The Effects of Local Warming on Surgical Site Infection

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Abstract

Background: Surgical site infections (SSI) account for a major proportion of hospital-acquired infections. They are associated with longer hospital stay, readmissions, increased costs, mortality, and morbidity. Reducing SSI is a goal of the Surgical Care Improvement Project and identifying interventions that reduce SSI effectively is of interest. In a single-blinded randomized controlled trial (RCT) we evaluated the effect of localized warming applied to surgical incisions on SSI development and selected cellular (immune, endothelial) and tissue responses (oxygenation, collagen).

Methods: After Institutional Review Board approval and consent, patients having open bariatric, colon, or gynecologic-oncologic related operations were enrolled and randomly assigned to local incision warming (6 post-operative treatments) or non-warming. A prototype surgical bandage was used for all patients. The study protocol included intra-operative warming to maintain core temperature $\geq 36^{\circ}\text{C}$ and administration of 0.80 F_1O_2 . Patients were followed for 6 wks for the primary outcome of SSI determined by U.S. Centers for Disease Control (CDC) criteria and ASEPIS scores (additional treatment; presence of serous discharge, erythema, purulent exudate, and separation of the deep tissues; isolation of bacteria; and duration of inpatient stay). Tissue oxygen (PscO_2) and samples for cellular analyses were obtained using subcutaneous polytetrafluoroethylene (ePTFE) tubes and oxygen micro-electrodes implanted adjacent to the incision. Cellular and tissue ePTFE samples were evaluated using flow cytometry, immunohistochemistry, and SircolTM collagen assay (Biocolor Ltd., Carrickfergus, United Kingdom).

Results: One hundred forty-six patients participated ($n=73$ per group). Study groups were similar on demographic parameters and for intra-operative management factors. The CDC defined rate of SSI was 18%; occurrence of SSI between groups did not differ ($p=0.27$). At 2 wks, warmed patients had better ASEPIS scores ($p=0.04$) but this difference was not observed at 6 wks. There were no significant differences in immune, endothelial cell, or collagen responses between groups. On post-operative days one to two, warmed patients had greater PscO_2 change scores with an average PscO_2 increase of 9–10 mm Hg above baseline ($p<0.04$).

Conclusions: Post-operative local warming compared with non-warming followed in this study, which included intra-operative warming to maintain normothermia and F_1O_2 level of 0.80, did not reduce SSI and had no effect on immune, endothelial cell presence, or collagen synthesis. PscO_2 increased significantly with warming, however, the increase was modest and less than expected or what has been observed in studies testing other interventions.

SURGICAL SITE INFECTIONS (SSI) account for a major proportion of hospital-acquired infections. They are associated with longer hospital stay, readmissions, increased costs and mortality, and reduced quality of life [1,2]. Reducing SSI is a goal addressed by the Surgical Care Improvement Project [3,4]. Whereas a number of perioperative care processes have been implemented to decrease SSI, these in-

fections remain a common complication [5]. Identifying new interventions is of particular interest for patients at high risk of SSI either because of type of surgery, individual factors, or both. Patients who undergo colorectal surgery or certain obstetric-gynecologic procedures, such as cesarean delivery and radical oncologic resections, are among those with higher than average SSI risk [1,6].

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Oxygen influences healing in a number of ways and increasing local oxygen delivery may benefit tissue repair. Controlling core temperature and local warming are means to decrease infection and promote surgical incision repair largely by modifying perfusion and oxygen availability to local cells [7]. Surgical patients are at risk for complications related to hypothermia because perioperative reductions in core temperature elicit cutaneous vasoconstriction, reduced tissue oxygen, and impaired immune cell function [8,9]. Data suggest that methods aimed at maintaining perfusion and higher oxygen levels in injured tissues limit SSI after general surgery [10]. Total body warming to normothermia in patients having colorectal surgery reduced SSI by 67% compared with those with core temperatures below 36.5°C [11]. Warming may also support macrophage and T-cell responses required for normal healing [12]. Local warming of injured tissues may have similar benefit to total body warming, although few clinical studies have tested localized warming to determine if this is an effective approach to minimize SSI.

The primary aim of this randomized trial was to evaluate the effect of a post-operative localized warming treatment applied to surgical incisions on the development of SSI in patients known to be at greater risk for SSI and wound complications. Secondary study aims included testing the effect of local warming on selected cellular and tissue responses important to bacterial clearance and healing, including presence of immune and endothelial cells, collagen, and subcutaneous tissue oxygen tension (PscO₂) temperature (Tsc) and perfusion.

Patients and Methods

Study design, patient eligibility, and enrollment

This randomized controlled trial enrolled 146 patients (73 per group) scheduled for abdominal surgery within specific surgical populations at risk for SSI. The target enrollment was 180 patients (83% power, α 0.05), which was based on our pilot data and published report of SSI reduction with warming. We projected infection rates of 36% with non-warming and 18% warming. Patients enrolled in the study were English speaking, 18 years or older, and scheduled for elective open bariatric, colectomy, colostomy, or gynecologic-oncologic related operations. Patients with serum albumin <3.0, serum creatinine >2.5 mg/dL, history of pulmonary edema, or who had received glucocorticoids, chemotherapy, or radiation in the 6 wks prior to surgery were excluded. The individuals responsible for SSI, cellular, and collagen assessments were blinded to the treatment group. Treatment assignment was known during measurement of PscO₂ and Tsc as it occurred during warming; data were collected directly from the monitoring system.

The study was reviewed and approved by the University of Washington Human Subjects Division, and the internal review boards of the medical centers from which the patients were recruited. The study sites included an academic medical center and two community hospitals in the Seattle area. Potential participants were sent a letter of introduction to the study and were then contacted by members of the study team to determine their interest in the study, provide detailed information, and obtain written informed consent. Enrolled patients were randomly assigned to either the local warming group or the non-warming group at the time of surgery using

a computerized system with varied block size and stratified by agency, gender, surgical procedure, diagnosis of diabetes mellitus, and body mass index (BMI).

Procedures

Study protocol. Standard pre-operative protocols at each of the clinical study sites were followed for bowel preparation and prophylactic antibiotic administration. Patients received either general anesthesia alone or general anesthesia with the addition of epidural anesthesia. Fluid administration was based on the judgment of individual anesthesia providers caring for the patients. During the surgical procedure patients were actively warmed with a forced-air warming blanket and monitored with the goal to maintain a core temperature of $\geq 36^\circ\text{C}$. Per protocol, the fraction of inspired oxygen (F_IO₂) was established as 80% or higher. At the end of the surgery, the incision was closed with a running monofilament suture and the skin was closed with staples.

Subcutaneous catheters. After incision closure, study catheters were inserted subcutaneously. Two 10-cm polytetrafluoroethylene (ePTFE, International Polymer Engineering, Tempe, AZ) catheters were inserted parallel to and 2–3 cm distant to each side of the incision using a Keith needle and sutured in place. The catheters were removed on the eighth to ninth post-operative day and processed for the cellular studies.

In a subset of the sample, (n=51; 22 non-warming, 29 warming) a third micro-catheter for measuring PscO₂ and temperature (LICOX CC1.P1, GMS, Kiel-Mielkendorf, Germany) was inserted subcutaneously and adjacent to one of the ePTFE catheters using an introducer (Becton Dickinson 18 GA Introsyte™ Autoguard™, BD Medical Systems, Sandy, UT). The catheters were removed on the second post-operative day.

Surgical dressing. The surgical incisions of all patients were covered with a latex-free, sterile, prototype dressing that consisted of a polyethylene foam frame, cross strips, and a transparent urethane film cover. The dressing was held in place with foam-backed adhesive strips (Arizant Healthcare, Eden Prairie, MN).

Local warming. Patients were randomly assigned to localized warming received this treatment via a chemical warming pack of non-toxic components inside of a self-adhesive, oxygen-permeable polyolefin pouch that generated thermal energy through the reaction of iron with oxygen. The warming reaction was activated once the external foil packaging was removed. The warming pack was placed on the surgical dressing described above. The pack reaches a temperature of 40°–42°C within 10 min of activation and maintains this for 2 h. The first treatment was given in the post-anesthesia recovery unit. Five additional treatments were given thereafter at approximately 8-h intervals so that the last treatment was received on the second post-operative day.

Outcome measures

Surgical site infection. Incision infection and complications were evaluated and documented during the 6-wk period after discharge from the hospital. Two measures were used: ASEPIS wound scoring and U.S. Centers for Disease

Control (CDC) SSI classification. ASEPSIS is an acronym for assessment of wound characteristics that comprises an infection score based on: Additional therapy (antibiotics, debridement), separation of deep tissue, erythema, purulent exudate, serous exudate, isolation of bacteria, and a hospital stay greater than 14 d. Surgical incisions and patient records were evaluated for the ASEPSIS factors. The proportion of the incision that demonstrated any of the characteristics was assigned a score within the range of 0 to 10. The possible range for the ASEPSIS score was 0 to 30. Additional points were added once only for extra treatment (antibiotics, drainage, or debridement of the wound under anesthesia), deep tissue separation, erythema exceeding 5 mm, purulent exudate, serous exudate, isolation of bacteria, and inpatient stay longer than 14 d. ASEPSIS scores were recorded on the ninth post-operative day, and again at two follow-up visits occurring 2 and 6 wks after hospital discharge.

Criteria for SSI established by the CDC differentiate superficial incisional, deep incisional, and organ/space infections based on specific characteristics present at the surgical site [13.] Using the CDC criteria, presence of SSI was documented during the period from hospital discharge to 6 wks. After discharge SSI was evaluated during home visits at 2 wks and 5–6 wks. If an SSI was identified at the 2-wk visit it was documented at that time and followed. At the second follow-up visit, only newly identified SSIs were added to the total SSI events.

Cellular measures. Flow cytometry and immunohistochemistry (IHC) were performed on dedicated sections of the ePTFE catheters removed on post-operative day eight to nine to determine the presence of endothelial cells, macrophages, T cells, and B cells. Our specific methods for these studies are described in detail elsewhere [14].

One portion of the ePTFE was analyzed for presence of collagen using the Sircol™ collagen assay (Biocolor Ltd., Carrickfergus, United Kingdom). Briefly, ePTFE implants were thawed, measured, weighed, and placed in microfuge tubes and incubated in a solution of pepsin A (Worthington, Lakewood, NJ) in 1N acetic acid overnight on a rocker plate at 4°C, as was a standard collagen control solution. The samples were then centrifuged at 13,000g for 10 min and a sample of the supernatant was transferred to a clean tube. Sircol dye reagent was added to this tube according to the kit manufacturer's protocol and the tube was returned to the rocker plate at room temperature. The tubes were then centrifuged and the supernatant discarded. The pellet left behind was dissolved in the kit's alkali reagent. An aliquot of this solution was transferred to a well of a 96-well flat-bottom plate and the absorbance was read at 540 nm on an Emax (Molecular Devices, Sunnyvale, CA). Values were calculated using a standard curve of known values of collagen run on the same plate using the Softmax® Pro Software on the plate reader. Collagen results are expressed as a concentration (mcg)/cm of ePTFE tube.

Tissue oxygen and temperature measures. Subcutaneous tissue oxygen and temperature were measured using the LICOX CC1.P1 combined oxygen and temperature micro-catheter and the LICOXCMP oxygen monitor. The micro-catheter uses a polarographic electrochemical micro-cell for oxygen sensing and uses a Type K thermocouple. The

monitor provides continuous determination of oxygen partial pressure in tissue via the minimally invasive micro-catheter. The system was calibrated automatically and prior to each use using calibration data stored on a smart card that was supplied with each micro-catheter. Accuracy for tissue oxygen tension between 0–20 mm Hg is $\pm 2\%$, 20–50 mm Hg, $\pm 10\%$, and 50–150 mm Hg, $\pm 12\%$ and temperature accuracy is $\pm 0.2^\circ\text{C}$ (GMS Technical Specifications). Intermittent measures were performed in the post-anesthesia recovery unit, and repeated the first and second post-operative days on the patient care unit. For all patients a baseline PscO₂ was established over approximately 20 min. After recording a stable baseline (three consecutive PscO₂ readings varying no more than 1–2 mm Hg) patients received 5 L/min supplemental oxygen via nasal cannula and PscO₂ monitoring continued for an additional 30 min. For patients randomly assigned to warming, the warming pack was applied to the incision at the time baseline PscO₂ and Tsc were recorded and the supplemental oxygen started. The measurement continued for up to 60 min in order to allow tissue temperature to increase in response to warming. At the end of the measurement period the PscO₂ and Tsc were recorded.

Perfusion. Non-invasive measures of perfusion were performed on post-operative days three, five, and nine using laser Doppler flowmetry (LDF) with a two module/probe instrument (PeriFlux 5000, PeriMed, Järfälla, Sweden). A probe attached to the main unit was applied to the skin and micro-vascular blood movement assessed by Doppler effect. The system uses a beam of laser light carried through an optic fiber probe that is scattered and partly absorbed by the tissue. Light hitting moving blood cells undergoes a change in wavelength (Doppler shift) whereas light that contacts static structures is unchanged. The magnitude and frequency distribution of the wavelength changes depending on the number and velocity of blood cells but not their direction of movement [15]. The wavelength data return to the unit by an optic fiber and are converted to electronic signal and analyzed. Measurements are expressed as units of perfusion (PU). Laser Doppler flowmetry results can be affected by tissue temperature, therefore, a provocative heat test in which probe temperature was controlled was used [16]. Use of the heat test allows determination of micro-vascular reserve capacity within the tissue in addition to the total blood flow, when considered with results obtained in the unheated state. Laser Doppler flowmetry measurements were taken at two consistent locations: One laser Doppler probe was positioned next to the surgical incision, the second was placed 15 cm lateral to the incision. After allowing time for equilibration (2 min) LDF readings were recorded for 3 min, establishing baseline flow. The probe was then warmed to 44°C and maximum LDF recorded after 20 min. All data were downloaded to a dedicated laptop computer using companion software (PeriSoft Windows program, PeriMed).

Statistical analysis

Analysis of variance, Mann-Whitney *U*, or Pearson χ^2 or Student *t*-test were used to compare treatment groups on demographic, descriptive, and primary and secondary outcome measures depending on normality of distribution and level of measurement (continuous, categorical). The main

analysis for the effect of the warming intervention was between group comparison on ASEPSIS scores and SSI incidence. Change scores for PscO₂ and Tsc for the 3 d of measurement were calculated between baseline values and after 25 min of non-warming or the warming treatment and analyzed. For analysis of LDF perfusion data, the percent change in perfusion units was calculated on each day between the baseline and in response to the heat challenge. *p* Values were considered significant at *p* < 0.05 (two tailed). Data were analyzed using SPSS version 15.0 for Windows (SPSS, Chicago, IL).

Results

One hundred forty-six patients were enrolled. Recruitment and enrollment history are presented in Figure 1. Four patients in each treatment group were lost to follow-up for the SSI evaluation during the 6 wks of post-discharge follow-up. Of those lost to SSI follow-up, three died from complications unrelated to their surgical site infection, three did not keep their follow-up appointments or could not be contacted, and two required a repeat surgery in the first post-operative week and SSI evaluation of the original surgical wound was not possible.

Demographic and clinical characteristics of patients in the study groups were similar and without statistical differences. Thirteen percent of the study sample was within normal BMI range, 22.6% were overweight, 27.4% were obese, and 37% morbidly obese. Comparisons of clinical characteristics of the study groups are reported in Table 1.

Primary study outcome: Local warming effect on SSI and incision complications

Centers for Disease Control criteria. Twenty-six SSI were identified based on CDC criteria, a rate of 19% in the total sample available for follow-up (*n* = 138). Infection rates by surgical procedure did not differ significantly ($\chi^2 = 4.8$, *p* = 0.09). The CDC categorized SSI occurrences reported by study group are shown in Table 2. The overall infection rate was 38% higher in the warming group than in the control group, with the confidence interval for this estimate ranging from -32% to +180%, i.e., from 32% lower in the warming

group to 180% higher in the warming group. Because this confidence interval (CI) includes zero, the difference between groups was not statistically significant ($\chi^2 = 0.82$, *p* = 0.36). The majority of infections (23/26) were categorized as superficial incision infection by CDC criteria with two deep incision infections (non-warming) and one organ space infection (warmed). The majority of SSI were identified 2–3 wks after hospital discharge. All but one infection occurred in patients who were above normal weight, with the majority (18/26) in the obese or morbidly obese based on BMI.

ASEPSIS evaluation. On post-operative day nine and at 6 wks after discharge there were no significant differences in the category of infection ($\chi^2 3.29$, *p* = 0.348; $\chi^2 2.22$, *p* = 0.32) or the total ASEPSIS score (post-operative day nine: *t* = 0.33 *p* = 0.74, 95% CI -1.5–2.1; 6 wks post-discharge: *t* = 0.85 *p* = 0.39, 95% CI -0.5–1.3). At the 2-wk follow-up assessment there were significant differences between the warming and non-warming treatment groups in both category of infection and comparison of ASEPSIS scores. In the non-warming group there were more disturbances of healing in the surgical incision compared with the warmed group ($\chi^2 8.30$, *p* = 0.04). Mean ASEPSIS scores were 3.9 (non-warming) and 1.6 (warming) (*t* = 2.0, *p* = 0.04, 95% CI 0.05–1.3). Tables 3 and 4 present ASEPSIS data for the treatment groups.

Secondary study outcomes: Cellular and tissue responses to local warming

Angiogenesis and immune cells.

Flow cytometry. Sufficient numbers of cells were isolated from ePTFE incision tissue samples for flow cytometry analysis in 49 patients (*n* = 27 non-warming and 22 warming) although not all samples were tested for all antibodies. We obtained an average of 4.95×10^4 cells/cm of ePTFE tubing. Using fluorescently labeled antibodies CD133 (endothelial progenitor), CD31, CD34, and VEGFR2 endothelial progenitor cells and endothelial cells were identified. The percent of cells staining positively for the respective antigens was identified in each sample and compared between the two study groups. There were no statistically significant differences in

FIG. 1. Patient recruitment, enrollment, and loss to follow-up.

TABLE 1. PATIENT CHARACTERISTICS

	Group	
	Non-warming (n=69)	Warming (n=69)
Demographic		
Age mean (SD)	48.0 (16)	49.0 (13)
BMI mean (SD)	37.0 (12)	36.0 (11)
Gender female (%)	78.1	78.1
Comorbidities (%)		
Current tobacco use	06.8	05.5
Cancer	20.0	31.5
Diabetes mellitus	20.5	17.8
Hypertension	53.4	56.2
Sleep apnea	20.5	26.0
Surgery and anesthesia (%)		
Bariatric surgery	42.5	42.5
Colectomy	28.8	27.4
Gyn/Onc	28.8	30.1
General+epidural analgesia	26.0	26.0
Intra-operative mean (SD)		
ASA score ^a	03.0 (1)	02.0 (1)
Intra-operative F _I O ₂	87.0 (12)	86.0 (12)
Intra-operative core temperature (°C)	36.1 (0.5)	36.5 (0.6)
Intra-operative crystalloids (mL)	3477.7 (1449)	3273.2 (1577)
PACU temperature	36.7 (0.4)	36.7 (0.5)
Hospital stay (days)	04.8 (2.6)	04.9 (3.1)
Post-operative mean (SD)	n=39	n=31
Body temperature (°C) ^b POD 1	36.5 (0.5)	36.7 (0.5)
Body Temperature (°C) POD 2	36.7 (0.5)	37.1 (0.6)

*ASA reported as median (interquartile range, IQR).

**Post-operative temperature prior to tissue oxygen measures with warming/non-warming POD-1 and 2 in sub-sample.

ASA=American Society of Anesthesiologists; BMI=body mass index; SD=standard deviation; PACU=post-anesthesia care unit; Gyn/Onc=gynecologic oncology; POD=post-operative day.

the presence of progenitor or endothelial cells. Mean ranks (non-warming and warming), Mann-Whitney *U* statistic and significance were as follows: For CD 133 (4, 5, *U*=7.5, *p*=0.55); for CD 31 (17, 15, *U*=114, *p*=0.60); for CD 34 (18, 14, *U*=101, *p*=0.26) and for VEGFR2 (17, *p*=0.64).

Immune cells were identified using fluorescently labeled antibodies to CD68 (macrophages), CD3 (T cells), and CD20 (B

cells). The percent of cells staining positively for the respective antigens was identified in each sample and compared between the two study groups. Group differences in immune cell presence within the ePTFE samples were analyzed using the Mann-Whitney *U* statistic. No statistically significant difference in presence of macrophages, and global T cell or B cell populations was found. Mean ranks (non-warming and warming), Mann-Whitney *U* statistic and significance were as follows: CD68 (25, 18, *U*=157, *p*=0.07); CD3 (16, 13, *U*=79 *p*=0.32); CD20 (11, 12, *U*=62 *p*=0.83).

Immunohistochemistry. Analysis of angiogenesis using immunohistochemistry (IHC) was performed on samples of ePTFE of 55 patients in non-warming and 57 who received the warming treatment. Analysis of endothelial cells was performed using antibodies for CD34. There was no statistically significant difference in presence of endothelial cells. Mean rank (non-warming and warming), Mann-Whitney *U* statistic and significance for CD34: 57, 53, *U*=1421, *p*=0.55.

Immunohistochemistry analysis of macrophages and T cells was performed using antibodies to CD68, CD3, and CD20. There were no statistically significant differences in presence of macrophages, global T cell or B cell populations. Mean ranks (non-warming and warming), Mann-Whitney *U* statistic and significance were as follows: CD68 (618, 510, *U*=257, *p*=0.70); CD3 (61, 52, *U*=1335 *p*=0.17); CD20 (55, 58, *U*=1465, *p*=0.41).

Collagen. Micrograms of collagen per centimeter of ePTFE were measured and transformed to a natural logarithmic scale because of skewed distribution of the data. Mean micrograms of collagen per centimeter ePTFE for the warming group was 5.0 mcg (standard deviation [SD] ±0.94) compared with 4.6 mcg (SD ±1.18) for the non-warming treatment group; this difference was not statistically significant (*t*= -1.79; *p*=0.075).

Subcutaneous oxygen and temperature. On the day of surgery in the post-anesthesia unit, there were no differences in the change between baseline and with non-warming or the warming treatment in PscO₂ and Tsc (Mann-Whitney *U* 240, *p*=0.9). Baseline PscO₂ on the three measurement days is shown in Table 5. On the first post-operative day the mean change above baseline for PscO₂ was significantly higher in warmed patients, mean change of 9.7 mm Hg (±8.8) compared with 5.1 (±9.3) (Mann-Whitney *U* 184, *p*=0.01), and a significant increase in Tsc of 0.43°C (±0.73) for warmed patients compared with 0.15 (±0.20) for non-warmed patients (Mann-Whitney *U* 210, *p*=0.04). On the second post-operative day, the mean change in PscO₂ with warming was significantly higher: 10 mm Hg (±9.6) compared with 3.1 (±8.5) non-warming (Mann-Whitney *U* 191, *p*=0.007). However, whereas the mean increase in Tsc with warming was 0.31°C (±0.68) compared with 0.23°C (±0.21) non-warming, this difference was not statistically different.

Perfusion. Because many patients were discharged before the fifth post-operative day there were fewer patients with data at this time point (n=34 per group) compared with post-operative day three (n=65 non-warming, 63 warming) and post-operative day nine (home visit; n=63 non-warming, 57 warming). There was a greater percent change in perfusion

TABLE 2. COMPARISON OF SURGICAL SITE INFECTION FREQUENCY IN NON-WARMING AND WARMING GROUPS BASED ON U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION CRITERIA

CDC SSI category	Non-warming	Warming	Total
Superficial	9	14	23
Incisional			
Deep incisional	2	0	2
Organ space	0	1	1
Total count (%)	11 (15.1)	15 (21)	26 (17.9)

CDC=U.S. Centers for Disease Control; SSI=surgical site infection.

TABLE 3. ASEPSIS INFECTION CATEGORY BY TREATMENT GROUP (FREQUENCY)

Treatment group	Time of follow-up	ASEPSIS category of wound status or infection			
		Satisfactory healing	Disturbed healing	Minor infection	Severe infection
Non-warming (n=65)	POD 9	61	1	1	1
Warmed (n=65)		60	5	0	0
Non-warming (n=63)	2 wks	52	9	1	1
Warmed (n=63)		60	1	2	0
Non-warming (n=62)	6 wks	60	1	1	0
Warmed (n=68)		68	0	0	0

ASEPSIS=wound assessment scale for additional therapy, separation of deep tissue, erythema, purulent exudate, serous exudate, isolation of bacteria, hospital stay > 14 days; POD=post-operative day.

units from baseline to heat challenge on postoperative day three in the non-warming patients (Mann-Whitney U 1614, $p=0.04$); on all other days there were no significant differences between the groups.

Adverse effects of warming

We monitored patients for any adverse effects that might occur with warming or the prototype dressing. We did not observe any adverse events attributable to the warming treatment or dressing, such as discomfort, increased pain, increased wound drainage, inability to contain drainage or skin irritation.

Discussion

Oxygen influences incision healing in a number of ways. Initially, incision tissue is hypoxic, a condition that acts as a stimulus for repair. However, production of reactive oxygen derivatives (ROS) and correction of hypoxia with increased oxygen availability are also necessary to achieve optimum repair [17]. During healing, resistance to pathogens depends largely on oxygen as a substrate for the production of ROS [18]. Control of bacteria by neutrophil and macrophage ROS production at the infection site is in part dependent on local tissue PO_2 levels [19]. Evidence suggests that oxidants also serve as cellular messengers that regulate gene expression associated with promotion of incision healing processes [20]. Micromolar concentrations of H_2O_2 induce expression of vascular endothelial growth factor, a potent activator of endothelial cells during angiogenesis [21]. In addition, synthesis of collagen and new vessels within the forming matrix are responsive to oxygen-dependent enzymes and local oxygen levels [22].

Methods to increase local oxygen delivery are of interest because of their potential to support infection healing and in the case of surgical incisions, to reduce complications such as

infection. Infections in surgical sites account for nearly 20% of all health care associated infections in U.S. hospitals, emphasizing the continuing need for prevention efforts [23]. Mild perioperative hypothermia, a factor that impacts peripheral oxygen availability, is associated with increased SSI risk [24]. Total body warming that maintains normothermic levels in colorectal surgery cases reduced SSI by 67% compared with those with core temperatures below 36.5°C [11]. Extending systemic warming 2 hr prior to and after surgery in addition to during surgery confers additional benefit in limiting SSI in open abdominal bowel resection operations [25]. It has also been shown that local heat increases tissue oxygen dose dependently in normothermic healthy subjects and also during conditions where shivering was induced to elicit thermoregulatory vasoconstriction similar to that produced during anesthesia [26–28]. A limited number of clinical studies suggest a benefit of local warming to clinical wound outcomes, showing higher tissue oxygen and lower SSI rates with local warming. [29] In a randomized clinical trial, Plattner et al. [29] applied local warming to abdominal incisions of 40 patients. Significantly higher $PscO_2$ was reported in patients receiving local warming during immediate post-surgery recovery and on the first post-operative day. Another three-arm study using pre-operative warming techniques found significant differences in infection rates: 4% with local warming, 6% with systemic warming, and 14% in non-warmed patients undergoing clean, elective operations [30].

In pilot work, we evaluated SSI in relation to application of local warming to incisions compared with standard care immediately after surgery and for five additional treatments in patients having gastric bypass or colorectal surgery (total $n=54$). We observed lower rates of SSI with warming compared with standard care (22% versus 37%; unpublished data). Based on these early studies, we hypothesized that local

TABLE 4. TOTAL ASEPSIS SCORES AT POST-HOSPITAL DISCHARGE FOLLOW-UP (MEAN $\pm$ STANDARD DEVIATION)

Treatment group	ASEPSIS score at follow-up		
	POD 9	2 wks	6 wks
Non-warming (n=65)	2.2 (6.5)	3.9 (8.0)*	0.73 (3.7)
Warmed (n=65)	1.8 (3.5)	1.6 (4.5)	0.32 (0.8)

* t -test, $p=0.04$.

POD=post-operative day.

TABLE 5. SUBCUTANEOUS TISSUE OXYGENATION AT STABLE BASELINE

Study day	$PscO_2$ mm Hg mean (SD)	
	Non-warming	Warming
Day of surgery	51.8 (29.8)	48.5 (20.1)
First POD	54.4 (08.8)	50.6 (11.2)
Second POD	45.1 (13.0)	47.6 (22.3)

$PscO_2$ =tissue oxygenation; SD=standard deviation; POD=post-operative day.

warming would reduce SSI and promote healing by increasing oxygen availability and supporting both production of matrix components (angiogenesis, collagen) and immune response. However, in our randomized clinical trial there was no difference in CDC-defined SSI frequency or type, the primary study outcome, with the use of local warming provided early in the post-anesthesia recovery period and for five additional treatments at 8-h intervals compared with non-warming. The majority of SSIs observed in this study were classed as superficial according to CDC criteria. Differences observed based on surgical incision characteristics and ASESIS scores 2 wks after discharge did not persist to the 6-wk point. Therefore, any early benefit to warming does not seem to influence longer term outcome. Observed differences may also have been chance occurrences among the repeated measures and comparisons. The local warming treatment also demonstrated no effect on the secondary outcomes related to our hypothesis of increasing cellular responses. Immune and endothelial cell recruitment and the production of collagen did not differ by treatment group. It is possible that some baseline characteristics between the treatment groups might have influenced results, but among the many factors that we evaluated we found groups to be equivalent.

Several years ago, observational data suggested that higher oxygen levels in injured tissues are associated with lower infection rates after general surgery [10]. Initial research on the use of higher oxygen concentrations during surgery compared with control demonstrated significant benefit [31]. However, subsequent clinical trials aimed to reduce SSI by raising incision oxygen levels through increasing the fraction of inspired oxygen (F_{iO_2}), as well as recent meta-analyses have produced mixed results in terms of the benefit of higher F_{iO_2} and reduction in SSI [6,32–40]. One meta-analysis of seven clinical trials evaluating hyperoxia to low oxygen or control to prevent SSI found that hyperoxia was not beneficial overall, although benefit was found after sub-analysis of general anesthesia cases (exclusion of neuraxial anesthesia specifically) and colorectal operations [38]. Several factors related to study design, protocols, and SSI outcome measurement have been identified as explanations for the wide variance in outcome regarding the efficacy of perioperative high inspired oxygen therapy to reduce SSI [41].

Another approach to increasing tissue oxygen is through total body warming using forced air warming devices or local warming application as noted in the studies described. Patients in this study were warmed during surgery with forced air warming to maintain normothermia. With local warming we observed significant increases in $PscO_2$ and Tsc in response to warming during measurements recorded on the first 2 d after surgery. The mean increase in $PscO_2$ observed in our study patients with warming (10 mm Hg) is lower than results of Plattner et al. [29] who reported higher mean $PscO_2$ (17–32 mm Hg) adjacent to incisions warmed with a temperature-controlled, experimental bandage system compared with an incision dressing of gauze and elastic adhesive. They also noted that $PscO_2$ was higher using the experimental dressing without the heat application compared with the gauze/elastic combination dressing, suggesting that bandage pressure is an important factor in limiting tissue oxygen. Compared with our results, $PscO_2$ was higher in the study by Ikeda et al. [27] who observed a 50% increase in $PscO_2$ with local warming in normal volunteer subjects. The collagen results they reported

were similar to ours as they observed no benefit of local warming to collagen deposition in ePTFE created surgical incisions. Whereas these studies documented a positive effect of warming on $PscO_2$, neither included measures of incision infection.

The timing of local warming may be a critical factor. It is not currently known if post-operative local warming in addition to pre-operative warming would add benefit to the effects demonstrated with pre-operative local warming. In the only other study of which we are aware to test local warming in patients having surgery and document development of SSI, Melling et al. [30] found that pre-operative warming (systemic or local) was effective in reducing SSI, but did not include measures of tissue oxygen in their trial. In our study we initiated local warming soon after surgery, in the post-anesthesia care unit, but did not warm pre-operatively. The increases in Tsc with post-operative warming that we observed were in the range of 0.3° – 0.5° C. In healthy subjects the increase has typically been higher with reports of increased Tsc in the range of 0.5° – 3.0° C within a similar period of warming application (30 min) [26].

Overall, we found that the effect of warming on $PscO_2$ and Tsc showed increases that were modest, less than expected, and less than what has been observed in other studies testing local warming. In our study, we did not use a standard bandage for comparison, but instead used the prototype dressing without warming as a control. It is possible that some of the differences in $PscO_2$ and Tsc in our study compared with earlier reports are because of this difference. Any detrimental pressure exerted by the bandage would have been essentially the same in each group and it is possible that the prototype bandage alone produced an insulating effect on tissue temperature. This was reported by Plattner et al. [29], although the bandage and heating system used an earlier version of the system, which was different than what was used in this study. They also reported a higher $PscO_2$ with warming, on average 17 mm Hg higher for warming compared with conventional surgical bandage. The warming system used an electrically powered warming card rather than a chemical pack. This was also the system used in our pilot study but was no longer available at the time of this study. The two systems were designed by the same manufacturer and provided the same temperatures when heated or activated.

During $PscO_2$ measurement and after baseline was established, patients received supplemental oxygen via nasal cannula rather than face mask because it was better tolerated. This might account for the lower $PscO_2$ levels we observed. Another factor may be the direct electrode insertion measurement method for $PscO_2$ that was used rather than an electrode-tonometer system, although direct measurement correlates significantly ($R=0.64$; $p<0.01$) with the electrode-tonometer system [42]. In addition, we enrolled a large number of patients with high BMI, which may have been a factor. Lower tissue oxygen levels are reported in studies of obese individuals although these studies did not involve local warming [42,43].

Type of anesthesia is an additional factor to consider that may have affected tissue oxygenation and perfusion outcomes. The patients enrolled in this trial received general anesthesia or a combination of general and epidural. General and epidural anesthesia inhibit central thermoregulatory vasoconstriction and are reported to increase tissue oxygenation [44,45]. The

addition of epidural to general anesthesia is associated with significant increase in tissue oxygen levels [45]. Although the precise impact of epidural analgesia on incision perfusion and P_{scO_2} in our study patients is uncertain, we believe this is unlikely to be a factor in light of the balanced distribution of the use of epidural analgesia between the study groups. In addition to anesthesia, tissue oxygenation may have been influenced by intra-operative fluid administration, which was determined based on anesthesia provider judgment. During the time period of the study, anesthesia providers in general and in the participating institutions were evaluating the merits of liberal or more restrictive fluid administration practices. There was no evidence that the providers in the participating institutions were outliers in the area of fluid resuscitation practices and our data did not show differences for intra-operative fluids between study groups.

Limitations

The number of patients enrolled in this study and the rate of infection were lower than what was planned or expected prior to the study. Twenty-six infections were observed, lower than the predicted number of 48. The power for the study is therefore less than what was expected in advance. This is reflected in the wide CI for the ratio of infection rates given in the results section. However, as reflected in the CI, the data are not consistent with a 50% reduction in SSI with warming as was expected.

The warming system we used was different than that described in other studies and that used in our preliminary study. That system was no longer available when this study was conducted. We used the next generation warming device manufactured by the same company. This may have influenced our results, although the temperature, timing, and duration of warming provided with the warming system were similar to what was delivered in our pilot work.

Local warming delivered according to the protocol followed in this study, which included intra-operative warming to maintain normothermia and an F_{iO_2} level of 0.80, did not provide additional benefit in terms of limiting SSI. Our results did not elucidate cellular- or tissue-specific mechanisms that might be present under conditions of local warming. Surgical site infection remains an important focus for patient safety; indeed, even less serious cases of SSI can result in additional costs, slowed recovery, or delayed return to normal activities or work. Whereas the importance of oxygen and perfusion are understood in terms of biologic mechanisms that assist the control of infection [46], clinical interventions to support these factors effectively in hopes of achieving better SSI clinical outcomes remain to be studied and confirmed.

Acknowledgment

This research was supported by the National Institutes of Health, NINR Grant R01 NR009057.

Author Disclosure Statement

The authors have no conflicts of interest.

References

1. Murray BW, Huerta S, Dineen S, et al. Surgical site infection in colorectal surgery: A review of the non-pharmacologic tools of prevention. *J Am Coll Surg* 2010;211:812–822.
2. Wick EC, Hirose K, Shore AD, et al. Surgical site infections and cost in obese patients undergoing colorectal surgery. *Arch Surg*. 2011;146:1068–1072.
3. Bratzler DW, Hunt DR. The surgical infection prevention and surgical care improvement projects: National initiatives to improve outcomes for patients having surgery. *Clin Infect Dis* 2006;43:322–330.
4. Fry DE. Surgical site infections and the surgical care improvement project (SCIP): Evolution of national quality measures. *Surg Infect* 2008;9:579–584.
5. Anthony T, Murray BW, Sum-Ping JT, et al. Evaluating an evidence-based bundle for preventing surgical site infection: A randomized trial. *Arch Surg*. 2011;146:263–269.
6. Scifres CM, Leighton BL, Fogertey PJ, et al. Supplemental oxygen for the prevention of postcesarean infectious morbidity: A randomized controlled trial. *Am J Obstet Gynecol* 2011;205:267e1–9.
7. Sessler DI, Akca O. Nonpharmacological prevention of surgical wound infections. *Clin Infect Dis* 2002;35:1397–1404.
8. Lee SL, Battistella FD, Go K. Hypothermia induces T-cell production of immunosuppressive cytokines. *J Surg Res* 2001;100:150–153.
9. Salman H, Bergman M, Bessler H, et al. Hypothermia affects the phagocytic activity of rat peritoneal macrophages. *Acta Physiol Scand* 2000;168:431–436.
10. Hopf HW, Hunt TK, West JM, et al. Wound tissue oxygen tension predicts the risk of wound infection in surgical patients. *Arch Surg* 1997;132:997–1004.
11. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. *N Engl J Med* 1996;334:1209–1215.
12. Schaffer M, Barbul A. Lymphocyte function in wound healing and following injury. *Br J Surg* 1998;85:444–460.
13. Horan TC, Gaynes RP, Martone WJ, et al. CDC definitions of nosocomial surgical site infections, 1992: A modification of CDC definitions of surgical wound infections. *Infect Control Hosp Epidemiol* 1992;13:606–608.
14. Tsuji JM, Whitney JD, Tolentino EJ, et al. Evaluation of cellular wound healing using flow cytometry and expanded polytetrafluoroethylene implants. *Wound Repair Regen* 2010;18:335–340.
15. Fischer JC, Parker PM, Shaw WW. Laser Doppler flow-meter measurements of skin perfusion changes associated with arterial and venous compromise in the cutaneous island flap. *Microsurgery* 1985;6:238–243.
16. Sheffield PJ, Smith APS, Fife CE (eds): *Wound Care Practice*. Flagstaff, AZ: Best Publishing, 2004.
17. Hunt TK, Ellison EC, Sen CK. Oxygen: At the foundation of wound healing—Introduction. *World J Surg* 2004;28:291–293.
18. Benhaim P, Hunt TK. Natural resistance to infection: Leukocyte functions. *J Burn Care Rehabil* 1992;13:287–292.
19. Allen DB, Maguire JJ, Mahdavian M, et al. Wound hypoxia and acidosis limit neutrophil bacterial killing mechanisms. *Arch Surg* 1997;132:991–996.
20. Sen CK, Khanna S, Gordillo G, et al. Oxygen, oxidants, and antioxidants in wound healing: An emerging paradigm. *Ann NY Acad Sci* 2002;957:239–249.
21. Sen CK, Khanna S, Babior BM, et al. Oxidant-induced vascular endothelial growth factor expression in human keratinocytes and cutaneous wound healing. *J Biol Chem* 2002;277:33284–33290.

22. Gordillo GM, Hunt TK, Sen CK. Significance of oxygen therapeutics. *Wound Repair Regen* 2003;11:393.
23. Klevens RM, Edwards JR, Richards CL Jr, et al. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. *Public Health Rep* 2007;122:160–166.
24. Flores-Maldonado A, Medina-Escobedo CE, Rios-Rodriguez HM, et al. Mild perioperative hypothermia and the risk of wound infection. *Arch Med Res* 2001;32:227–231.
25. Wong PF, Kumar S, Leaper DJ. Systemic warming as an adjunct to resuscitation in peritonitis: A pilot, randomized controlled trial. *Surg Infect* 2007;8:387–395.
26. Rabkin JM, Hunt TK. Local heat increases blood flow and oxygen tension in wounds. *Arch Surg* 1987;122:221–225.
27. Ikeda T, Tayefeh F, Sessler DI, et al. Local radiant heating increases subcutaneous oxygen tension. *Am J Surg* 1998;175:33–37.
28. Sheffield CW, Sessler DI, Hopf HW, et al. Centrally and locally mediated thermoregulatory responses alter subcutaneous oxygen tension. *Wound Repair Regen* 1996;4:339–345.
29. Plattner O, Akca O, Herbst F, et al. The influence of 2 surgical bandage systems on wound tissue oxygen tension. *Arch Surg* 2000;135:818–822.
30. Melling AC, Ali B, Scott EM, et al. Effects of preoperative warming on the incidence of wound infection after clean surgery: A randomised controlled trial. *Lancet* 2001;358:876–880.
31. Greif R, Akca O, Horn EP, et al. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *N Engl J Med* 2000;342:161–167.
32. Pryor KO, Fahey TJ 3rd, Lien CA, et al. Surgical site infection and the routine use of perioperative hyperoxia in a general surgical population: A randomized controlled trial. *JAMA* 2004;291:79–87.
33. Belda FJ, Aguilera L, Garcia de la Asuncion J, et al. Supplemental perioperative oxygen and the risk of surgical wound infection: A randomized controlled trial. *JAMA* 2005;294:2035–2042.
34. Gardella C, Goltra LB, Laschansky E, et al. High-concentration supplemental perioperative oxygen to reduce the incidence of postcesarean surgical site infection: A randomized controlled trial. *Obstet Gynecol* 2008;112:545–552.
35. Meyhoff CS, Wetterslev J, Jorgensen LN, et al. Effect of high perioperative oxygen fraction on surgical site infection and pulmonary complications after abdominal surgery: The PROXI randomized clinical trial. *JAMA* 2009;302:1543–1550.
36. Bickel A, Gurevits M, Vamos R, et al. Perioperative hyperoxygenation and wound site infection following surgery for acute appendicitis: A randomized, prospective, controlled trial. *Arch Surg* 2011;146:464–470.
37. Myles PS, Leslie K, Chan MT, et al. Avoidance of nitrous oxide for patients undergoing major surgery: A randomized controlled trial. *Anesthesiology* 2007;107:221–231.
38. Togioka B, Galvagno S, Sumida S, et al. The role of perioperative high inspired oxygen therapy in reducing surgical site infection: A meta-analysis. *Anesth Analg* 2012;114:334–342.
39. Patel SV, Coughlin SC, Malthaner RA. High-concentration oxygen and surgical site infections in abdominal surgery: A meta-analysis. *Can J Surg* 2013;56:E82–90.
40. Hovaguimian F, Lysakowski C, Elia N, et al. Effect of intraoperative high inspired oxygen fraction on surgical site infection, postoperative nausea and vomiting, and pulmonary function: Systematic review and meta-analysis of randomized controlled trials. *Anesthesiology* 2013;119:303–316.
41. Qadan M, Akca O. Reassessing the role of supplemental oxygen in the prevention of surgical site infection. *Ann Surg* 2012;256:902–903.
42. Pasarica M, Sereda OR, Redman LM, et al. Reduced adipose tissue oxygenation in human obesity: Evidence for rarefaction, macrophage chemotaxis, and inflammation without an angiogenic response. *Diabetes* 2009;58:718–725.
43. Kabon B, Rozum R, Marschalek C, et al. Supplemental postoperative oxygen and tissue oxygen tension in morbidly obese patients. *Obes Surg* 2010;20:885–894.
44. Kabon B, Fleischmann E, Treschan T, et al. Thoracic epidural anesthesia increases tissue oxygenation during major abdominal surgery. *Anesth Analg* 2003;97:1812–1817.
45. Treschan TA, Taguchi A, Ali SZ, et al. The effects of epidural and general anesthesia on tissue oxygenation. *Anesth Analg* 2003;96:1553–1557.
46. Sessler DI. Supplemental oxygen and surgical site infection. *Arch Surg* 2011;146:1221–1222.

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