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PERIOPERATIVE NORMOTHERMIA TO REDUCE THE INCIDENCE OF SURGICAL-WOUND INFECTION AND SHORTEN HOSPITALIZATION

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Abstract *Background.* Mild perioperative hypothermia, which is common during major surgery, may promote surgical-wound infection by triggering thermoregulatory vasoconstriction, which decreases subcutaneous oxygen tension. Reduced levels of oxygen in tissue impair oxidative killing by neutrophils and decrease the strength of the healing wound by reducing the deposition of collagen. Hypothermia also directly impairs immune function. We tested the hypothesis that hypothermia both increases susceptibility to surgical-wound infection and lengthens hospitalization.

Methods. Two hundred patients undergoing colorectal surgery were randomly assigned to routine intraoperative thermal care (the hypothermia group) or additional warming (the normothermia group). The patients' anesthetic care was standardized, and they were all given cefamandole and metronidazole. In a double-blind protocol, their wounds were evaluated daily until discharge from the hospital and in the clinic after two weeks; wounds containing culture-positive pus were considered infected. The patients' surgeons remained unaware of the patients' group assignments.

Results. The mean (±SD) final intraoperative core temperature was 34.7±0.6°C in the hypothermia group and 36.6±0.5°C in the normothermia group ($P<0.001$). Surgical-wound infections were found in 18 of 96 patients assigned to hypothermia (19 percent) but in only 6 of 104 patients assigned to normothermia (6 percent, $P=0.009$). The sutures were removed one day later in the patients assigned to hypothermia than in those assigned to normothermia ($P=0.002$), and the duration of hospitalization was prolonged by 2.6 days (approximately 20 percent) in the hypothermia group ($P=0.01$).

Conclusions. Hypothermia itself may delay healing and predispose patients to wound infections. Maintaining normothermia intraoperatively is likely to decrease the incidence of infectious complications in patients undergoing colorectal resection and to shorten their hospitalizations. (N Engl J Med 1996;334:1209-15.)

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WOUND infections are common and serious complications of anesthesia and surgery. A wound infection can prolong hospitalization by 5 to 20 days and substantially increase medical costs.[1,2] In patients undergoing colon surgery, the risk of such an infection ranges from 3 to 22 percent, depending on such factors as the length of surgery and underlying medical problems.[3] Mild perioperative hypothermia (approximately 2°C below the normal core body temperature) is common in colon surgery.[4] It results from anesthetic-induced impairment of thermoregulation,[5,6] exposure to cold, and altered distribution of body heat.[7] Although it is rarely desired, intraoperative hypothermia is usual because few patients are actively warmed.[8]

Hypothermia may increase patients' susceptibility to perioperative wound infections by causing vasoconstriction and impaired immunity. The presence of sufficient intraoperative hypothermia triggers thermoregulatory vasoconstriction,[9] and postoperative vasoconstriction is universal in patients with hypothermia.[10] Vasoconstriction decreases the partial pressure of oxygen in tissues, which lowers resistance to infection in animals[11,12] and humans (unpublished data). There is decreased microbial killing, partly because the production of oxygen and nitroso free radicals is oxygen-dependent in the range of the partial pressures of oxygen in wounds.[13,14] Mild core hypothermia can also directly impair immune functions, such as the chemotaxis and phagocytosis of granulocytes, the motility of macrophages, and the production of antibody.[15,16] Mild hypothermia, by decreasing the availability of tissue oxygen, impairs oxidative killing by neutrophils. And mild hypothermia during anesthesia lowers resistance to inoculations with *Escherichia coli*[17] and *Staphylococcus aureus*[18] in guinea pigs.

Vasoconstriction-induced tissue hypoxia may decrease the strength of the healing wound independently of its ability to reduce resistance to infection. The formation

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of scar requires the hydroxylation of abundant proline and lysine residues to form the cross-links between strands of collagen that give healing wounds their tensile strength.[19] The hydroxylases that catalyze this reaction are dependent on oxygen tension,[20] making collagen deposition proportional to the partial pressure of arterial oxygen in animals[21] and to oxygen tension in wound tissue in humans.[22]

Although safe and inexpensive methods of warming are available,[8] perioperative hypothermia remains common.[23] Accordingly, we tested the hypothesis that mild core hypothermia increases both the incidence of surgical-wound infection and the length of hospitalization in patients undergoing colorectal surgery.

METHODS

With the approval of the institutional review board at each participating institution and written informed consent from the patients, we studied patients 18 to 80 years of age who underwent elective colorectal resection for cancer or inflammatory bowel disease. Patients scheduled for abdominal–peritoneal pull-through procedures were included, but not those scheduled for minor colon surgery (e.g., polypectomy or colostomy performed as the only procedure). The criteria for exclusion from the study were any use of corticosteroids or other immunosuppressive drugs (including cancer chemotherapy) during the four weeks before surgery; a recent history of fever, infection, or both; serious malnutrition (serum albumin, less than 3.3 g per deciliter, a white-cell count below 2500 cells per milliliter, or the loss of more than 20 percent of body weight); or bowel obstruction.

The number of patients required for this trial was estimated on the basis of a preliminary study in which 80 patients undergoing elective colon surgery were randomly assigned to hypothermia (mean [±SD] temperature, 34.4±0.4°C) or normothermia (involving warming with forced air and fluid to a mean temperature of 37±0.3°C). The number of wound infections (as defined by the presence of pus and a positive culture) was evaluated by an observer unaware of the patients' temperatures and group assignments. Nine infections occurred in the 38 patients assigned to hypothermia, but there were only four in the 42 patients assigned to normothermia ($P = 0.16$). Using the observed difference in the incidence of infection, we determined that an enrollment of 400 patients would provide a 90 percent chance of identifying a difference with an alpha value of 0.01. We therefore planned to study a maximum of 400 patients, with the results to be evaluated after 200 and 300 patients had been studied. The prospective criterion for ending the study early was a difference in the incidence of surgical-wound infection between the two groups with a P value of less than 0.01. To compensate for the two initial analyses, a P value of 0.03 would be required when the study of 400 patients was completed. The combined risk of a type I error was thus less than 5 percent.[24]

Study Protocol

The night before surgery, each patient underwent a standard mechanical bowel preparation with an electrolyte solution. Intraluminal antibiotics were not used, but treatment with cefamandole (2 g intravenously every eight hours) and metronidazole (500 mg intravenously every eight hours) was started during the induction of anesthesia; this treatment was maintained for about four days postoperatively. Anesthesia was induced with thiopental sodium (3 to 5 mg per kilogram of body weight), fentanyl (1 to 3 μg per kilogram), and vecuronium bromide (0.1 mg per kilogram). The administration of isoflurane (in 60 percent nitrous oxide) was titrated to maintain the mean arterial blood pressure within 20 percent of the preinduction values. Additional fentanyl was administered on the completion of surgery, to improve analgesia when the patient emerged from anesthesia.

The patients were hydrated aggressively during and after surgery, because hypovolemia decreases wound perfusion and increases the incidence of infection.[25,26] We administered 15 ml of crystalloid per kilogram per hour throughout surgery and replaced the volume of blood lost with either crystalloid in a 4:1 ratio or colloid in a 2:1 ratio. Fluids were administered intravenously at rates of 3.5 ml per kilogram per hour for the first 24 postoperative hours and 2 ml per kilogram per hour for the subsequent 24 hours. Leukocyte-depleted blood was administered as the attending surgeon considered appropriate.

At the time of the induction of anesthesia, each patient was randomly assigned to one of the following two temperature-management groups with computer-generated codes maintained in numbered, sealed, opaque envelopes: the normothermia group, in which the patients' core temperatures were maintained near 36.5°C, and the hypothermia group, in which the core temperature was allowed to decrease to approximately 34.5°C. In both groups, intravenous fluids were administered through a fluid warmer, but the warmer was activated only in the patients assigned to extra warming. Similarly, a forced-air cover (Augustine Medical, Eden Prairie, Minn.) was positioned over the upper body of every patient, but it was set to deliver air at the ambient temperature in the hypothermia group and at 40°C in the normothermia group. Cardboard shields and sterile drapes were positioned in such a way that the surgeons could not discern the temperature of the gas inflating the cover. Shields were also positioned over the switches governing the fluid heater and the forced-air warmer so that their settings were not apparent to the operating-room personnel. The temperatures were not controlled postoperatively, and the patients were not informed of their group assignments.

Supplemental oxygen was administered through nasal prongs at a rate of 6 liters per minute during the first three postoperative hours and was then gradually eliminated while oxygen saturation was maintained at more than 95 percent. To minimize the decrease in wound perfusion due to activation of the sympathetic nervous system, postoperative pain was treated with piritramide (an opioid), the administration of which was controlled by the patient.

The attending surgeons, who were unaware of the patients' group assignments and core temperatures, determined when to begin feeding them again after surgery, remove their sutures, and discharge them from the hospital. The timing of discharge was based on routine surgical considerations, including the return of bowel function, the control of any infections, and adequate healing of the incision.

Measurements

The patients' morphometric characteristics and smoking history were recorded. The preoperative laboratory evaluation included a complete blood count; determinations of the prothrombin time and partial-thromboplastin time; measurements of serum albumin, total protein, and creatinine; and liver-function tests. The risk of infection was scored with a standardized algorithm taken from the Study on the Efficacy of Nosocomial Infection Control (SENIC) of the Centers for Disease Control and Prevention; in this scoring system, one point each is assigned for the presence of three or more diagnoses, surgery lasting two hours or more, surgery at an abdominal site, and the presence of a contaminated or infected wound.[2] The scoring system was modified slightly from its original form by the use of the diagnoses made at admission, rather than discharge. The risk of infection was quantified further with the use of the National Nosocomial Infection Surveillance System (NNISS), a scoring system in which the patient's risk of infection was predicted on the basis of the type of surgery, the patient's physical-status rating on a scale developed by the American Society of Anesthesiologists, and the duration of surgery.[3]

Core temperatures were measured at the tympanic membrane (Mallinckrodt Anesthesiology Products, St. Louis), with values recorded preoperatively, at 10-minute intervals intraoperatively, and at 20-minute intervals for 6 hours during recovery. Arteriovenous-shunt flow was quantified by subtracting the skin temperature of the fingertip from that of the forearm, with values exceeding 0°C indicating thermoregulatory vasoconstriction.[27] End-tidal concentrations of isoflurane and carbon dioxide were recorded at 10-minute intervals during anesthesia. Measurements of arterial blood pressure and heart rate were recorded similarly during anesthesia and for six hours thereafter. Oxyhemoglobin saturation was measured by pulse oximetry.

Thermal comfort was evaluated at 20-minute intervals for 6 hours postoperatively with a 100-mm visual-analogue scale on which 0 mm denoted intense cold, 50 mm denoted thermal comfort, and 100 mm denoted intense warmth. The degree of surgical pain was evaluated similarly, except that 0 mm denoted no pain and 100 mm the most intense pain imaginable. Shivering was assessed qualitatively, on a scale on which 0 denoted no shivering; 1, mild or intermittent shivering; 2, moderate shivering; and 3, continuous, intense shivering. All

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the qualitative assessments were made by observers unaware of the patients' group assignments and core temperatures.

The patients' surgical wounds were evaluated daily during hospitalization and again two weeks after surgery by a physician who was unaware of the group assignments. Wounds were suspected of being infected when pus could be expressed from the surgical incision or aspirated from a loculated mass inside the wound. Samples of pus were obtained and cultured for aerobic and anaerobic bacteria, and wounds were considered infected when the culture was positive for pathogenic bacteria. All the wound infections diagnosed within 15 days of surgery were included in the data analysis.

Wound healing and infections were also evaluated by the ASEPSIS system,[28] in which a score is calculated as the weighted sum of points assigned to the following factors: the duration of antibiotic administration, the drainage of pus during local anesthesia, the débridement of the wound during general anesthesia, the presence of a serous discharge, the presence of erythema, the presence of a purulent exudate, the separation of deep tissues, the isolation of bacteria from fluid discharged from the wound, and a duration of hospitalization exceeding 14 days. Scores exceeding 20 on this scale indicate wound infection. As an additional indicator of infection, preoperative differential white-cell counts were compared with counts obtained on postoperative days 1, 3, and 6.

Collagen deposition in the wound was evaluated in a subgroup of 30 patients in the normothermia group and 24 patients in the hypothermia group. A 10-cm expanded polytetrafluoroethylene tube (Impra, International Polymer Engineering, Tempe, Ariz.) was inserted subcutaneously several centimeters lateral to the incision at the completion of surgery. On the seventh postoperative day, the tube was removed and assayed for hydroxyproline, a measure of collagen deposition.[29] The ingrowth of collagen in such tubes is proportional to the tensile strength of the healing wound[29] and the subcutaneous oxygen tension.[22]

Statistical Analysis

Outcomes were evaluated on an intention-to-treat basis. The number of postoperative wound infections in each study group and the proportion of smokers among the infected patients were analyzed by Fisher's exact test. Scores for wound healing, the number of days of hospitalization, the extent of collagen deposition, postoperative core temperatures, and potential confounding factors were evaluated by unpaired, two-tailed t-tests. Factors that potentially contributed to infection were included in a univariate analysis. Those that correlated significantly with infection were then included in a multivariate logistic regression with backward elimination; a P value of less than 0.25 was required for a factor to be retained in the analysis.

All the results are presented as means ±SD. A P value of less than 0.01 was required to indicate a significant difference in our major outcomes (the incidence of infection and the duration of hospitalization); a P value of less than 0.005 was considered to indicate a significant difference in postoperative temperature (to compensate for multiple comparisons); for all other data, a P value of less than 0.05 was considered to indicate a statistically significant difference.

RESULTS

Patients were enrolled in the study from July 1993 through March 1995; 155 were evaluated at the University of Vienna, 30 at the University of Graz, and 15 at Rudolfstiftung Hospital. According to the investigational protocol, the study was stopped after 200 patients were enrolled, because the incidence of surgical-wound infection in the two study groups differed with an alpha level of less than 0.01. One hundred four patients were assigned to the normothermia group, and 96 to the hypothermia group. An audit confirmed that the patients had been properly assigned to the groups and that the slight disparity in numbers was present in the original computer-generated randomization codes. All the patients allowed their wounds to be evaluated daily during hospitalization. Ninety-four percent returned for the two-week clinic visit after discharge; those who did not were evenly distributed between the study groups and mostly returned to visit the private offices of their attending surgeons. The wound status of these patients was determined by calling the physician. No previously unidentified wound infections were detected in the clinic for the first time.

Table 1 shows that the characteristics, diagnoses, types of surgical procedure, duration of surgery, hemodynamic values, and types of anesthesia of the patients in the two study groups were similar. Nor did smoking status, the results of preoperative laboratory tests, or preoperative laboratory values differ significantly between the groups. The patients assigned to hypothermia required more transfusions of allogeneic blood (P=0.01). Intraoperative vasoconstriction was observed in 74 percent of the patients assigned to hypothermia but in only

Table 1. Characteristics of the Patients in the Two Study Groups.*

CHARACTERISTIC	NORMOTHERMIA (N=104)	HYPOTHERMIA (N=96)	P VALUE
Male sex (no. of patients)	58	50	0.70
Weight (kg)	73±14	71±14	0.31
Height (cm)	170±9	169±9	0.43
Age (yr)	61±15	59±14	0.33
History of smoking (no. of patients)	33	29	0.94
Diagnosis (no. of patients)			
Inflammatory bowel disease	10	8	0.94
Cancer	94	88	
Duke's stage			1.0
A	29	30	
B	37	34	
C	26	21	
D	2	3	
Operative site			0.61
Colon	59	51	
Rectum	35	37	
Preoperative variables			
Core temperature (°C)	36.8±0.4	36.7±0.4	0.08
Hemoglobin (g/dl)	12.6±2.3	12.7±2.0	0.74
Intraoperative variables			
Fentanyl administered (mg)	0.7±0.3	0.6±0.5	0.09
End-tidal isoflurane (%)	0.6±0.1	0.6±0.2	1.0
Arterial blood pressure (mm Hg)	91±17	95±18	0.11
Heart rate (beats/min)	74±17	76±13	0.35
Crystalloid (liters)	3.3±1.5	3.2±0.9	0.57
Colloid (liters)	0.2±0.3	0.2±0.3	1.0
Red-cell transfusion (no. of patients)	23	34	0.054
Volume of blood transfused (units)	0.4±1.0	0.8±1.2	0.01
Urine output (liters)	0.6±0.4	0.7±0.4	0.08
Duration of surgery (hr)	3.1±1.0	3.1±0.9	1.0
Ambient temperature (°C)	21.9±1.2	22.1±0.9	0.19
Oxyhemoglobin saturation (%)	97.3±1.5	97.5±1.3	0.32
Final core temperature (°C)	36.6±0.5	34.7±0.6	<0.001
Postoperative variables			
Hemoglobin (g/dl)	11.7±1.9	11.6±1.4	0.67
Prophylactic antibiotics (days)	3.7±1.9	3.6±1.4	0.67
SENIC score (no. of patients)			0.98
1	3	3	
2	95	88	
3	6	5	
NNISS score (no. of patients)			0.6
0	32	31	
1	49	39	
2	23	26	
Infection rate predicted by NNISS (%)	8.9	8.8	—
Oxyhemoglobin saturation (%)	98±1	98±1	1.0
Piritramide (mg)†	20±13	22±12	0.26

*Plus–minus values are means ±SD. SENIC denotes Study on the Efficacy of Nosocomial Infection Control, and NNISS National Nosocomial Infection Surveillance System.

†The administration of this analgesic agent was controlled by the patient.

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6 percent of those assigned to normothermia (P<0.001). Core temperatures at the end of surgery were significantly lower in the hypothermia group than in the normothermia group (34.7±0.6 vs. 36.6±0.5°C, P<0.001), and they remained significantly different for more than five hours postoperatively (Fig. 1).

Postoperative vasoconstriction was observed in 78 percent of the patients in the hypothermia group; the vasoconstriction continued throughout the six-hour recovery period. In contrast, vasoconstriction, usually short-lived, was observed in only 22 percent of the patients in the normothermia group (P<0.001). Shivering was observed in 59 percent of the hypothermia group, but in only a few patients in the normothermia group. Thermal comfort was significantly greater in the normothermia group than in the hypothermia group (score on the visual-analogue scale one hour after surgery, 73±14 vs. 35±17 mm). The difference in thermal comfort remained statistically significant for three hours. Pain scores and the amount of opioid administered were virtually identical in the two groups at every postoperative measurement; hemodynamic values were also similar.

The overall incidence of surgical-wound infection was 12 percent. Although the SENIC and NNISS scores for the risk of infection were similar in the two groups, there were only 6 surgical-wound infections in the normothermia group, as compared with 18 in the hypothermia group (P=0.009) (Table 2). Most positive cultures contained several different organisms; the major ones were *E. coli* (11 cultures), *S. aureus* (7), pseudomonas (4), enterobacter (3), and candida (3). Culture-negative pus was expressed from the wounds of two patients assigned to hypothermia and one patient assigned to normothermia. The ASEPSIS scores were higher in the hypothermia group than in the normothermia group (13±16 vs. 7±10, P=0.002) (Table 2); these scores exceeded 20 in 32 percent of the former but only 6 percent of the latter (P<0.001).

In a univariate analysis, tobacco use, group assignment, surgical site, NNISS score, SENIC score, need for transfusion, and age were all correlated with the risk of infection. In a multivariate backward-elimination analysis, tobacco use, group assignment, surgical site, NNISS score, and age remained risk factors for infection (Table 3).

Four patients in the normothermia group and seven in the hypothermia group required admission to the intensive care unit (P=0.47), mainly because of wound dehiscence, colon perforation, and peritonitis. Two patients in each group died during the month after surgery. The incidence of infection was similar at each study hospital, and no one surgeon was associated with a disproportionate number of infections.

Table 2 shows that significantly more collagen was deposited near the wound in the patients in the normothermia group than in the patients in the hypothermia group (328±135 vs. 254±114 μg per centimeter). The patients assigned to hypothermia were first able to tolerate solid food one day later than those assigned to normothermia (P=0.006); similarly, the sutures were removed one day later in the patients assigned to hypothermia (P=0.002). The duration of hospitalization was 12.1±4.4 days in the normothermia group and 14.7±6.5 days in the hypothermia group (P=0.001). This difference was statistically significant even when the analysis was limited to the uninfected patients. In the normothermia group, the duration of hospitalization was 11.8±4.1 days in patients without infection and 17.3±7.3 days in patients with infection (P=0.003). In the hypothermia group the duration of hospitalization was 13.5±4.5 days in patients without infection and 20.7±11.6 days in patients with infection (P<0.001).

The postoperative hemoglobin concentrations did not differ significantly between the two groups (Table 1). On the first postoperative day, leukocytosis was impaired in the hypothermia group as compared with the normothermia group (white-cell count, 11,500±3500 vs. 13,400±2500 cells per cubic millimeter; P<0.001). On the third postoperative day, however, white-cell counts were significantly higher in the hypothermia group (10,100±3900 vs. 8900±2900 cells per cubic millimeter). The difference in values on the third day was not statistically significant when only uninfected patients were included in the analysis. By the sixth postoperative day, the white-cell counts were similar in the two groups.

Among smokers, the number of cigarettes smoked per day was similar in the two groups (22±20 in the hy-

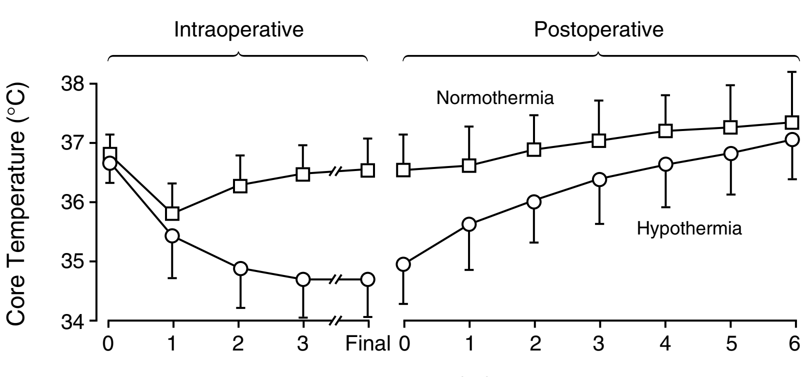

Figure 1. Core Temperatures during and after Colorectal Surgery in the Study Patients.

The mean (±SD) final intraoperative core temperature was 34.7±0.6°C in the 96 patients assigned to hypothermia, who received routine thermal care, and 36.6±0.5°C in the 104 patients assigned to normothermia, who were given extra warming. The core temperatures in the two groups differed significantly at each measurement, except before the induction of anesthesia (first measurement) and after six hours of recovery.

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Table 2. Postoperative Findings in the Two Study Groups.*

Variable	Normothermia (N = 104)	Hypothermia (N = 96)	P Value
All patients			
Infection — no. of patients (%)	6 (6)	18 (19)	0.009
ASEPSIS score	7±10	13±16	0.002
Collagen deposition — μg/cm	328±135	254±114	0.04
Days to first solid food	5.6±2.5	6.5±2.0	0.006
Days to suture removal	9.8±2.9	10.9±1.9	0.002
Days of hospitalization	12.1±4.4	14.7±6.5	0.001
Uninfected patients			
No. of patients	98	78	
Days to first solid food	5.2±1.6	6.1±1.6	<0.001
Days to suture removal	9.6±2.6	10.6±1.6	0.003
Days of hospitalization	11.8±4.1	13.5±4.5	0.01

*Plus–minus values are means ±SD.

pothermia group vs. 22±14 in the normothermia group). The morphometric characteristics, anesthetic care, and SENIC and NNISS scores of smokers and nonsmokers were not significantly different. Nonetheless, the proportion of patients with wound infection was significantly higher among smokers (23 percent, or 14 of 62) than among nonsmokers (7 percent, or 10 of 138; P=0.004). Furthermore, the length of hospitalization was significantly greater among smokers (14.9±6.7 days, vs. 12.9±5.0 days among nonsmokers; P=0.02) (Table 4).

DISCUSSION

The initial hours after bacterial contamination are a decisive period for the establishment of infection.[25] In surgical patients, perioperative factors can contribute to surgical-wound infections, but the infection itself is usually not manifest until days later.

In our study, forced-air warming combined with fluid warming maintained normothermia in the treated patients, whereas the unwarmed patients had core temperatures approximately 2°C below normal.[8] Perioperative hypothermia persisted for more than four hours and thus included the decisive period for establishing an infection.[25,30] The patients with mild perioperative hypothermia had three times as many culture-positive surgical-wound infections as the normothermic patients. Moreover, the ASEPSIS scores showed that in the patients assigned to hypothermia the reduction in resistance to infection was twice that in the normothermia group.

The types of bacteria cultured from our patients' surgical wounds were similar to those reported previously.[2,3] These organisms are susceptible to oxidative killing, which is consistent with our hypothesis that hypothermia inhibits the oxidative killing of bacteria.[31] The overall incidence of infection in our study was approximately 35 percent higher than in previous reports.[3] One explanation for this relatively high incidence is that we considered all wounds draining pus that yielded a positive culture to be infected, although some may have been of minor clinical importance. The hospitalizations of infected patients were one week longer than those of patients without surgical-wound infections, however, indicating that most infections were substantial. Similar prolongation of hospitalization has been reported previously.[1,2]

It is interesting to note that hospitalization was also prolonged (by about two days) in the uninfected patients in the hypothermia group (Table 2). A number of factors influenced the decision to discharge patients, but healing of the incision (formation of a "healing ridge," for example) was among the most important. As is consistent with a delay in clinical healing, sutures were removed significantly later and the deposition of collagen (an index of scar formation and the strength of the healing wound) was significantly less in the hypothermia group than in the normothermia group. That the patients assigned to hypothermia required significantly more time before they could tolerate solid food is also consistent with impaired healing.

In Austria's medical system, administrative factors and costs of hospitalization do not influence the length of stay in the hospital. No data on individual costs are tabulated by the participating hospitals, and they are therefore not available for our patients. Nonetheless, the cost of a prolonged hospitalization must exceed the cost of fluid and forced-air warming (approximately $30 in the United States). In a managed-care situation, the duration of hospitalization might have differed less, or not at all. However, our data suggest that patients kept at normal temperatures during surgery would be better prepared for discharge at a fixed time than those allowed to become hypothermic.

Among all 200 patients in our study, those who smoked had three times more surgical-wound infections and significantly longer hospitalizations than the nonsmokers. Similar data have been reported previously.[32] Numerous factors contributed to these results; one may have been that smoking markedly lowers oxygen tension in tissue for nearly an hour after each cigarette.[33] (Thermoregulatory vasoconstriction produces a similar reduction.[34]) The distribution of factors known to influence infection was similar between smokers and nonsmokers, but the smokers may have had other behavioral or physiologic factors predisposing them to infection.

The prevalence of smoking was similar in the two

Table 3. Multivariate Analysis of Risk Factors for Surgical-Wound Infection.

Risk Factor	Odds Ratio (95% Confidence Interval)
Tobacco use (yes vs. no)	10.5 (3.2–34.1)
Group assignment (hypothermia vs. normothermia)	4.9 (1.7–14.5)
Surgical site (rectum vs. colon)	2.7 (0.9–7.6)
NNISS score (per unit increase)*	2.5 (1.2–5.3)
Age (per decade)	1.6 (1.0–2.4)

*NNISS denotes National Nosocomial Infection Surveillance System.

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Table 4. Postoperative Findings in the Study Patients According to Smoking Status.*

Variable	Smokers (N = 62)	Nonsmokers (N = 138)	P Value
Infection — no. of patients (%)	14 (23)	10 (7)	0.004
ASEPSIS score	15±18	8±10	<0.001
Days to suture removal	10.9±3.5	10.1±2.0	0.04
Days of hospitalization	14.9±6.7	12.9±5.0	0.02
SENIC score			0.25
1	0	6	
2	58	125	
3	4	7	
NNISS score			0.08
0	23	40	
1	30	58	
2	9	40	

*Plus–minus values are means ±SD. SENIC denotes Study on the Efficacy of Nosocomial Infection Control, and NNISS National Nosocomial Infection Surveillance System.

study groups. Other factors may have influenced the patients' susceptibility to wound infections, such as arterial hypoxemia, hypovolemia, the concentration of the anesthetic used, and vasoconstriction resulting from pain-induced stress.[25,26,35,36] However, the administration of oxygen, oxyhemoglobin saturation, fluid balance, hemodynamic responses, end-tidal concentrations of anesthetic, pain scores, and quantities of opioid administered were all similar between the two groups. These factors are therefore not likely to have confounded our results. It is also unlikely that exaggerated bacterial growth aggravated the infections in the hypothermia group, because small reductions in temperature actually decrease growth in vitro.[37]

Mild hypothermia can increase blood loss and the need for transfusion during surgery.[38] In vitro studies suggest that perioperative hypothermia may aggravate surgical bleeding by impairing the function of platelets and the activity of clotting factors.[39,40] Blood transfusions may increase susceptibility to surgical-wound infections by impairing immune function.[41] Our patients assigned to hypothermia required significantly more allogeneic blood to maintain postoperative hemoglobin concentrations than did the patients assigned to normothermia. However, we administered only leukocyte-depleted blood, and multivariate regression analysis indicated that a requirement for transfusion did not independently contribute to the incidence of wound infection. It is thus unlikely that the differences in the incidence of infection in the two groups we studied resulted from transfusion-mediated immunosuppression.

In summary, this double-blind, randomized study indicates that intraoperative core temperatures approximately 2°C below normal triple the incidence of wound infection and prolong hospitalization by about 20 percent. Maintaining intraoperative normothermia is thus likely to decrease infectious complications and shorten hospitalization in patients undergoing colorectal surgery.

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APPENDIX

The following investigators also participated in this study: **patient safety and data auditing:** H.W. Hopf and T.K. Hunt (University of California, San Francisco); **site directors:** G. Polak (Hospital Rudolfstiftung, Vienna, Austria) and W. Kröll (University of Graz, Graz, Austria); **patient care:** F. Lackner and R. Fuegger (University of Vienna); **data acquisition:** E. Narzt (University of Vienna), C. Wolrab (University of Vienna), E. Marker (University of Vienna), A. Bekar (Orthopedic Hospital, Speising, Vienna), H. Kaloud (University of Graz), U. Stratil (Hospital Rudolfstiftung), and R. Csepan (University of Vienna); **wound evaluation:** V. Goll (University of Vienna), G.S. Bayer (University of Vienna), and P. Steindorfer (University of Graz); and **data management:** B. Petschnigg (University of Vienna).

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