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The value of perioperative, local and systemic warming to prevent surgical site infection: a systematic review and meta-analysis

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Abstract

Background

Surgical site infection (SSI) is a common cause of postoperative morbidity. Perioperative hypothermia may contribute to surgical complications including increased risk of SSI. In this systematic review and meta-analysis the effectiveness of active and passive perioperative warming interventions to prevent SSI was compared with standard (non-warming) care.

Methods

Ovid MEDLINE; Ovid EMBASE; EBSCO CINAHL Plus; The Cochrane Wounds Specialised Register; The Cochrane Central Register of Controlled Trials were searched with no restrictions on language, publication date or study setting for randomised controlled trials (RCTs) and cluster RCTs; including adult patients undergoing elective or emergency surgery under general anaesthesia, receiving any active or passive warming intervention perioperatively. Two review authors independently performed study selection, risk of bias assessment and data extraction. Outcomes studied were SSI (primary outcome), inpatient mortality, hospital length of stay and pain (secondary outcomes).

Results

Four studies, including 768 patients, were identified. The risk ratio for SSI in warming groups was 0.36 (95% confidence interval [CI]: (0.23, 0.56); $p < 0.001$). Length of hospitalisation was 1.13 days less in warming groups (95% CI: (-3.07, 5.33); $p = 0.600$). The risk ratio for mortality in the warming groups was 0.77 (95% CI: (0.17, 3.43); $p = 0.730$). A meta-analysis for pain outcome could not be conducted.

Interpretations

This review provides evidence in favour of active warming to prevent SSI, and insufficient evidence of active warming to reduce length of hospital stay and mortality. Benefits of passive warming remain unclear and warrant further research.

Introduction

Humans have evolved to be homeothermic; their physiological processes generally work optimally at 37°C, although it is recognised some people may be slightly above or below this, maintained through a balance of heat production and heat loss, control of which is commonly lost during anaesthesia and exposure during operative procedures. Heat supports processes conducive to optimal healing, with reduction of infection through improvement of blood flow and oxygenation. Loss of perioperative homeostasis, related to hypothermia, leads to coagulopathy, immunosuppression and reduced resistance to infection, reduced basal metabolic rate and oxygen consumption leading to tissue hypoxia and ischaemia.^{1,2}

Clinical perioperative hypothermia (core temperature <36°C) is common and related to several clinical complications: bleeding and greater need for blood transfusion, cardiac dysrhythmias, myocardial ischaemia and infarction, and risk of pressure injury; accompanied by an increased need for intensive care and overall hospital stay and hospital costs.^{3,4} Systemic and local normothermia can be maintained through available technologies; the most successful have been those using forced-air warming or conductive polymer mattresses/overblankets.^{1,8-10} These interventions, and their effectiveness to avoid inadvertent perioperative hypothermia, have been the basis of a National Institute for Health and Care Excellence (NICE) guideline, but this did not specifically review the primary outcome of surgical site infection (SSI).¹¹

Patients who are hypothermic during the operative period are more likely to develop SSIs^{2,12-13}, but relatively few randomised clinical trials (RCTs) have been undertaken in this field. This systematic review and meta-analysis aimed to examine the value of local and systemic warming for the prevention of SSI, reduction in length of hospital stay, and mortality; based on current evidence presented in RCTs.

Methods

Search strategy and selection criteria

Ovid MEDLINE (including In-Process & Other Non-Indexed Citations and Epub Ahead of Print); Ovid EMBASE and EBSCO CINAHL Plus; the Cochrane Wounds Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library) were searched for relevant trials (See appendix 1 for search terms). Clinical trials registries for ongoing and unpublished studies, and scanned reference lists of relevant reports to identify additional studies, were also searched. No restrictions were made with respect to language, date of publication or study setting. RCTs and cluster RCTs were included which involved adult patients undergoing any elective or emergency surgery under general anaesthesia who received any active or passive warming intervention perioperatively. Two pairs of review authors (DJL & KE; JD & KW) independently assessed study selection, risk of bias assessment and data extraction. Disagreement occurring during selection was resolved by discussion between pairs of review authors. Studies published in duplicate were included once. Corresponding authors of studies were contacted for clarification where necessary. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart to summarise the selection of studies was completed (Figure 1).¹⁴ Any authors involved in this systematic review who had authored any of the included studies did not review or extract data from them, to avoid any conflicts of interest.

Data analysis

Information was extracted on:

- patient characteristics: gender, age, type of surgery, type of anaesthesia, duration of surgery, American Society of Anesthesiologists (ASA) grade¹⁵;
- study details: dates, design, location, eligibility criteria, sample size;
- intervention details: type/description of warming therapy, duration and frequency of intervention, body site, temperature settings;

- comparators: no/passive warming devices; no/active warming; any standard care versus active/passive warming; any alternate form of warming versus standard care;
- outcome data by group, relating to both primary and secondary outcomes (using outcomes as defined above);
- funding-related information.

Risk ratios (RRs) with associated 95% confidence intervals (CIs) were calculated for dichotomous outcomes using the Mantel-Haenszel method. Unstandardized weighted mean differences (WMDs) between groups with associated 95% CIs for continuous outcomes, using the inverse variance method. If two or more interventions were compared with control and were eligible for the same meta-analysis, the intervention arms were pooled and compared with controls. Where a trial did not specify participant group numbers prior to dropout, only complete case data were presented.

Fixed effects models were conducted for the analysis of SSI and mortality, for which limited clinical heterogeneity between studies (e.g. characteristics of participants, interventions or outcomes studied) was recorded. Random-effects models were conducted for the analysis of the length of stay outcome. Insufficient data was obtained for a meta-analysis of the pain outcome.

Statistical heterogeneity was assessed using a standard χ^2 test and the I^2 statistic.¹⁶ An I^2 estimate of around 75% accompanied by a significant result from the χ^2 statistic was interpreted as evidence of substantial levels of statistical heterogeneity.¹⁷

Forest plots were used to present outcome measures and associated 95% CIs. Any adverse events were planned to be recorded and presented narratively. Funnel plots were planned subject to a suitable number of studies being identified but were not constructed due to a lack of suitable number of studies for any of the outcomes.

Results

Main results are presented in Summary of Findings (table 1), providing key information concerning quality of evidence, the magnitude of the effect of the interventions examined and the sum of the available data on the main outcomes. The primary outcome of SSI and secondary outcomes of mortality and length of stay were included in the table as these were common to all papers included for analysis. Evidence related to all outcomes was graded using the GRADE approach.¹⁸

All analysis was conducted using Stata I/C 14 statistical software.

Table 1: Summary of findings

Patient or population: Patients undergoing surgery.¹ Settings: Hospital setting, outpatient clinic.

Intervention: Any patient warming (active/passive). Comparison: No patient warming

Outcome	Illustrative comparative risks (95% CI)		Relative effect (95% CI); significance level	Number of participants (studies)	Quality of evidence	Comments
	Assumed risk	Corresponding risk				
	No patient warming	Patient warming (active and/or passive)				
Proportion of group with SSI (follow-up 2-8 weeks)	Moderate²		RR 0.36 (0.23 to 0.56); $p < 0.001$	763 (4 studies)	High	The low relative risk score indicates lower incidence of infection in warmed patients
	173.8 per 1000 (71.4 to 267.9)	54.6 per 1000 (0 to 127.7)				
Duration of hospital stay (number of days) (follow-up 2-8 weeks)	Low³		Mean difference - 1.13 (-5.33 to 3.07); $p = 0.600$	303 (2 studies)	Low	The negative mean difference score indicates shorter length of hospital stay in warmed patients
	The mean number of days of hospitalisation ranged across control groups from 9.0 to 14.7	The mean number of days of hospitalisation ranged across intervention groups from 11.0 to 12.1				
Mortality (follow-up 2-8 weeks)	Low³		RR 0.77 (0.17 to 3.43); $p = 0.730$	303 (2 studies)	Low	The low relative risk score indicates lower non-significant incidence of mortality in warmed patients
	26.3 per 1000 (20.8 to 35.7)	19.9 per 1000 (19.2 to 21.3)				

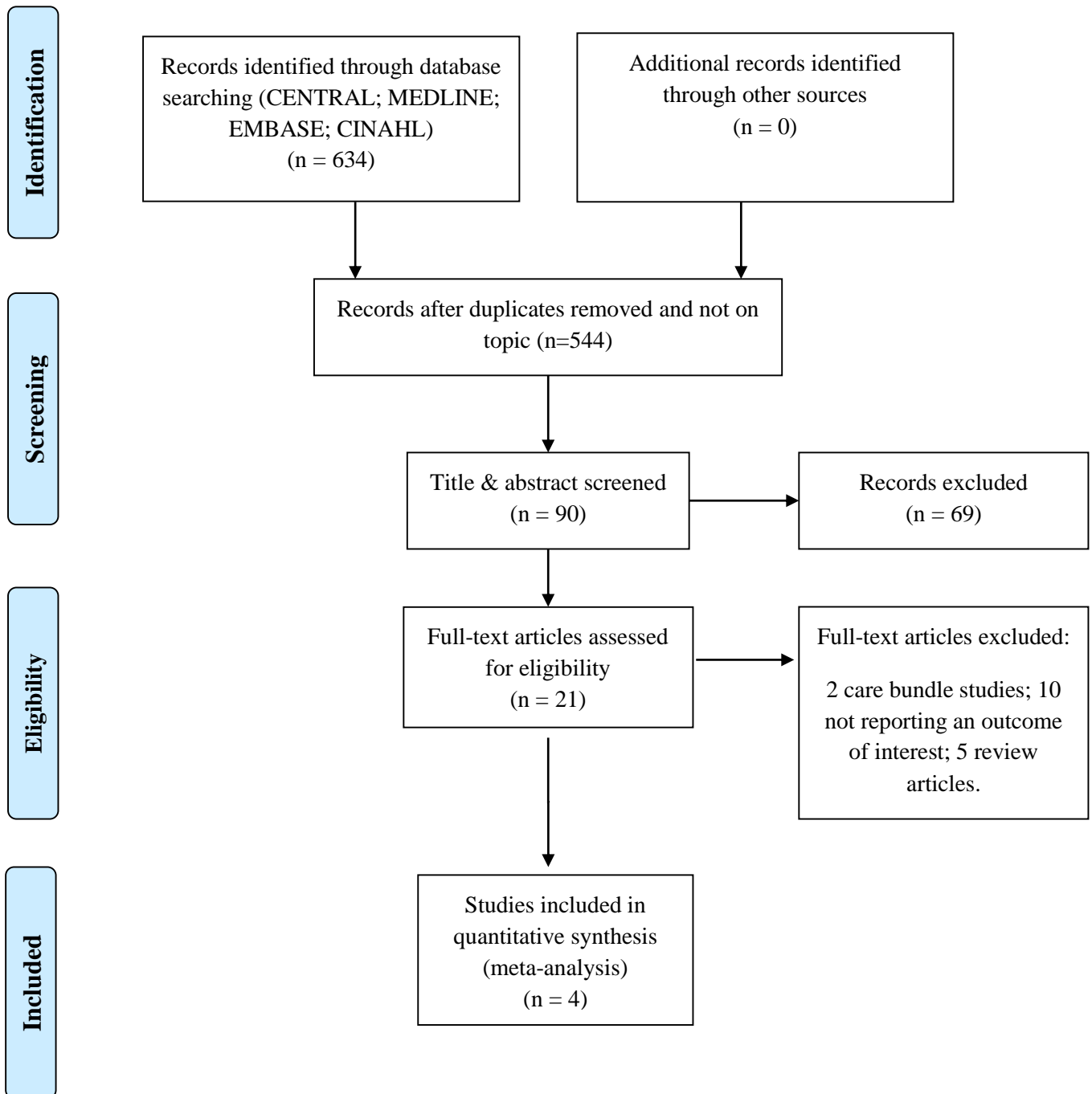
¹All studies considered elective surgery. Surgical procedures included abdominal, hernia, breast, varicose vein, colorectal.

²Limited number of participants including this outcome found for analysis, also limited number of outcome events.³Very serious imprecision due to small study sizes and small number of events and 95% CI including no effect

Study Selection

The search yielded 634 records. Four were included in the review. Full-text copies of 21 papers were assessed for eligibility; 17 were excluded. Results of the search and selection of studies are summarised in the PRISMA flow diagram (Figure 1).

Figure 1: PRISMA Flowchart



Study Characteristics

The four included studies (768 patient participants) were single blinded, parallel RCTs, published in English. They compared no warming with active warming using a forced air warming device^{19,20}, a heated underbody mattress²¹, or a radiant heat surgical dressing.^{20,22} In one study²¹, all patients were warmed using forced air warming, but the warming group had an additional heated mattress with the intervention delivered peri-operatively.

Outcome measures reported by Kurz¹⁹ were: SSI; ASEPSIS (Additional treatment, Serous discharge, Erythema, Purulent exudate, Separation of deep tissues, Isolation of bacteria, Stay in hospital >14 days) score; collagen deposition; days to first solid food; days to suture removal. Outcomes reported by Melling²⁰ were: SSI; ASEPSIS score; haematoma; seroma; wound aspirated and prescription of postoperative antibiotics. Outcomes reported by Melling²² were: SSI; number of dressing changes needed; ASEPSIS score. Outcomes reported by Wong²¹ were: SSI; chest infection; ileus; urinary tract infection; pelvic collection; cardiac complications; renal failure; anaesthetic complications; *C. difficile* diarrhoea; pressure ulcer; intravenous fluids; urine output; blood loss; patients requiring blood transfusion; duration of antibiotics; flatus passed; bowels opened; diet tolerated; duration of hospital stay.

Kurz¹⁹ was funded by the National Institute of Health (USA) and charitable foundations; Melling²⁰ was funded by Action Research, Smith and Nephew Foundation, and Augustine Medical Inc. No details of funding were provided for Wong²¹ or Melling.²² The Kurz¹⁹ study was conducted in two major teaching hospitals in the United States and in Austria. Melling²⁰; Melling²² and Wong²¹ were all conducted in a surgical day-case centres or involved in-patients at a university teaching hospital in the United Kingdom. All patients in Kurz¹⁹ and most in Wong²¹ were undergoing elective open colorectal surgery. Patients in Melling²⁰ were undergoing breast, varicose vein, or hernia surgery; patients in Melling²² were exclusively undergoing hernia surgery. Across the included studies, most patients were female and aged 50+ years. Kurz¹⁹, Melling²⁰ and Wong²¹ were short-term studies involving warming applied

to patients for several hours pre- and/or post-operatively. Melling²² included long-term (7-day) warming. The largest study was Melling²⁰ (421 patients recruited; 416 analysed) and the smallest was Melling²² (45 patients recruited; 44 analysed). Kurz¹⁹ recruited and analysed 200 patients; Wong²¹ recruited and analysed 103 patients.

The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). All studies have between 1-3 unclear “risk of bias” domains. An overall summary of the risk of bias is illustrated in Figure 2; a graphical breakdown of bias for each trial is illustrated in Figure 3.

Figure 2: Risk of Bias

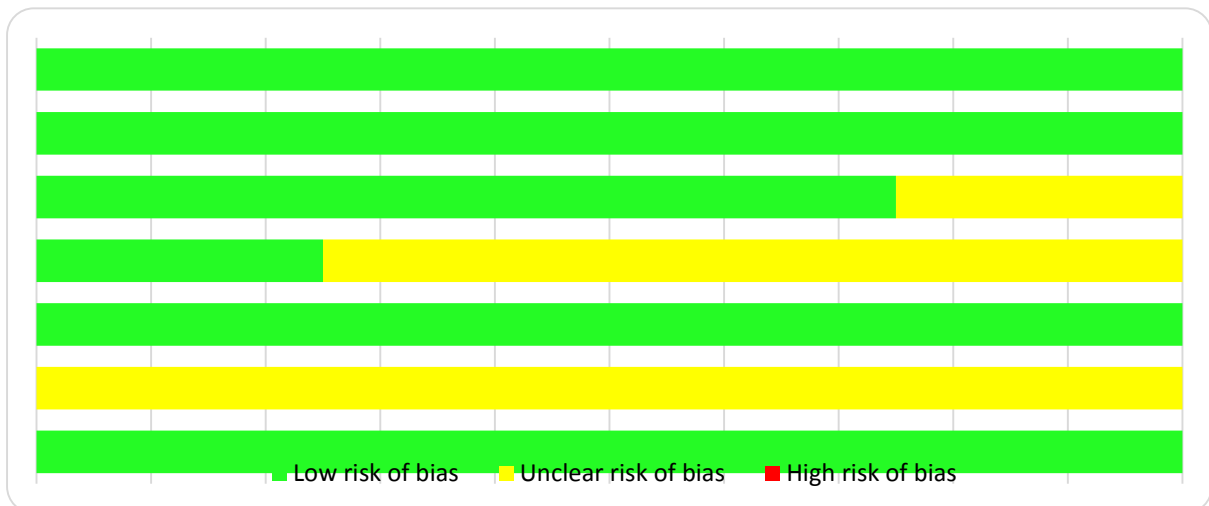


Figure 3: Assessed bias of individual trials

	Kurz 1996	Melling 2001	Melling 2006	Wong 2007
Random sequence generation (selection bias)	+	+	+	+
Allocation concealment (selection bias)	+	+	+	+
Blinding of participants and personnel (performance bias)	+	+	?	+
Blinding of outcome assessment (detection bias)	?	+	?	?
Incomplete outcome data (attrition bias)	+	+	+	+
Selective reporting (reporting bias)	?	?	?	?
Other bias	+	+	+	+

All included studies were randomised using computer generation^{19,20-21} or a random number table.²² All reported using sequentially numbered opaque sealed envelopes for allocation concealment. Three studies^{19,20-21} reported adequate blinding of participants and personnel; the risk was unclear in one study²². Risk of detection bias was judged as unclear for three studies^{19,21-22} as they did not report on the blinding of the individual assessing whether infection was present. One study²⁰ reported blinding of the outcomes assessment.

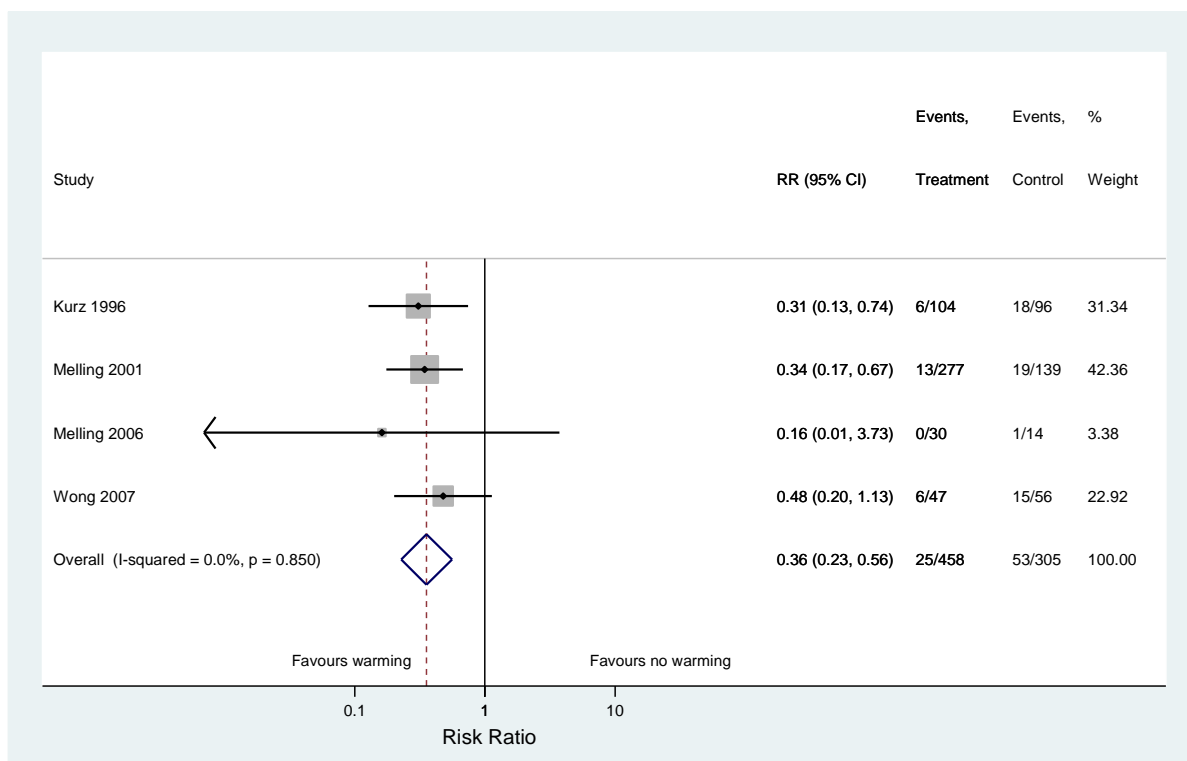
Risk of attrition bias was assessed as low in all studies, and included complete reported outcome data. It was not possible to check reporting of complete outcomes in study protocols or be certain that studies included no selective or other sources of bias.

Primary outcome: SSI

768 participants (99.3% of recruited participants potentially available for comparison from all included studies) contributed data. All studies reported an effect in favour of warming. Kurz¹⁹ reported 6 SSIs out of 104 patients in the warming group and 18 SSIs out of 96 patients in the comparator group (Mantel-Haenszel RR 0.31; 95% CI (0.13, 0.74); $p < 0.001$). Melling²⁰ reported 13 SSIs out of 277 patients in the warming group and 19 SSIs out of 139 patients in the comparator group (Mantel-Haenszel RR 0.34; 95% CI (0.17, 0.67); $p = 0.001$). Melling²² reported 0 SSIs out of 29 patients in the warming group and 1 SSI out of 14 patients in the comparator group (Mantel-Haenszel RR 0.16; 95% CI (0.01, 3.73); $p = 0.159$). Wong²¹ reported 6 SSIs out of 47 patients in the warming group and 15 SSIs out of 56 patients in the comparator group (Mantel-Haenszel RR 0.48; 95% CI (0.20, 1.13); $p = 0.079$). A χ^2 test of homogeneity found no evidence for statistical heterogeneity ($p = 0.850$). The I^2 statistic was 0.0%, indicating negligible variation across studies due to heterogeneity. The synthesised estimate of the RR was 0.36 (95% CI (0.23, 0.56)). A test of overall effect indicated strong evidence for a greater risk of SSI in the non-warmed groups ($Z = 4.50$; $p < 0.001$).

The data is summarised in a forest plot in Figure 4. These plots provide an illustration of the individual effects, and associated 95% confidence intervals, recorded in each include study; plus the synthesised estimate, plus its associated 95% confidence interval, represented by a diamond on the plot. The effect of warming is assessed in terms of risk ratios for binary outcomes and in terms of mean differences for continuous outcomes; with the point of no effect marked in all cases to facilitate interpretation of the significance of the synthesised estimate.

Figure 4: Forest plot for SSI outcome

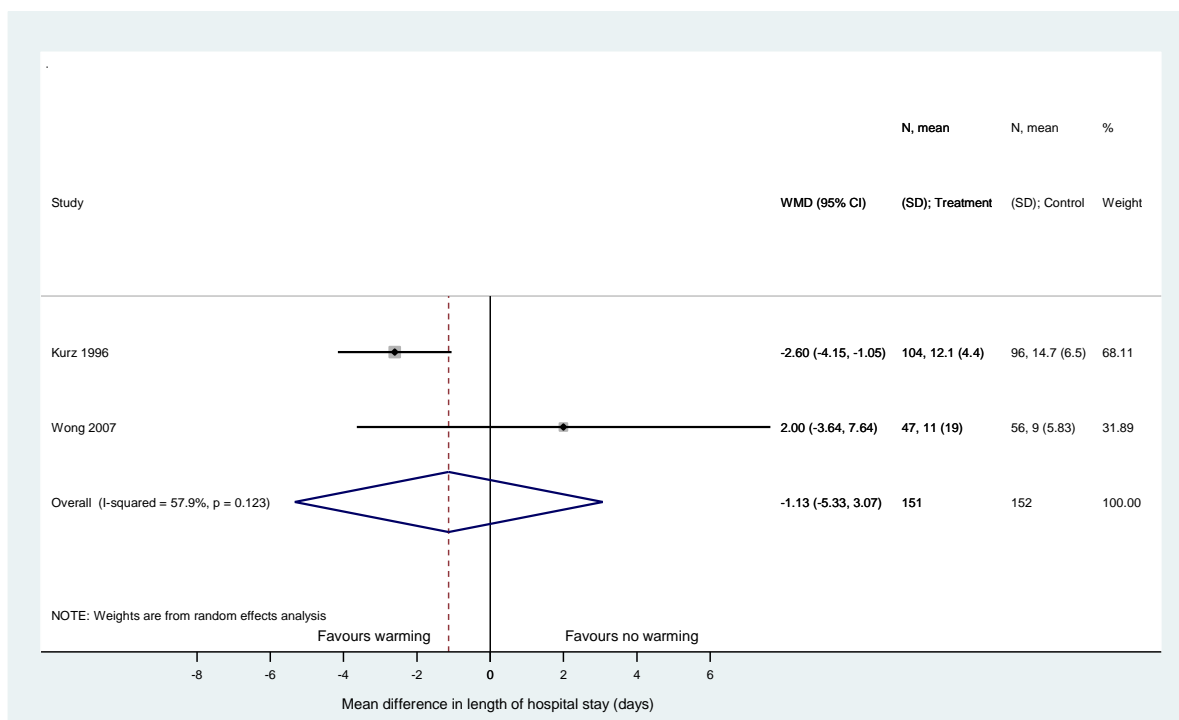


Secondary outcomes: Length of hospital stay

Two studies^{19,21} reported days of hospitalisation as an outcome. Kurz¹⁹ reported an effect in favour of the warming intervention group (i.e. shorter periods of hospitalisation) with the group being hospitalised for 2.60 days less than the no warming group (95% CI (1.05, 4.15); p=0.001). Wong²¹ reported an effect in favour of the no-warming group with this group hospitalised for 2.00 days less than the warming intervention group (95% CI (-3.64, 7.64); p=0.217). A χ^2 test of homogeneity found

no evidence for heterogeneity ($p=0.123$). The I^2 statistic was 57.9%, indicating moderate variation across studies due to heterogeneity. The synthesised estimate of the difference using the inverse variance method for a random effects model was 1.13 days less in the warming intervention groups. This effect was not statistically significant at the 5% level (95% CI (-3.07, 5.33)). A test of overall effect indicated no evidence for a greater duration of hospital stay in the no-warming groups ($Z=0.53$; $p=0.600$). The data is summarised in Figure 5.

Figure 5: Forest plot for length of stay outcome

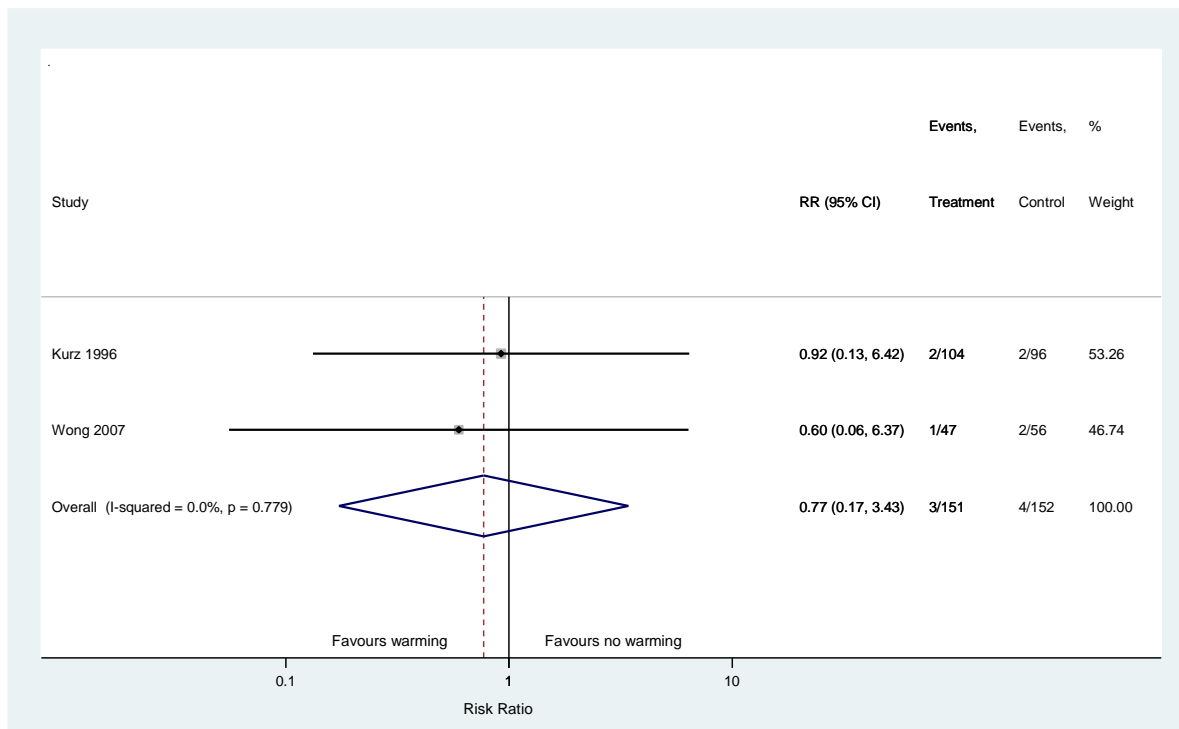


Secondary outcomes: Inpatient mortality (all-cause)

Two studies^{19,21} reported mortality as an outcome. In both cases the effect was in favour of the warming intervention groups. Kurz¹⁹ reported 2 deaths in each group (Mantel-Haenszel RR 0.92; 95% CI (0.13, 6.42); $p=0.908$) Wong²¹ reported 2 deaths in the no-warming group and 1 death in the warming group (Mantel-Haenszel RR 0.60; 95% CI (0.06, 6.37); $p=0.664$). A χ^2 test of homogeneity found no evidence for heterogeneity ($p=0.779$). The I^2 statistic was 0%, indicating negligible variation due to heterogeneity. The synthesised estimate of the risk ratio using the Mantel-Haenszel method

was 0.77 (95% CI (0.17, 3.43); low quality evidence). A test of overall effect indicated no evidence for a greater risk of mortality in the either group ($Z=0.34$; $p=0.73$). The data is summarised in Figure 6.

Figure 6: Forest plot for mortality outcome



Secondary outcomes: Pain

Pain was the only patient-reported outcome assessed in two of the included studies.^{19,22} Kurz¹⁹ reported however, that pain scores were virtually identical in control and intervention groups but did not report numerical values. Melling²² reported pain scores graphically but also did not report precise numerical values. Pain was assessed hourly after surgery and daily over the first seven days. There was no statistically significant difference at any point in time (except 2 hours after surgery in favour of no warming) ($p=0.014$). No meta-analysis was conducted on this outcome.

Discussion

This review included four studies with 768 participants comparing active warming against a control, finding that active warming reduces SSI. No statistically significant reduction in length of stay or

mortality was found; this was expected, as patients were undergoing elective operations with many being undertaken as day cases. Pain was reported in numerical values which could not be included in the meta-analysis.

While all relevant studies have been included in this review, few RCTs met the search criteria, although a wide spectrum of procedures was represented. Limited evidence was available because of this. Additionally no comparisons of active warming versus passive warming or passive warming versus control (no warming) were found. Many studies were excluded because they did not report relevant outcomes; most used maintenance of core temperature as a proxy for other patient outcomes. None of the studies reported adverse events associated with perioperative warming. The NICE guideline²³, based on avoidance of inadvertent hypothermia, reported that potential adverse effects of warming may include burns, but this risk is negligible if devices are used according to manufacturer's instructions.

Included studies were of high to moderate quality. Quality of evidence was high with respect to the primary outcome of SSI, and low with respect to secondary outcomes. Although all included studies were found to have unclear risk of bias related to blinding of participants, personnel, or outcomes assessors, it was judged that this risk would have a minimal effect on the results of this review.

SSI is one of the most common health care associated infection (HCAI) alongside urinary and respiratory tract infections, MRSA bacteraemia and *C. difficile* infection. They are associated with considerable morbidity and mortality and economic costs.^{24,25-27} Despite many national and international guidelines the incidence of SSI is not lessening^{28,29-30} unlike other HCAIs. This relates, at least in part, to the accuracy of SSI definition, adequacy of SSI surveillance of compliance with perioperative care bundles.

Only 4 studies were identified for the outcome of SSI, and two studies were identified for both secondary outcomes. Hence, sub-group analyses could not be conducted. Additionally, levels of

detection and reporting bias were uncertain in some included studies. Low numbers of included studies precluded construction of funnel plots to assess publication bias.

Maintenance of perioperative normothermia is part of many guidelines and surgical check lists.^{11,27}

The results of this systematic review and meta-analysis reinforce that warming should be part of all perioperative care bundles. With monitored compliance it would be expected that the SSI rate

would fall but prospective research is needed to confirm this.

APPENDIX 1. Search strategy MeSH terms

#1 MeSH descriptor Body Temperature, this term only

#2 MeSH descriptor Heating, this term only

#3 MeSH descriptor Rewarming explode all trees

#4 (Active warming system*) or ((Mattress* or blanket*) near (warm water or Electric)) or Forced-air warming or (((Intravenous or

irrigation) near fluid*) and warming) or (CO2 near warming) or (anesthetic near warming) or ((thermal or temperature) near manag*)

or (warming or blanket*):ti,ab

#5 (#1 OR #2 OR #3 OR #4)

#6 MeSH descriptor Surgical Procedures, Operative, this term only

#7 MeSH descriptor Operating Rooms explode all trees

#8 MeSH descriptor Recovery Room explode all trees

#9 ((operat* or recovery) near room*):ti,ab

#10 MeSH descriptor General Surgery, this term only

#11 MeSH descriptor Intraoperative Complications explode all trees

#12 MeSH descriptor Postoperative Complications, this term only

#13 MeSH descriptor Preoperative Care explode all trees

#14 MeSH descriptor Postoperative Care explode all trees

#15 MeSH descriptor Intraoperative Care explode all trees

#16 ((operat* or surg*) near complic*):ti,ab or (surg* or operat*):ti,ab or (post?operativ* or pre?operativ* or peri?operativ*):ab

#17 (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)

#18 (#5 AND #17)

#19 BairHugger OR Bair Hugger OR ThermaCare OR Gaymar OR Optisan OR WarmAir OR FilteredFlow OR WarmTouch OR

CareDrape OR Life-Air OR Snuggle Warm OR Warm-Gard

#20 (#18 OR #19)

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