and Sample Size Rationale

Analysis Plan

Data will be analyzed independently of the sponsor Augustine Medical. Demographic and clinical characteristics will be presented using means with standard deviation for continuous variables and

counts with proportions for categorical variables. The distribution of potential confounding variables across the different groups will be assessed using analysis of variance and chi-squared tests. These variables include the type of surgical procedure, the length of the procedure, the duration of prewarming, the subject's BMI, and operating room ambient temperature.

The analysis will be carried out using "intention-to treat" and "per-protocol" approaches. The primary outcome of intraoperative hypothermic magnitude for the three hypotheses will be assessed by the AUC for core temperature <36 °C after the start of anesthesia until removal of the esophageal probe just prior to extubation using the 1 minute sampled intraoperative core temperature data. For subjects whose surgery extends beyond the preoperatively estimated 4 hours in duration we will use the AUC up to 4 hours into surgery. The overall incidence of hypothermia (<36 °C) will also be assessed, as well as the lowest temperature reached intraoperatively. Even though we will use stratified random sampling to pursue equal case length distribution between groups, we will also calculate the duration of hypothermia relative to the esophageal temperature measurement length as a percentage to further assess any potential influence of case length.

Prior to analysis, model residuals will be tested for normality using the Shapiro Wilk test. If the residuals are found to be not normally distributed, a normalized rank transformation will be applied prior to analysis. The AUC below 36 degrees and other continuous outcome measures will be analyzed using two way analysis of variance with factors 'Warming System' (CW, FAW) and 'Warming Timing' (preoperative warming + intraoperative warming, intraoperative warming only) with interactions. Pair-wise group comparisons using a Bonferroni adjustment will be based on the final model. Non-inferiority among the groups (hypothesis 1) will be established based on the hypothesized non-inferiority margin of 1 in the <36 ^{o}C AUC occurring in the lower bound of the 95% confidence interval of the difference in group mean. Secondary regression analyses will be conducted to assess the effect of type of surgical procedure, the length of the procedure, the duration of prewarming, the subject's BMI, and operating room ambient temperature on the AUC <36 °C. If any of these variables are significantly influencing the AUC and if they are not balanced across groups they will be included in the analyses of variance as a covariate.

Ordinal (warming comfort scores) and binary (hypothermia incidence) outcome data will be analyzed using a 2-factor linear model based on a binomial or multinomial distribution with group testing as described above.

We will accept hypothesis 1 if the 95% confidence interval of the mean AUC <36 °C of CW groups (prewarming/intraoperative warming + intraoperative warming only) does not exceed ≥ 1.0 °C*hr over the mean AUC <36 °C of FAW groups (prewarming/intraoperative warming + intraoperative warming only).

We will accept hypothesis 2 if the mean AUC < 36 °C of the preoperative warming + intraoperative warming groups (Hot Dog Warming System + FAW) is significantly smaller than the mean AUC < 36 °C of the intraoperative only warming groups (CW + FAW).

We will accept hypothesis 3 if the AUC < 36 °C in the active preoperative warming combined with intraoperative warming using CW group is significantly smaller vs. only intra-operative warming with the CW, only intraoperative warming with FAW, and pre-operative and intra-operative warming with FAW.

Power Analysis

We base our sample size estimation on hypothesis 3 because all hypotheses depend on the same

primary outcome measure (AUC <36 °C) and have the same margin (1.0 °C*hr) to assess non inferiority or superiority. Hypothesis 1 and 2 will require a smaller sample size since they can be tested using two out of the four study groups whereas hypothesis 3 will be tested using only one group vs. the other groups. A 1.0 °C*hr difference is a clinically relevant difference that manifests as a subject remaining 1.0 °C below 36 °C for an hour. Prior studies have shown hypothermia to occur in as many as 45% of patients after 100 minutes past induction with only intraoperative active warming [11].

Power for hypothesis 3: based on a standard deviation in the AUC <36° of 0.3 to 0.6 [10] and assuming similar variability in the AUC with CW [6, 7, 12], a N of 40 per group would be sufficient to detect a 1.0 °C*hr difference in AUC < 36 °C with 80% power and a p-value of 0.0083 between the prewarming + intraoperative active warming CW group vs. intra-operative warming only with the CW, intraoperative warming only with FAW, or pre-operative and intra-operative warming with FAW

We assume a 15% drop-out rate throughout the study due to potential logistical problems or subject withdrawal from the study. We will thus enroll 184 participants into this study (4 x 40 X 1.15).

J References

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