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RESEARCH ARTICLE

COMPARING ECONOMIC BENEFITS FOR PATIENTS USING ACTIVE V.S. PASSIVE WARMING SYSTEM UNDERGOING MAJOR SURGERIES: A PROTOCOL OF RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background: Incidence rate of intra-operative hypothermia during surgeries is estimated to be around 40% in China, causing damages as cardiovascular complications and also increase costs due to treatment for adverse reactions and prolonged hospital stay. However in current stage, hypothermia and effective warming measurements are attached with relatively low importance in aesthesia procedures. This study aims to compare the potential economic benefits for patients using active warming system during major surgeries.

Methods: A randomized controlled open-label trial was design in Beijing, China. Target population were patients undergoing surgeries. A total of 240 patients receiving Pancreatectomy and Esophagectomy were randomized into active warming group (using forced air warming system) and passive warming group (using cotton blanket). Health outcomes as incidence of intra-operative hypothermia and adverse clinical events including surgical site infection would be observed, and costs following these events would be measured. Economic benefit would be analyzed using cost-consequence analysis and cost-utility analysis between two groups. Incremental cost-utility ratio would be used for decision-making.

Discussion: Economical evaluation evidence application in insurance entry for pharmaceuticals and medical devices is in its early stage in China. This study may help to provide as a template for trial-based economical evaluation for medical devices. We also hope to promote discussion on proper use of cost-consequences analysis which is less often applied but with high appropriateness in economical evaluation studies for medical devices.

Trial registration: Trial registration: This trial was registered on the Chinese Clinical Trial Registry (ChiCTR) on 2017/4/9. ChiCTR is one of the primary registries in the WHO Registry Network. Trial registry number: ChiCTR-IPR-17011099. http://www.chictr.org.c n/edit.aspx?pid=18892&htm=4

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INTRODUCTION

Intra-operative hypothermia occurs when the core body temperature falls below 36℃, the incidence rate of which can be as high as 90% worldwide (Burger, 2009). Intra-operative hypothermia mainly damages the function of coagulation, leading to increased bleeding capacity along with the possibility of an increased wound infection rate, delayed post-operative recovery, and cardiovascular complications (de Brito, 2013). Therefore, according to the National Institute for Health and Care Excellence, Association of Perioperative Registered Nurses, and other international organizations, measures to keep warm during surgery are recommended, especially for patients about to undergo major surgery. An epidemiology study was conducted in 2015, showing that the incidence rate of intra-operative was estimated to be 39.9%-44.5% during in China.

Active warming system was a useful protection for preventing hypothermia (OR = 0.46, 95% CI 0.26-0.81), however only

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14.2% of the patients received active warming protection (Yi, 2017). The study also indicated that hypothermia is associated with more postoperative shivering, increased ICU admissions, and longer postoperative hospital days. The present methods of thermal retardation consists of active and passive maneuvers, including quilt supplies, liquid heating, body wrapping, medical insulation blankets, moist dressing heat, forced air warming, and washing liquid heating. Forced air warming (FAW) belongs to the active thermal retardation. FAW increases the total body heat and offsets the heat dissipation in order to retard the temperature loss possibly caused by the temperature redistribution effect during conventional warm nursing.FAW is primarily applied in obstetrics and gynecologic surgery (mainly cesarean sections) (Oshvandi, 2014; Adriani, 2013), plastic surgery, orthopedics surgery (Sikka, 2014), shoulder arthroscopic surgery (Yoo, 2009), open surgery (Egan, 2011; Leung, 2007; Zhao, 2015),laparoscopic cholecystectomy (Wong, 2004), cardiovascular surgery (Insler 2016), prostate removal (Torrie, 2005), and other major surgeries worldwide.

In a clinical control study, Borms *et al.* (1994) utilized a FAW Bair Hugger™ and reflective insulation material to evaluate the thermal retardation effect during total hip replacement (RCT/N=20). The results indicated that the FAW Bair Hugger™ achieved better intra-operative normothermia than reflective insulation material (Borms, 1994). Rembert *et al.* (2004) compared three types of active heat preservation measures (FAW, circulating-water blanket, and infrared thermal emitter) with the physical heating effect of a traditional heating measure. FAW showed a favorable effect on the heating rate or heating temperature compared to common heat preservation measures (Rembert, 2004). Trentman *et al.* (2009) compared the effect of thermal retardation during unilateral total knee arthroplasty (trial/N=55) between a VitalHeat body temperature management system (through conduction heating of the circulating water) and the Bair Hugger™ forced air warming system. The results showed that VitalHeat was not superior to Bair Hugger™ in preservation of sublingual temperature and intra-operative esophageal temperature (Trentman, 2009). Roder *et al.* (2011) evaluated the heating effect on patients with low body temperature undergoing maxillary tumor removal (RCT/N=28) in comparison with Bair Hugger™ and HotDog® resistive heating. The data revealed that the temperature rate of Bair Hugger™ was twice that of HotDog® ($P<0.001$) (Roder 2001). Kim *et al.* (2014) determined no significant difference between FAW and the circulating-water mattress method (RCT/N=46) in the function of core temperature conservation during general anesthesia in elderly total knee arthroplasty. FAW was more effective in reducing the occurrence and intensity of post-anesthesia shivering (Kim *et al*., 2014).

However, studies also reported that FAW exhibited no advantages in reducing intra-operative hypothermia (Ng, 2006), shortening peri-operative period / low temperature after anesthesia (Borms *et al*., 1994; Fettes, 2013), and decreasing bacterial infection compared with traditional insulation measures, such as an electric blanket (Occhipinti, 2013). The potential adverse events were also reported using FAW, including surgical incision infection add hidden danger in clean air ventilation (Augustine, 2014; Wood *et al*., 2014).Taken together, our comprehensive research demonstrated the following: first, the studies of FAW mainly focused on clinical research, although there are disagreements in the thermal retardation effect, but most of the research tends to hold the point of view that active thermal insulation is better than passive thermal insulation; and second, in active thermal insulation, FAW is the mainstream and more effective method, but some adverse events also occur (Poveda *et al*., 2012). Current warming procedure in China is simple and crude. Most of the hospitals use cotton sheet or blanket for patient warming during major surgeries. This study aims to compare both the clinical and economic benefits using active warming systems compared to passive warming procedures for patients undergoing major surgeries in China.

METHODS

Study aim

This study aims to compare the economic benefits of patients who undergo major surgeries using active forced air warming system and traditional passive warming system.

Trial design

The study is a randomized, controlled, open label, parallel two-arm, single-center clinical trial. To determine economic benefits of maintaining normothermia through Active Forced Air Warming System in patients undergoing major surgeries, we observe critical clinical endpoints directly related to hypothermia and evaluate the costs resulting by these consequence compared to standard of care.

Setting and location

The trial would be conducted in Department of Anesthesiology, Peking Union Medical College Hospital (PUMCH).PUMCH is one of the leading hospitals in China with around 2,000 beds and discharge over 950,000 patients yearly. Patients undergo major surgeries will normally be admitted into Department of Anesthesiology on the date of the surgery and discharged to Post-anesthesia Care Unit (PACU) to stay being observed for 10-60 minutes after ceasing anesthesia, and then they will be transferred to the wardor the Intensive Care Unit (ICU) if necessary. Within a certain period of stay (usually 7-60 days), the patients will be discharged from the hospital and take a further visit by appointment. The average length of stay depends on the recovery progress and severity of the diseases. The frequency of after-discharge visits is related to the risks of infection and other adverse reactions.

Target population

This study planned to enroll approximately 240 patients. Pancreatectomy and Esophagectomywere selected by the anesthetists and cliniciansfor following reasons: 1)incidences of hypothermia are relatively high in Pancreatectomy and Esophagectomy, and maintain normothermia have high clinical significance; 2) PUMCH has a leading position in these two surgeries in China and could meet the sample size requirement.

Inclusion Criteria: 1) Adult patients≥18 years old; 2) Preoperative core temperature between 36.0 and 37.5°C; 3) ASA (American Society of Anesthesiologists) Physical Status Classification System scoring from I to III; 4)One of the following elective major surgeries: Pancreatectomy, Esophagectomy.

Exclusion Criteria: 1) Uncontrolled insulin-dependent diabetes mellitus (preoperative glucose >250 mg/dL); 2) Hyperthyroidism and hypothyroidism; 3) Raynaud disease; 4) History of infection and fever within 4 weeks before surgery; 5) Use of steroid or immunosuppressant within 4 weeks before surgery; 6) History of bleeding disorders; 7) Clinically significant laboratory abnormalities (at least one of the followings): Hgb ≤ 10.0 g/dL; Platelets≤100,000/mL; WBC <3000/dL or >14,000/dL; Fibrinogen<200mg/dL; Thromboplastic time>40s, or Prothrombin time (INR<70%) (Normal range is 70%-140%).

Randomization and patient enrollment

Randomization

Randomization process will be conducted on the date when participants are sent to department of anesthesiology. Candidate patients will be screened by fully trained clinical research coordinators (CRC). Informed Consent Form (ICF) will be signed by patients or their legally authorized representatives (e.g. family member) and all inclusion/exclusion criteria must be met upon patient enrollment. Eligible participants will then be assigned into treatment/control group by sealed envelopes containing numbers. Odd numbers indicate assignment of active warming system group and vice versa.

Patient withdrawal

The patient has the right to withdraw from the study at any time without penalty or loss of benefit, otherwise they shall remain in the clinical trial until the end of follow-up. Conceivable reasons for discontinuation may include, but not be limited to, the following: 1) death; 2) voluntary withdrawal; 3) withdrawal under the discretion of investigator who propose the study termination.

Termination

Specific instances that may precipitate termination include the following:1) unsatisfactory patient enrollment; 2) failure to comply with protocol; 3) failure to comply with applicable CFDA guidelines; 4) inaccurate and/or incomplete data recording on a recurrent basis.

Sample size Estimation

Based on preliminary results from pilot study and previous references (see Tab. 1), we estimated the sample size using estimation for comparison of proportions/means. Statistical power of 80% and significant levelα=0.05 were applied. The SSI was cited from literature reference and other outcomes are all from pilot study. Surgeries in this study were confined to contaminated surgeries. Bound by the budget restraint, we finally decided the minimum sample size to be 116 /arm and 232 in total (see Tab. 2). Considering there are two types of surgery, we plan to conduct an interim analysis to see if there is enough statistical power to do sub-group analysis.

Comparators

Treatment group

Patients in the treated groupwill be using Forced Air Warming system (FAW) during surgery.FAW starts at least 30 min preoperatively and then continue throughout the entire operation. Air forced blankets (Bair Hugger, 3M, Minnesota, USA), connected to its corresponding warming unit, will be placed in operation rooms and turned on prior to patient arrival. All patients should be pre-warmed for 30 minutes prior to anesthesia induction. Active warming will be terminated by the end of each surgery and then switched to passive warming using cotton blanket (thermal insulation). Patients will be then transported to either PACU or ICU. The core temperature will be measured at the beginning of pre-warming procedure and then throughout the surgical procedures.

Control group

Patients in the control groupwill be using cotton blanket warming (CBW). CBW is currently the standard of care inperioperative warming practice.CBW care starts at least 30 min preoperatively and then continue throughout the entire operation. CBW will continue regardless the end of surgery and patients will be then transported to either PACU or ICU. The operation room ambient temperature will be maintained between 19-22°C as usual. Then patients will be transferred to PACU (or ICU on physician's discretion) where FAW will be terminated and patients will be on thermal insulation (cotton blanket). CBW group patients will keep on thermal insulation (cotton blanket). Criteria for discharging the patient from the PACU are as below: patient alert and responsive; stable vital signs; stable hemoglobin (Hb) without sign of active bleedings; oxygen saturation > 95% at room air; core temperature of 36°C or higher.

Time horizon

Patients will be followed up 30 days after surgery. In case of early trial termination, investigators are responsible for notifying Institutional Review Board (IRB).

Study perspectives

The study will be based on the *Patient Perspective*. Direct/indirect costs and related health outcomes will be estimated.

Choice of health outcomes

We mainly consider *incidence of intraoperative hypothermia*as the primary outcome, however, this outcome could neither be considered as the final endpoint of surgery or to be directly related to costs of consequences. Therefore we also take the following two indicators as the primary health outcomes: 1) intraoperative blood loss/blood transfusion; 2) surgical site infection (SSI).

Costs estimation

Cost will include both direct medical cost and direct non-medical cost.The costs of related resources will be calculated at the end of the study period (see Tab.3). The cost of FAW will be calculated by using retail costs for the blankets and costs for the warming units amortized cost over 5 years and assuming use in 10 cases per week based on current usage at PUMCH.The CBW cost includes cost of cotton blankets and laundry/acquisition. The costs of PACU, ICU and hospital stay care include fixed semi-variable and variable costs and incorporate the costs of basic supplies, equipment, and institutional overhead.

Table 1. Primary Endpoints of Interest from Previous Studies and Estimated Sample Size

Primary Outcomes	Treatment Group	Control Group	Minimum sample size(/arm)	P-Value
Surgical site infection*% [Kurz et al., 1996]	6	19	116	0.009
Surgical site infection**% [Melling, 2001]	5	14	187	0.001
Intraoperative hypothermia %	0.00	74.19	8	<0.0001
Blood loss (ml)	464.00±324.15	676.87±432.05	51	0.0258
Transfusion in surgery and PACU (ml)	457.11±385.41	649.45±278.43	48	0.2114
Hemoglobin reduction (ml)	21.00±9.98	28.33±17.77	61	0.0578

* : For contaminated surgery; **: For clean surgery

Table 2. Sample Size Estimation for Each Category of Surgery

Type of Surgery	FAW	CBW	Randomization Ratio
Esophagostomy	60	60	1:1
Pancreatectomy	60	60	1:1
Total	120	120	240

Table 3. Costs Identification from Provider Perspective

Direct medical cost	Direct non-medical cost	Indirect cost
Cost of FAW and CBW warming system and materials	Cost of professional care-giver	Productivity loss of patient and families
Cost of mechanical ventilation		
Cost of stay in PACU, ICU and hospital		
Cost of anesthesia providers		
Cost of blood transfusion		
Cost of medication for postoperative pain, nausea, and vomiting		
Cost of surgical site infection treatment		
Cost of subsequent visit		
Cost of readmission		

Table 4. Data Collection Plan

PROCEDURE/TEST	Baseline* & Pre-procedure	Intra-Procedure	Post-Procedure	30 days after surgery
Demographic, comorbidities, physical exam	✓			
Inclusion/Exclusion Criteria	✓			
Patient Informed Consent	✓			
Core body temperature	✓	✓	✓	
Blood transfusion		✓		
Recovery time after anesthesia			✓	
Shivering/Nausea/Vomiting			✓	
Medications	✓	✓	✓	
Reportable Adverse Events		✓	✓	✓
Surgical Site Infection				✓
Health Utility			✓	✓
Cost Information		✓	✓	✓

Assuming that all costs are variable, then the per-minute-cost for operating room and PACU time can be calculated based on resource use and labor requirements for the period when the study is conducted. Specifically, intraoperative costs reflect total nursing cost plus the institutional overhead costs divided by total operating room minutes billed for the 1-yr period when the study is conducted. The PACU costs will be based on calculations of staffing and resource allocations in the PACU. The PACU per-minute nursing cost will be determined by total PACU minutes billed for the study period. Anesthesia provider costs will be assessed based on the medical care payment fee schedule on a per-minute basis. The cost of blood transfusion will be calculated based on blood product cost and blood transfusion care service fee. The cost of medications to manage postoperative pain, nausea, and vomiting will be determined based on hospital pharmacy drug acquisition costs.

The cost of SSI will be calculated based on data on the extra length of stay and the unit cost per bed day attributable to SSI and cost for diagnosing and treating the SSI. Other direct and indirect cost will be defined and calculated according to pre-defined analysis plan. All treatment-related cost could be obtained from the hospital bill by the end of study period.

Currency, price date and conversion

Monetary costs will be calculated when all the follow-ups are finished. RMB yuan will be used in cost measurement and then be converted into US dollar according to exchange rate on the date of database closing. Unit price and resources amount with potential adjustment in each group will be extracted from CRF and hospital bill to estimate the total costs.

Discounting

The study will take 20 months as estimated by the enrollment progress. We will use 3% as the discount rate and 0~8% as an adjustment in uncertainty analysis according to the *Chinese Pharmacoeconomics Guideline (2015)*.

Data Collection

Baseline data collection

The following data should be collected at baseline:1) Demographics; 2) Comorbidities; 3)Physical Exam; 4) Evaluation of ASAPhysical Status Class/NNIS; 5)Concomitant medication (ant platelet, anticoagulants, ant arrhythmic, per operative antibiotics, NSAIDs, steroid, immunosuppressant, etc.); 6)Lab test (complete blood count and serum glucose).The baseline data can be collected up to 4 weeks prior to elective surgeries. If multiple assessments are performed within 4 weeks prior to the elective surgeries, it is recommended that the most recent assessment value be included with the baseline information. Patients will be prepared according to the healthcare facility standard of care for elective major surgery patients. The core temperature will be measured at the beginning of pre-warming procedure and then throughout the surgical procedures. Infrared tympanic membrane thermometer (Thermo Scan PRO-4000, Braun GmbH, Romberg, Germany), used for core temperature measurement in this study, will be calibrated according to the manufacturer's instruction and label appropriately 1 day before surgery. On the date of surgery, baseline core temperature will be measured 5 minutes prior to anesthesia induction. After anesthesia induction, core temperature will be measured every hour after induction until the end of surgery.

Follow-ups

For health economic endpoints, we will collect information of in-hospital diagnosis, medications, procedures, consultation, referrals, nursing, etc. upon discharge. Moreover, quality of life assessment will be undertaken by using EQ-5D (3L Chinese Simplified, Version Number 1.0). The clinical events, health states and corresponding resource use can be collected through access to medical records, discharge financial reports and patient interviews. Patient will be followed up for 30 days after surgery (see Tab.4).

Analytical methods

Cost-consequences analysis (CCA) and cost-utility analysis (CUA) will be used in this study. Under each interested clinical event that need potential treatment, cost will be recorded. All clinical endpoints and costs will be listed parallel and compared between two groups. We will mainly compared costs of blood transfusion, surgical site infection, prolonged PACU, ICU and hospital stay between two groups. CUA will also be used to estimate the extra cost per QALY specifically by FAW. The EuroQol-5D will also be used to measure health utilities. Expected life years will be extracted from life table. The incremental cost-utility ratio (ICUR) of FAW care vs. CBW care will be calculated. The willingness-to-pay for a QALY is set to one to three times of per capital gross domestic product (GDP) of China on date of database closing. All randomized subjects data will be used for primary outcome analysis according to intent to treat (ITT) principle.

Categorical in each study group will be analyzed by Chi-square or Fisher's exact test. Continuous variables will be analyzed using unpaired, two-tailed t-tests or non-parametric analysis for non-normal distributed data.P value of less than 0.05 will be considered to indicate a statistically significant difference. Potential comparison of baseline characteristics, effectiveness outcomes, costs and cost-utility analysis are given in Table 5, 6, 7 and 8.

Uncertainty Analysis

One-way sensitivity analysis will be performed on intra-operative hypothermia rate, SSI rate and total cost. Tornado diagrams will be drawn to identify the most sensitive factors. Probability sensitivity analysis will be used in CUA. Cost-utility acceptability curve will be drawn to explore the threshold range of accepting FAW.

Trial status

This trial was registered on the Chinese Clinical Trial Registry (ChiCTR). ChiCTR is one of the primary registries in the WHO Registry Network. Trial registry number: ChiCTR-IPR-17011099. The ethical approval was achieved in August, 2016. Patient enrollment started in November, 2016, and was estimated to finish in June, 2018.

DISCUSSION

Choice of analytical method

Inputs on certain interventions including drugs will sometimes produce benefits from savings on other resources such as stay in hospital and treatment on adverse reaction. In 1998, Mauskopf, J. A. introduced CCA to compare the economic benefits by listing out all the health related input and output between treatment group and control group (Mauskopf, 1998). Based on the results given by CCA, different stakeholder may make decision from different perspective choosing to use different outcome and cost. Therefore, CCA is often regarded as the intermediate step or a transformation of CEA (Weijers, 2017)。CCA were often used in economical evaluation for medical devices whose clinical outcomes could not be directly related to the application of the device patient used and whose economic benefits would be estimated by a series of clinical events that happened or not. Burri H (2013) used CCA to compare the costs and outcomes for different approach of applying remote implanted heart electronic equipment (Burri, 2013). Craig, (2013) applied CCA in economic benefit estimation of using soft-heel casting to prevent diabetic foot ulcers (Craig, 2013). Tantraworasin, A (2014) used CCA to compare the efficiency of using surgical suture device with artificial suture in Lobectomy (Tantraworasin, 2014). CCA can determine costs and consequences without attempting to isolate a single consequence or aggregate consequences into a single measure. Since the clinical benefits of FAW are potentially reflected in multiple intermediate endpoints including lower SSI, less blood loss/transfusion and shorter LOS in hospital, ICU and PACU, etc., Cost-Effectiveness Analysis (CEA) is not appropriate for current economic evaluation. Therefore, we choseCCA to describe the clinical outcomes and costs of FAW and CBW groups under the assumption that FAW is cost-saving when clinical outcomes are at least non-inferior.

Table 5. Baseline characteristics

Variable	FAW	CBW
Age		
Gender	%	%
BMI		
ASA physical status		
I	%	%
II	%	%
III	%	%
Surgery method		
Open surgery	%	%
Endoscopic surgery	%	%

Table 6. Effectiveness

Outcome	FAW	CBW
Intra-operative hypothermiarate		
SSI rate		

Table 7. Cost

Cost		FAW	CBW
Direct medical cost	Warming unit		
	Transfusion		
	Anesthesia		
	ICU/PACUunit		
	SSI treatment		
	Treatment of other adverse reaction		
	Prolonged stay		
	Out-patient visit		
Direct non-medical cost	Nursing assistant		
	Accommodation		
Indirect cost	Productivity loss of patient		
	Productivity loss of families		
Total cost			

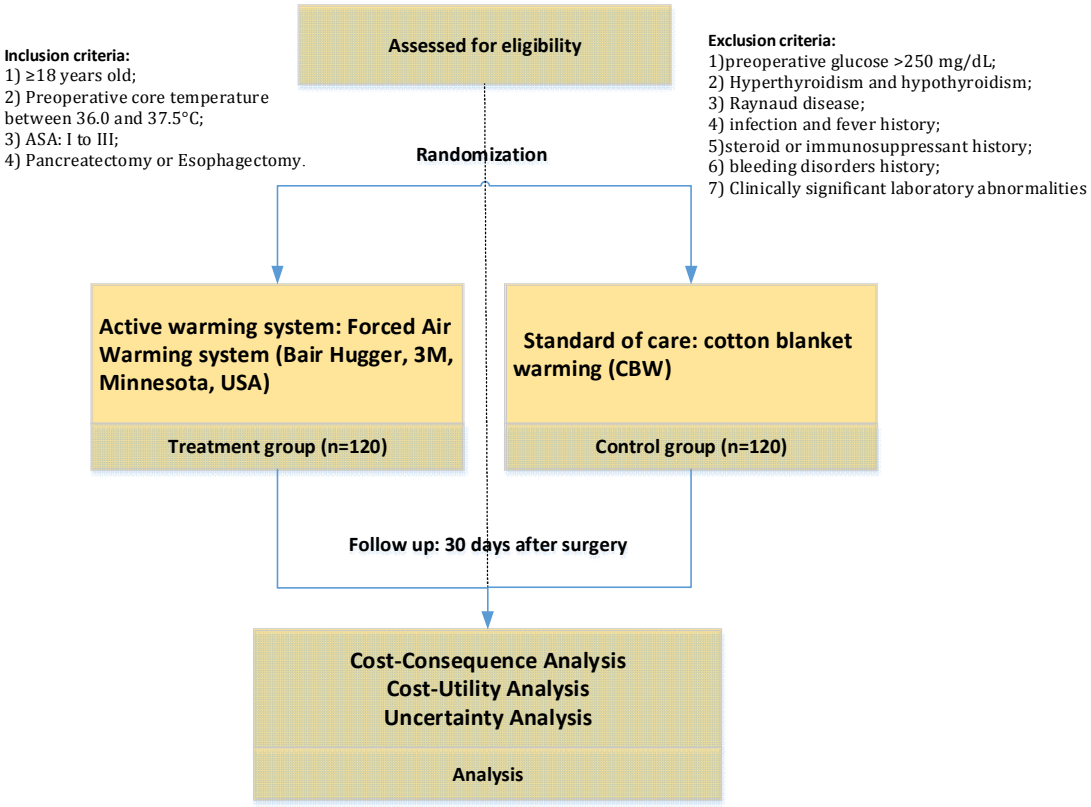

Figure 1. Study flowchart

Table 8. Incremental cost utility analysis

Group	Cost/case	QALY/case	CUR	ICUR
CBW				
FAW				

Strengths and Limitations

In 2017, China begins to apply economical evaluation evidence in its national drug reimbursement list entry. However the good practice of evidence production, submission and review is still in discussion at this stage. We designed this study hoping to provide as an acceptable template for trial-based health economical evaluation for health products and its use for administration decisions. We also hope to explore the proper evaluation method for medical devices evaluation and discuss on its use in reimbursement list entry decision-making. CCA has its limitations in making choices. For one thing, CCA gives out a series of clinical outcomes instead of an aggregated final endpoint such as the health related quality of life and life year gained, which makes it hard to decide the overall cost-effectiveness compared to alternative medical intervention. Therefore, CCA is currently more often used in areas as screening (Posso, 2016; Buja, 2015; Bensink *et al*., 2014; Handels *et al*., 2012; Schinco *et al*., 2015) and diseases prevention (30, 36). For another, the result could not be directly used in decision-making. To solve this problem, we also introduced in CUA and planned to apply methodology as modelling to estimate the final economic benefits.

Declarations

Ethics approval and consent to participate

Ethical approval has been obtained through the Ethic Committee of Peking Union Medical College Hospital (HS-1121). Any protocol amendments and/or associated informed consent changes were submitted to the EC, with written approval obtained prior to implementation, as needed. The Investigator or designee who has been trained on the protocol is to explain the nature and scope of the study and answer patient questions. All patients or their legally-authorized representatives (e.g., family member) must sign and date the EC-approved informed consent form prior to randomization. Patients must be assessed and deemed not under the influence of mind-altering medications at the time of signing Failure to obtain signed informed consent will render the patient ineligible for the study. The signed informed consent will then be kept in the patient's medical records and a copy given to the patient or legally-authorized patient representative (e.g., family member). The informed consent form will include language that satisfies the Chinese Food and Drug Administration (CFDA) and accounts for any applicable regulations. To ensure compliance with the CFDA and any applicable private information protection laws, confidentiality of protected health information shall be maintained by all parties throughout the study. All data should be secured against unauthorized access.

Consent for publication

Not applicable.

Availability of data and material

Request for access of data and supporting materials will be considered by the funder and investigators.

Competing interests

The authors declare no competing interest in this publication.

Funding

Not applicable.

Authors' contributions

WT designed the study and wrote this protocol. HG is in charge of the clinical trial implementation and will help identify the cost of treatment for adverse events. HL helped with the discussion of choice of health outcomes, analytical method and sample size estimation. XG assisted in literature collection and discussion for CCA. YH and AM developed the idea of comparing clinical and economic benefits of using warming system to prevent intra-operative hypothermia for patients undergoing major surgeries.

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REFERENCES

Adriani MB, Moriber N. 2013. Preoperative forced-air warming combined with intraoperative warming versus intraoperative warming alone in the prevention of hypothermia during gynecologic surgery. *AANA J.*, 81(6):446-451.

Augustine S. 2014. Another perspective on forced-air warming and the risk of surgical site infection. *AORN J*, 99(3):350-351.

Bensink ME, Ramsey SD, Battaglia T, Fiscella K, Hurd TC, McKoy JM, Patierno SR, Raich PC, Seiber EE, Warren-Mears V *et al*. 2014. Costs and outcomes evaluation of patient navigation after abnormal cancer screening: evidence from the Patient Navigation Research Program. *Cancer-am cancer Soc.,* 2014, 120(4):570-578.

Borms SF, Engelen SL, Himpe DG, Suy MR, Theunissen WJ. 1994. Bair hugger forced-air warming maintains normothermia more effectively than thermo-lite insulation. *J CLIN ANESTH*, 6(4):303-307.

Buja A, Martines D, Lobello S, Vinelli A, Bardelle G, Lopatriello S, De Lazzari F, Perrier L, Baldo V. 2015. A cost-consequence analysis of hepatitis B screening in an immigrant population. *Ann Ist Super Sanita*, 51(4):327-335.

Burger L, Fitzpatrick J. 2009. Prevention of inadvertent perioperative hypothermia. *Br J Nurs.,* 18(18):1114, 1116-1119.

Burri H, Sticherling C, Wright D, Makino K, Smala A, Tilden D. 2013. Cost-consequence analysis of daily continuous remote monitoring of implantable cardiac defibrillator and resynchronization devices in the UK. *Europace*, 15(11):1601-1608.

Craig J, Shenton R, Smith A. 2013. Economic analysis of soft-heel casting for diabetic foot ulcer: prevention and treatment. *j wound care.,* 22(1):44-48.

de Brito PV, Clark AM, Galvao CM. 2013. A systematic review on the effectiveness of prewarming to prevent perioperative hypothermia. *J CLIN NURS*, 22(7-8):906-918.

Egan C, Bernstein E, Reddy D, Ali M, Paul J, Yang D, Sessler DI. 2011. A randomized comparison of intraoperative PerfecTemp and forced-air warming during open abdominal surgery. *Anesth Analg*, 113(5):1076-1081.

Fettes S, Mulvaine M, Van Doren E. 2013. Effect of preoperative forced-air warming on postoperative temperature and postanesthesia care unit length of stay. *AORN J.*, 97(3):323-328.

Handels RL, Aalten P, Wolfs CA, OldeRikkert M, Scheltens P, Visser PJ, Joore MA, Severens JL, Verhey FR. 2012. Diagnostic and economic evaluation of new biomarkers for Alzheimer's disease: the research protocol of a prospective cohort study. *BMC NEUROL*, 12:72.

Insler SR, Bakri MH, Nageeb F, Mascha E, Mihaljevic T, Sessler DI. 2008. An evaluation of a full-access underbody forced-air warming system during near-normothermic, on-pump cardiac surgery. *ANESTH ANALG*, 106(3):746-750.

Kim HY, Lee KC, Lee MJ, Kim MN, Kim JS, Lee WS, Lee JH. 2014. Comparison of the efficacy of a forced-air warming system and circulating-water mattress on core temperature and post-anesthesia shivering in elderly patients undergoing total knee arthroplasty under spinal anesthesia. *Korean J Anesthesiol*, 66(5):352-357.

Kurz A, Sessler DI, Lenhardt R. 1996. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. *N Engl J Med.*, 334(19):1209-1215.

Leung KK, Lai A, Wu A. 2007. A randomised controlled trial of the electric heating pad vs forced-air warming for preventing hypothermia during laparotomy. *ANAESTHESIA* 2007, 62(6):605-608.

Mauskopf JA, Paul JE, Grant DM, Stergachis A. 1998. The role of cost-consequence analysis in healthcare decision-making. *Pharmacoeconomics*, 13(3):277-288.

Melling AC, Ali B, Scott EM, Leaper DJ. 2001. Effects of preoperative warming on the incidence of wound infection after clean surgery: a randomised controlled trial. *Lancet*, 358(9285):876-880.

Ng V, Lai A, Ho V. 2006. Comparison of forced-air warming and electric heating pad for maintenance of body temperature during total knee replacement. *ANAESTHESIA*, 61(11):1100-1104.

Occhipinti LL, Hauptman JG, Greco JJ, Mehler SJ. 2013. Evaluation of bacterial contamination on surgical drapes following use of the Bair Hugger((R)) forced air warming system. *CAN VET J.,* 54(12):1157-1159.

Oshvandi K, Shiri FH, Fazel MR, Safari M, Ravari A. 2014. The effect of pre-warmed intravenous fluids on prevention of intraoperative hypothermia in cesarean section. *Iran J Nurs Midwifery Res* 2014, 19(1):64-69.

Posso MC, Puig T, Quintana MJ, Sola-Roca J, Bonfill X. 2016. Double versus single reading of mammograms in a breast cancer screening programme: a cost-consequence analysis. *EUR RADIOL*, 26(9):3262-3271.

Poveda VB, Martinez EZ, Galvao CM. 2012. Active cutaneous warming systems to prevent intraoperative hypothermia: a systematic review. *Rev Lat Am Enfermagem.,* 20(1):183-191.

Rembert MS, Smith JA, Hosgood G. 2004. A comparison of a forced-air warming system to traditional thermal support for rodent microenvironments. *Lab Anim.,* 38(1):55-63.

Roder G, Sessler DI, Roth G, Schopper C, Mascha EJ, Plattner O. 2011. Intra-operative rewarming with Hot Dog((R)) resistive heating and forced-air heating: a trial of lower-body warming. *Anaesthesia*, 66(8):667-674.

Schinco P, Cultrera D, Valeri F, Borchiellini A, Mantuano M, Gorla F, Savarese A, Teruzzi C. 2015. Cost-consequence analysis of long-term prophylaxis in the treatment of von Willebrand disease in the Italian context. *Clinicoecon Outcomes Res* 2015, 7:17-25.

Sikka RS, Prielipp RC. 2014. Forced air warming devices in orthopaedics: a focused review of the literature. *J BONE JOINT SURG AM*, 96(24):e200.

Tantraworasin A, Seateang S, Bunchungmongkol N. 2014. Staplers versus hand-sewing for pulmonary lobectomy: randomized controlled trial. *Asian Cardiovasc Thorac Ann*, 22(3):309-314.

Torrie JJ, Yip P, Robinson E. 2005. Comparison of forced-air warming and radiant heating during transurethral prostatic resection under spinal anaesthesia. *Anaesth Intensive Care.,* 33(6):733-738.

Trentman TL, Weinmeister KP, Hentz JG, Laney MB, Simula DV. 2009. Randomized non-inferiority trial of the vitalHEAT temperature management system vs the Bair Hugger warmer during total knee arthroplasty. *Can J Anaesth*, 56(12):914-920.

Weijers L, Baerwald C, Mennini FS, Rodriguez-Heredia JM, Bergman MJ, Choquette D, Herrmann KH, Attina G, Nappi C, Merino SJ *et al*. 2017. Cost per response for abatacept versus adalimumab in rheumatoid arthritis by ACPA subgroups in Germany, Italy, Spain, US and Canada. *RHEUMATOL INT*.

Wong A, Walker S, Bradley M. 2004. Comparison of a radiant patient warming device with forced air warming during laparoscopic cholecystectomy. *Anaesth Intensive Care.,* 32(1):93-99.

Wood AM, Moss C, Keenan A, Reed MR, Leaper DJ. 2014. Infection control hazards associated with the use of forced-air warming in operating theatres. *J HOSP INFECT*, 88(3):132-140.

Yi J, Lei Y, Xu S, Si Y, Li S, Xia Z, Shi Y, Gu X, Yu J, Xu G *et al*. 2017. Intraoperative hypothermia and its clinical outcomes in patients undergoing general anesthesia: National study in China. *PLOS ONE* , 12(6):e177221.

Yoo HS, Park SW, Yi JW, Kwon MI, Rhee YG. 2009. The effect of forced-air warming during arthroscopic shoulder surgery with general anesthesia. *Arthroscopy*, 25(5):510-514.

Zhao J, Luo AL, Xu L, Huang YG. 2005. Forced-air warming and fluid warming minimize core hypothermia during abdominal surgery. *Chin Med Sci J.,* 20(4):261-264.

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