





# Effect of Aggressive Warming versus Routine Thermal Management on the Incidence of Perioperative Hypothermia in Patients Undergoing Thyroid Surgery: A Prospective, Randomized, Double-Blind Controlled Trial

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**Purpose:** Despite the implementation of various insulation measures, the incidence of hypothermia during thyroid surgery remains high. This randomized controlled study aimed to evaluate the effects of aggressive thermal management combined with resistive heating mattresses to prevent perioperative hypothermia in patients undergoing thyroid surgery.

**Patients and Methods:** 142 consecutive patients scheduled for elective thyroid surgery were enrolled in the study. They were randomly and equally allocated to the aggressive warming or routine care groups ( $n = 71$ ). The patients' body temperature was monitored before the induction of anesthesia until they returned to the ward. The primary outcome was the incidence of perioperative hypothermia. Secondary outcomes included postoperative complications, such as mortality, cardiovascular complications, wound infection, shivering, postoperative nausea and vomiting (PONV), visual analog scale (VAS) pain scores, fever, headache and hospital length of stay (LOS).

**Results:** In our study, the results showed that a significantly higher rate of hypothermia was observed in the routine care group compared with the aggressive warming group. The incidence of perioperative hypothermia was 19.72% (14/71) in the aggressive warming group and 35.21% (25/71) in the routine care group ( $P < 0.05$ ). The incidence of shivering in the aggressive warming group (1.41%) was significantly lower than that in the routine care group (11.27%) ( $P < 0.05$ ), and a one-day reduction in hospital length of stay was observed in the aggressive warming group ( $P < 0.05$ ). There was no significant difference in mortality or other postoperative complications, such as cardiovascular complications, wound infection, PONV, pain, fever or headache, between the two groups ( $P > 0.05$ ).

**Conclusion:** Our results suggest that aggressive thermal management combined with resistive heating mattresses provided improved perioperative body temperature and reduced the incidence of perioperative hypothermia and shivering compared to routine thermal management.

## Plain Language Summary:

- The incidence of perioperative hypothermia during thyroid surgery was high.
- The use of resistive heating mattresses during thyroid surgery can effectively reduce the occurrence of perioperative hypothermia.
- It is recommended to take aggressive thermal protection during the operation of minor and medium surgeries, and to continuously monitor the temperature.

**Keywords:** hypothermia, thyroid surgery, resistive heating mattresses, perioperative period



## Introduction

The significance of body temperature as one of the vital signs is increasingly being recognized. The normal body temperature range is typically stated as 36.5 to 37.5°C.<sup>1</sup> Perioperative hypothermia is defined as a core temperature of less than 36°C during the preoperative, intraoperative, and postoperative periods.<sup>2</sup> The incidence of perioperative hypothermia in patients undergoing elective surgery ranges from 26% to 90%.<sup>3,4</sup> However, not much focus is placed on perioperative temperature protection. According to a European survey on intraoperative patient warming, only 40% of patients under general anesthesia were warmed intraoperatively, and only 20% of the patients had temperature monitored.<sup>5,6</sup> A similar situation occurred in Beijing hospitals, showing a high incidence of inadvertent intraoperative hypothermia and a low rate of aggressive intraoperative warming and monitoring.<sup>7</sup> Numerous adverse outcomes have been linked to perioperative hypothermia, including morbid myocardial outcomes,<sup>8</sup> coagulopathy,<sup>9</sup> surgical site infections, shivering, and prolonged hospital stay.<sup>10</sup>

The occurrence of perioperative hypothermia may be related to the operation time > two hour, the intraoperative blood loss, the size of surgical wound, the use of anesthetic drugs, an age of > 60 years, or a low body mass index (BMI).<sup>2,11,12</sup> Current research on hypothermia primarily focuses on high-risk patients or specific types of surgery, such as hip replacement and thoracic surgeries.<sup>13</sup> The thermal management of thyroid surgery is often overlooked because of its small incisions, less trauma, and less bleeding. Under general anesthesia, anesthetic drugs contributed significantly to the development of hypothermia, particularly within 60 minutes of onset of anesthesia induction.<sup>14</sup> This phenomenon is caused by impairment of thermoregulation due to anesthesia, which significantly lowers the thresholds of shivering and vasoconstriction.<sup>15,16</sup>

Thyroid surgery is one of the most common operations among head and neck surgeries.<sup>17</sup> It is controversial whether perioperative thermal management is necessary during thyroid surgery. Some researchers think aggressive thermal management during such minor surgeries will cause overprotection of the body, resulting in hyperthermia. However, according to previous studies, the incidence of hypothermia can still be as high as 25%, even during outpatient plastic surgery.<sup>18</sup> Meanwhile, we have observed that many patients in our post-anesthesia care unit (PACU) are experiencing cold after thyroid surgery, either with or without shivering, despite a single-layer cotton blanket to keep them warm. After thyroid surgery, postoperative shivering caused by the cold may contribute to the disturbance of the intracellular environment and metabolism, resulting in poor outcomes.<sup>19</sup> Therefore, this randomized controlled trial aimed to evaluate the effect of aggressive thermal management combined with resistive heating mattresses on the incidence of perioperative hypothermia in patients who underwent thyroid surgery.

## Methods

### Participants

From February 1, 2023, to June 30, 2023, consecutive patients scheduled for elective thyroid surgery were enrolled in the study. The inclusion criteria included (1) age of 18–65 years, (2) elective thyroid surgery, (3) American Society of Anesthesiologists (ASA) classification of I–III, (4) BMI < 30 kg/m<sup>2</sup>, and (5) at least half of the dorsal skin tissue can be used for warming.

Exclusion criteria were as follows: (1) history of thyroid surgery, (2) preoperative hyperthermia (body temperature greater than 37.2°C), and (3) infectious disease. All participants signed informed consent forms.

### Randomization and Masking

After enrollment in the study, patients were randomly divided into 2 groups (routine care group and aggressive warming group). The randomization was conducted using computer-generated numbers and then sealed in an envelope. Before surgery, a nurse who was unaware of the details of the study opened a sealed envelope randomly and allocated the patient to the control or intervention group. The patients, anesthesiologists, and outcome assessors were blinded to the randomization result.

## General Procedure

All patients underwent general anesthesia with endotracheal intubation. Before the procedure, patients fasted overnight (at least six hours). On arrival in the operating room, the patients were routinely monitored with electrocardiograph (ECG), noninvasive blood pressure, pulse oximeter saturation (SpO<sub>2</sub>), and opened peripheral venous access. In this study, a standardized anesthetic protocol was used for all patients, including midazolam (0.02–0.04 mg<sup>-1</sup>.kg<sup>-1</sup>), propofol (1.5–2.5 mg<sup>-1</sup>.kg<sup>-1</sup>), sufentanil (0.2–0.3 µg<sup>-1</sup>.kg<sup>-1</sup>), cisatracurium (1.5–2.5 mg<sup>-1</sup>.kg<sup>-1</sup>) and methylprednisolone (40 mg). Endotracheal intubation was performed after two to three minutes. The ventilation parameters were set as follows: Volume-controlled ventilation was maintained with a tidal volume of 6–8 mL<sup>-1</sup>.kg<sup>-1</sup>, an inhaled oxygen concentration of 80%, an inspiratory/expiratory ratio of 1:2, and the respiratory rate was adjusted to maintain a carbon dioxide partial pressure of 35 to 45 mmHg during end-expiration. Anesthesia was maintained by continuous IV infusions of propofol (3–5 mg<sup>-1</sup>.kg<sup>-1</sup>.h<sup>-1</sup>), remifentanil (0.5–1 g<sup>-1</sup>.kg<sup>-1</sup>.h<sup>-1</sup>), and inhaled sevoflurane (1–2%). At the end of the surgery, neostigmine was used to reverse neuromuscular block and flumazenil was used to antagonize benzodiazepine residue. After the patient's respiratory and conscious recovery, the endotracheal tube was removed and the patient was transferred to the PACU.

## Temperature Monitoring and Perioperative Warming Strategies

Wireless thermometers connected to smartphones and iPads (iThermonitor; model WT705, Raiing Medical Company, Beijing, China) were used to monitor axillary temperature (monitoring every 4 seconds) throughout the surgery. iThermonitor was attached to the axilla with a hypoallergenic patch to avoid displacement. This device was approved by the FDA as a class II medical device.

The temperature of the operation room was maintained at 23 ± 1°C with relative humidity ranging from 40%–60%.<sup>20</sup> All patients arrived in the operating room covered with a single-layer cotton blanket and monitored body temperature. All operating tables are equipped with resistive heating mattresses. Before the induction of anesthesia, patients assigned to the aggressive warming group were covered with a single-layer cotton blanket and warmed using a resistive heating mattress (ASTOPAD OPT 100/104, Stihler Electronic GmbH, Germany) set to 37°C. In contrast, patients in the routine care group were only covered with a single-layer cotton blanket, and the resistive heating mattresses were not activated unless the core temperature decreased below 35.5°C. For both groups, all intravenous fluids were kept in an incubator (MIR-162; Sanyo, Osaka, Japan) heated to body temperature.

## Outcomes and Postoperative Evaluation

The perioperative demographic characteristics of each patient were recorded, including age, sex, weight, height, ASA and the duration of surgery. The primary outcome was the incidence of perioperative hypothermia. Preoperative hypothermia is defined as a temperature of <36°C one hour before anesthesia induction. Intraoperative hypothermia is defined as a temperature of <36°C for more than 30 minutes from the first anesthesia intervention to the patient's transfer to the PACU. Postoperative hypothermia is defined as a temperature of <36°C at any time within the first 24 hours after the patient is transferred to the PACU or the ward. Secondary outcomes included postoperative complications, such as mortality, cardiovascular complications, wound infection, shivering, postoperative nausea and vomiting (PONV), visual analog scale (VAS) pain scores, fever, headache and hospital length of stay (LOS). Postoperative mortality was defined as in-hospital mortality. Cardiovascular complications included cardiac failure after surgery, arrhythmia and acute coronary syndrome. Any postoperative complications and adverse events were recorded at any time. If the patient developed shivering, intravenous tramadol (1 mg<sup>-1</sup>.kg<sup>-1</sup>) was administered. Other outcomes were monitored within 24 hours postoperatively.

## Statistical methods

The sample size was calculated based on the results of a previous study. The incidence of intraoperative hypothermia is 39.9%,<sup>7</sup> with an 18% reduction in the incidence of intraoperative hypothermia in patients receiving aggressive thermal

management. With a target sample size of 64 patients per group ( $\alpha = 0.05$ ,  $\beta = 0.8$ ; PASS 11.0, NCSS Statistical and Data Analysis, USA) and considering a dropout rate of 10%, at least 71 patients were required in each group.

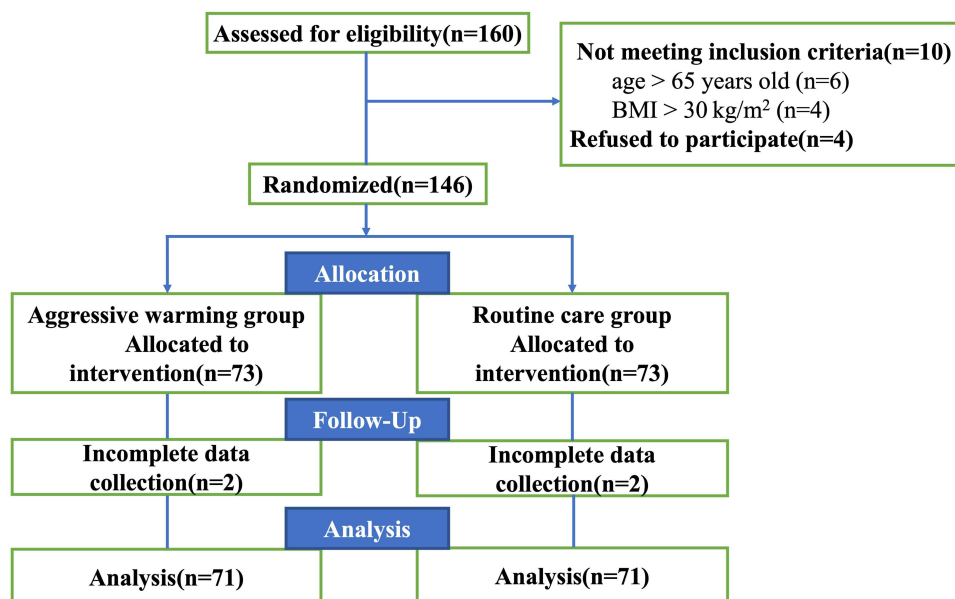
The homogeneity of variance was examined using the Levene test. Normally distributed data were expressed as mean  $\pm$  SEM, while non-normally distributed data were expressed as median and interquartile range. The categorical data were expressed as the number of cases (n) and the percentage of cases. For continuous variable data, the comparisons were performed using repeated measures of analysis of variance (ANOVA). Non-normally distributed data were analyzed using non-parametric tests (Mann–Whitney test, Kruskal–Wallis test), and categorical variables were compared using the chi-squared test. In this study,  $P$  value  $< 0.05$  was considered statistically significant. Statistical analysis was performed with SPSS (version 26.0, SPSS Inc., Chicago, IL, USA).

## Results

A total of 160 patients were screened. 10 patients were excluded because they did not meet the inclusion criteria and 4 patients refused to participate. Ultimately, 146 patients were enrolled and randomly assigned to either group: 73 patients were allocated to the aggressive warming group and 73 to the routine care group. However, two patients were lost to follow-up in each group due to missing perioperative body temperature data. Therefore, 142 patients completed the study (71 in each group). Patient screening, enrollment, and follow-up were displayed in Figure 1.

No significant difference was observed with respect to demographic variables (age, sex, weight, height, BMI), duration of surgery, and duration of anesthesia between the two groups (Table 1).

The incidence of perioperative hypothermia was 19.72% (14/71) in the aggressive warming group and 35.21% (25/71) in the routine care group ( $P < 0.05$ ) (Table 2). A steady decline in the Figure 2 was observed in both groups up to 60 minutes after induction of anesthesia. A gradual increase in temperature was observed in the aggressive warming group after 60 minutes, while it continued to decrease in the routine care group. From 60 minutes onward, a statistically significant difference was observed between the two groups ( $P < 0.05$ , Figure 2). Figure 3 showed the relative distribution of temperatures within each 30-minute interval of anesthesia. There was no significant difference in body temperature between the two groups at the start of the operation ( $P = 0.886$ ,  $P = 0.291$ ), while significant differences were observed in all other time periods. Furthermore, the incidence of hypothermia in the aggressive warming group gradually decreased after 60 minutes, while the incidence of hypothermia in the routine care group slowly increased. The



**Figure 1** Flow diagram showing screening, enrollment, randomization, and follow-up of study patients.

**Table 1** Patients' Baseline Characteristics and Surgical Characteristics

	<b>Aggressive Warming(n=71)</b>	<b>Routine Care (n=71)</b>	<b>P</b>
Gender			0.347
Female	54(76%)	49(69%)	
Men	17(24%)	22(31%)	
Age (y)	40(32–52)	41(32–53)	0.649
Height (cm)	164(160–170)	164(160–170.5)	0.799
Weight (kg)	65(60–70)	65(58–76)	0.400
BMI (kg/m <sup>2</sup> )	25.54±4.27	24.54±4.06	0.582
ASA			0.004
I	30(42.25%)	49(69.01%)	
II	37(52.11%)	18(25.35%)	
III	4(5.63%)	4(5.63%)	
Duration of surgery (minute)	140(119–230)	146(119–205)	0.951
Duration of anesthesia (minute)	168(153–237)	177(146–234)	0.674

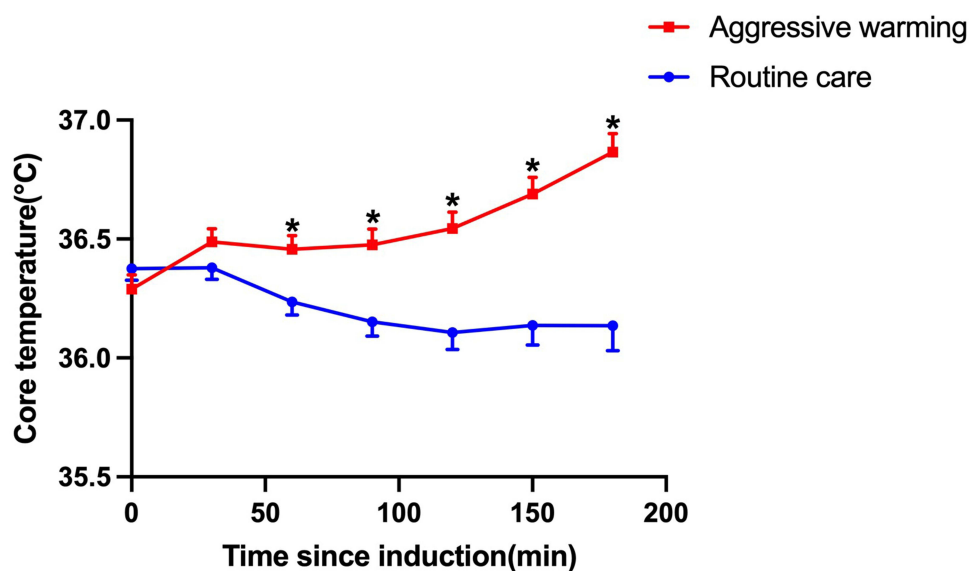
**Notes:** values are expressed as n (%), mean [range]. *p* < 0.05 indicates a statistically significant difference.  
**Abbreviations:** BMI, body mass index; ASA, American Society of Anesthesiologists.

**Table 2** Perioperative Inadvertent Hypothermia

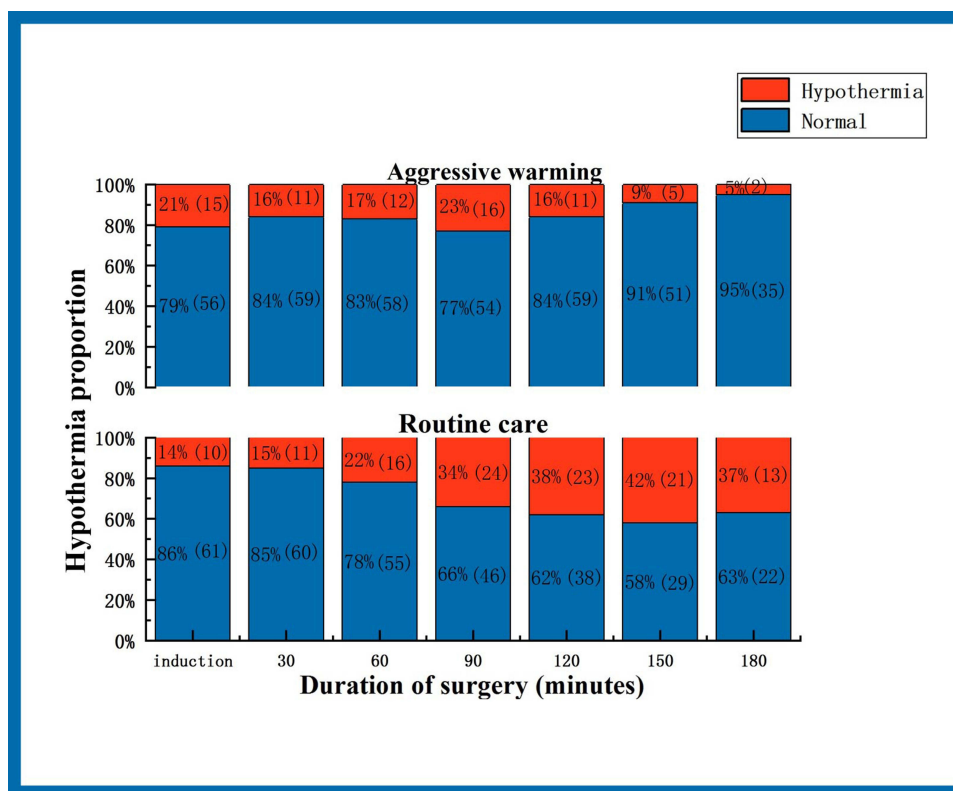
	<b>Group</b>				<b>P</b>
	<b>Aggressive warming (n=71)</b>		<b>Routine care (n=71)</b>		
	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>	
Hypothermia	14	19.72	25	35.21	0.039
Normothermia	57	80.28	46	64.79	

**Notes:** The variables are presented as number of patients, n (%). *p* < 0.05 indicates a statistically significant difference.

body temperature of the two groups showed a statistically significant difference from 60 minutes after induction until the end of the operation (*P* < 0.05). However, there was no significant difference in body temperature between the two groups after returning to the ward (*P* =0.506) (Table 3).



**Figure 2** Serial changes in patients' core temperatures during surgery. Values are the mean minus the standard error of the mean. Time 0 is the time of general anesthesia. Body temperatures differed significantly between routine care and aggressive warming after 60 minutes of general anesthesia induction (\**p* < 0.001).



**Figure 3** Incidence of perioperative hypothermia (< 36°C) within each 30-min interval. There was an overall increased risk for hypothermia during general anesthesia in the routine care group.

The results of the postoperative follow-up indicated that the incidence of shivering in the aggressive warming group (1.41%) was significantly lower than in the routine care group (11.27%) ( $P < 0.05$ ). The duration of hospitalization was 8 (7–9) days in the routine care group and 7 (5–7) days in the aggressive warming group ( $P < 0.001$ ), showing a significant one-day reduction in hospital length of stay in the aggressive warming group ( $P < 0.05$ ) (Table 4). In contrast, there was no significant difference in mortality or other postoperative complications, such as cardiovascular complications, wound infection, pain, PONV, fever or headache, between the two groups ( $P > 0.05$ ) (Table 4).

## Discussion

The results of our study demonstrated that aggressive thermal management combined with resistive heating mattresses could improve the perioperative core temperature in patients undergoing thyroid surgery, thereby reducing the incidence of perioperative hypothermia and postoperative shivering. In addition, an aggressive warming strategy may shorten the length of the hospital stay. However, perioperative hypothermia cannot be completely prevented. Perioperative inadvertent hypothermia represents a negative experience for patients, feeling cold and shivering after surgery is not life-

**Table 3** Core Temperature Values of the Patients in the Perioperative Period

	Start of operation (°C)	Intra-op 30 min (°C)	Intra-op 60 min (°C)	Intra-op 90 min (°C)	Intra-op 120 min (°C)	Intra-op 150 min (°C)	Intra-op 180 min (°C)	Post-op (°C)	P
	MD ± SEM	MD ± SEM	MD ± SEM	MD ± SEM	MD ± SEM	MD ± SEM	MD ± SEM	MD ± SEM	
Aggressive warming	36.29 ± 0.06	36.49 ± 0.06	36.46 ± 0.06	36.48 ± 0.07	36.54 ± 0.07	36.69 ± 0.07	36.87 ± 0.08	36.88 ± 0.04	0.0003
Routine care	36.38 ± 0.05	36.38 ± 0.05	36.24 ± 0.06	36.15 ± 0.06	36.11 ± 0.07	36.14 ± 0.08	36.14 ± 0.10	36.78 ± 0.03	
P	0.886	0.291	0.004	0.003	0.001	< 0.001	< 0.001	0.506	

**Notes:** Data are the mean ± SEM.  $p < 0.05$  indicates a statistically significant difference. The difference between two groups after intraoperative 60 minutes is significant.



**Table 4** Secondary Outcomes

	<b>Aggressive Warming(n=71)</b>	<b>Routine Care(n=71)</b>	<b>P</b>
Mortality	0	0	1
Cardiovascular complications	0	0	1
Wound infection	5(7.04%)	5(7.04%)	1
Shivering	1(1.41%)	8(11.27%)	0.033
Hospital length of stay (days)	7(5–7)	8(7–9)	0.000
PONV	19(26.76%)	12(16.90%)	0.155
VAS score	1(0–1)	1(0–2)	0.867
Fever	2(2.81%)	3(4.23%)	1.000
Headache	14(19.71%)	16(22.53%)	0.681

**Notes:** Values are expressed as n (%), mean [range].  $p < 0.05$  indicates a statistically significant difference.

**Abbreviations:** PONV, postoperative nausea and vomiting; VAS score, visual analogue scale score.

threatening, nor are pain or nausea and vomiting, but memories of postoperative thermal discomfort remain intense for years after surgery.<sup>16</sup>

Based on our findings (Table 2), the incidence of perioperative hypothermia was significantly lower in the aggressive warming group than in the routine care group (19.72% vs 35.21%). Our results are consistent with previous studies focus on minor surgeries, such as outpatient plastic surgery. In a clinical investigation that compared forced-air-warming blankets and self-warming techniques in the context of outpatient plastic surgery, 47% of patients experienced hypothermia after surgery, and 25% of patients experienced hypothermia despite the utilization of warming measure.<sup>18</sup> Meanwhile, compared with some studies focus on major surgeries, they reported that the incidence of perioperative hypothermia in total knee and total hip arthroplasty is about 26.3% and 28.0%, which is no higher than our results.<sup>21</sup> The above results demonstrate that the thyroid surgery, which little skin exposure is required, and little blood loss occurs during the procedure, the incidence of perioperative hypothermia is not low and cannot be completely avoided even with resistive heating mattresses. Therefore, we advocate that the use of aggressive thermal management is necessary in minor and medium-sized operations.

According to the temperature curve drawn from the continuous measurement (Figure 2), a rapid decrease in core temperature occurs within the first hour, which is consistent with most previous studies. The core temperature decreased by approximately 1–1.5°C during the first hour after induction of anaesthesia, with a mean body temperature of 35.8°C.<sup>12</sup> This can be attributed to the vasodilation induced by the anaesthetic, which facilitates the redistribution of heat to the peripheral regions. The body temperature gradually decreased within 60 minutes following anesthesia induction and then slowly increased and leveled off gradually in the aggressive warming group, while the body temperature continued to decrease more significantly from the induction of anesthesia until the end of surgery in the routine care group. After 90 minutes of general anesthesia induction, the aggressive warming group had a greater number of patients who reached a state of thermal equilibrium between heat loss and production as compared to the routine care group (Figure 3). Based on our data, the use of a resistive heating mattress before induction can reduce the inevitable drop in body temperature caused by anesthetics. Therefore, it is necessary to have aggressive thermal management before anesthesia induction. In addition, we found that the body temperature showed a continuous increasing trend with aggressive warming, even finally it did not exceed the upper range of normal temperature, which may be attributed to the fact that average duration of surgery is less than 200 minutes. Therefore, continuous temperature monitoring is required to prevent overheating during aggressive warming.

Perioperative hypothermia often leads to adverse outcomes. Shivering is one of the common complications after anesthesia. Previous research confirmed that most anesthetics lower shivering thresholds, reducing the patient's sensitivity to hypothermia.<sup>16,22</sup> Research has demonstrated that postoperative shivering can elevate total body oxygen consumption by up to 300–400%,<sup>23</sup> thereby contributing to the disorders of the intracellular environment and metabolism

occurrence of thyroid surgery and eventually leading to a poor prognosis. Our study found that the incidence of shivering after thyroid surgery is relatively high, which can be greatly reduced by implementation of aggressive warming. This finding is in accordance with prior research.<sup>24</sup> A recent study revealed that aggressive warming management could reduce the incidence of postoperative shivering from 31.75% to 14.06% in patients under general anesthesia.<sup>25</sup> Postoperative shivering is highly uncomfortable for patients. While pharmacological interventions can be applied to alleviate symptoms, preventative measures should be prioritized. Interestingly, we found a significantly shorter length of hospital stay in the aggressive warming group. However, despite the significant difference, other factors may have contributed to this result, and further experiments are required to validate this finding. These results may suggest that aggressive thermal management may be more beneficial to the postoperative recovery of patients.

The body temperature protection measures mainly include active heat preservation and passive heat preservation. Currently, three main types of heating methods are used: forced air,<sup>26</sup> resistive heating mattresses,<sup>27</sup> and circulating water.<sup>28</sup> A majority of patients undergoing surgery are actively warmed from the skin surface. The skin surface is easily accessible and can be safely warmed, and most of the body heat is lost through the skin, highlighting the viability of this approach. Some studies reported that resistive heating can maintain intraoperative normothermia as effectively as forced air heating.<sup>29–31</sup> Resistive heating mattresses were used in this study, providing an effective, inexpensive, and easy-to-use method for many patients and surgeries. The core temperature can be precisely detected by inserting a temperature probe into the esophagus or bladder.<sup>32</sup> However, there is no requirement for temperature monitoring at the bladder during thyroid surgery or other minor surgeries, and these devices may result in an increase in infection risks. In our study, a novel wireless axillary thermometer, the iThermonitor, was used to measure the body temperature. The axillary temperature recorded by the iThermonitor WT701 was reported to accurately represent the core temperature in adults undergoing noncardiac surgery<sup>33</sup> and was monitored in real time. And with the iThermonitor, all patients felt more comfortable and daily activities were not affected.<sup>34</sup>

Nevertheless, the limitations of the current study should be acknowledged. One is that our aggressive warming strategies did not take longer pre-warming strategy. The combination of intraoperative and preoperative warming would further enhance warming efficacy.<sup>35</sup> The short interval between surgeries did not allow for preoperative warming, but warming was initiated as early as possible. In addition, this study only examined the patients of 18–60 years, and BMI less than 30 kg/m<sup>2</sup>. This study excluded older patients and children, as well as patients with abnormally high BMI, so the impact of age and BMI on hypothermia remains unclear. Further research is needed to identify other factors involved in the occurrence of hypothermia. The last limitation of this study is that the perioperative warming effects were only studied in thyroid surgery. Therefore, the results in this article are only applicable to patients undergoing thyroid surgery. The objective of this study was to examine the management of perioperative temperature in minor surgical procedures, with the intention of establishing a foundation for future investigations.

## Conclusion

In conclusion, the results of this study should increase awareness concerning the risk of hypothermia during thyroid surgery. Aggressive thermal management combined with resistive heating mattresses could improve perioperative body temperature compared to routine thermal management, and reduce the incidence of perioperative hypothermia and postoperative shivering. Still, neither method could completely prevent inadvertent perioperative hypothermia.

## Data Sharing Statement

The data are not available to the general public due to the regulations of our institution, but they are available to researchers on reasonable request by emailing Yue Zhang (zhangyue971019@163.com).

## Ethics Statement

This prospective, randomized, double-blinded study was conducted in accordance with the Declaration of Helsinki. Ethical approval for this study was provided by the Beijing Tongren Hospital, Capital Medical University Ethics Committee (No. TREC2022-KY115). This trial was registered with the Chinese Clinical Trial Registry (No. chiCTR2300068190).



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## Author Contributions

Yue Zhang, Yafan Bai, Yi Zhang, Yingjie Du, Min Liu, Jiayu Zhu, and Guyan Wang made significant contributions to the reported work, whether in terms of conception, study design, implementation, data collection, analysis, and interpretation, or across all these areas. They have drafted, written, substantially revised, or critically reviewed the article. They have also reached a consensus on the journal to which the article will be submitted. All the authors mentioned above have reviewed and approved all versions of the article before submission, during revision, and at the proofing stage, and they are accountable for the contents of the article.

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## Disclosure

The authors declare no competing interests in this work.

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