Excerpta Medica

The American Journal of Surgery

The American Journal of Surgery 189 (2005) 651–655
Clinical surgery

Perioperative hypothermia does not enhance the risk of cancer dissemination

Yüksel Yücel, M.D.[a], Murat Barlan, M.D.[b], Rainer Lenhardt, M.D.[c,d], Andrea Kurz, M.D.[c,e], Daniel I. Sessler, M.D.[c,d,f,*]

[a]*Department of Special Gynaecology (Senology), Women's Clinic, Medical University of Vienna, General Hospital, Vienna, Austria*
[b]*Department of Surgery, Ludwig Boltzmann Institute, University of Vienna, Vienna, Austria*
[c]*Outcomes Research Institute, University of Louisville, Louisville, KY, USA*
[d]*Department of Anesthesiology, University of Louisville, Louisville, KY, USA*
[e]*Department of Anesthesiology, University of Bern, Bern, Switzerland*
[f]*Department of Pharmacology, University of Louisville, Louisville, KY, USA*

Manuscript received June 3, 2004; revised manuscript December 31, 2004

Abstract

Background: Resistance to cancer metastasis is mediated by host immunity, and mild perioperative hypothermia impairs immune function. We tested the hypothesis that mild perioperative hypothermia increases the risk of cancer recurrence and subsequent mortality

Methods: In a 5- to 9-year follow-up of 140 cancer patients enrolled in a study demonstrating that 2°C mild perioperative hypothermia triples wound infection risk, tumor characteristics likely to influence recurrence, patient outcome, and current health status were determined. Primary outcomes were tumor recurrence and all-cause mortality.

Results: Tumor status in the groups was similar and included Duke's and TNM classifications, preoperative carcinoembryonic antigen concentration, histologic differentiation, numbers of nodes biopsied and positive nodes, blood vessel invasion, and adhesion of tumor to adjacent organs. Cancer-free and overall survival rates were similar in normothermic and hypothermic patients. These data provide 80% power for detecting a 25% difference between the groups.

Conclusions: Mild perioperative hypothermia did not increase recurrent tumors, cancer death, or all-cause mortality.

Keywords: Cancer recurrence; Follow-up studies; Hypothermia; Neoplasm; Mortality; Surgery

Cancer surgery inevitably releases tumor cells into the systemic circulation [1,2]. Whether disseminated tumor cells are able to establish metastases depends largely on the efficacy of host immune responses [3,4]. Perioperative factors that impair host immunity are thus likely to facilitate establishment of metastatic tumor during cancer surgery. For example, metastasis formation in animal models is promoted by anesthetic drugs [5,6], most of which are immunosuppressive [7–11].

Surgery, mechanical ventilation, and general anesthesia each impair immune function [12–15]. Mild hypothermia is an additional perioperative factor that impairs immune function [16–18]. In vitro studies have suggested that mild core hypothermia directly impairs natural host defenses, in particular leukocyte mobility and phagocytosis [16], T-cell–mediated antibody production [17], and neutrophil function [18]. As might thus be expected, perioperative hypothermia augments the severity of test infections in animals [19,20] and markedly increases the risk of surgical wound infection in humans [21].

The immune suppression caused by mild perioperative hypothermia may similarly augment the risk of tumor metastases during cancer surgery. We therefore tested the hypothesis that hypothermia-induced immune suppression sufficient to triple the incidence of surgical wound infection also augments the risk of colon cancer recurrence and subsequent mortality.

Methods

This study is a 5- to 9-year follow-up of cancer patients enrolled in a previously published study that evaluated the effect of mild perioperative hypothermia (34.5°C) on the

* Corresponding author. Tel.: +1-502-852-2600; fax: +1-502-852-2610.
E-mail address: sessler@louisville.edu

0002-9610/05/$ – see front matter
doi:10.1016/j.amjsurg.2005.03.002

risk of surgical wound infection [21]. The major conclusion of the original report is that 2°C of intraoperative hypothermia increases the risk of surgical wound infection threefold, from 6% to 19% ($P < .01$). Both the original study and patient follow-up were conducted with approval of the Institutional Review Board of the University of Vienna.

Protocol

Briefly, we studied patients undergoing elective colorectal resection for cancer or inflammatory bowel disease who were between the ages of 18 and 80 years. Patients having abdominal-perineal pull-through procedures were included, but those scheduled for minor colon surgery (eg, polypectomy, isolated colostomy) were not included. Exclusion criteria were use of steroids or other immunosuppressive drugs (including cancer chemotherapy) within 4 weeks of surgery; a recent history of fever, infection, or both; serious malnutrition (serum album <3.3 mg/dL, white blood count <2500 cells/mL, or >20% weight loss); or bowel obstruction.

Antibiotic treatment and fluid management were standardized. Anesthesia was induced with sodium thiopental (3–5 mg/kg), fentanyl (1–3 μg/kg), and vecuronium bromide (.1 mg/kg). Isoflurane administration (in 60% nitrous oxide) was titrated to maintain mean arterial blood pressure within 20% of preinduction values. Additional fentanyl was administered on completion of surgery to improve analgesia on emergence from anesthesia. Blood was transfused as necessary per protocol. All blood was leukocyte filtered.

At the time of anesthetic induction, patients were assigned to 2 temperature management groups using computer-generated random codes maintained in sealed and numbered opaque envelopes: (1) normothermic: core temperature was maintained near 36.5°C and (2) hypothermic: core temperature was allowed to decrease to approximately 34.5°C. In both cases, intravenous fluids were administered by way of a fluid warmer, but the warmer was activated only in patients assigned to extra warming. Similarly, a forced-air cover (Augustine Medical, Eden Prairie, Minnesota) was positioned over the upper body in both groups; however, the warming unit was set to deliver air at ambient temperature in the hypothermic patients and at 40°C in those assigned to normothermia. Temperatures were not controlled after surgery. Neither the surgeons nor the patients were informed of group assignments.

Measurements

Data available from our previous study included potential confounding surgical and anesthetic factors such as patient age, duration of surgery, and allogeneic red blood cell transfusions. Follow-up was restricted to the 140 patients in the original study who had received a diagnosis of cancer. The medical records of each patient were searched to determine tumor characteristics likely to influence the risk of recurrence. These factors included preoperative serum carcinoembryonic antigen concentration; primary site; Duke's and TNM classifications; number of nodes biopsied and the number that demonstrated tumor; type of cancer and its histologic classification; and invasion of the tumor into blood vessels, nerves, or adjacent organs.

Medical records were also searched to determine patient outcomes. These included cancer-free interval, recurrence of cancer, and mortality. When mortality and its cause were undocumented in available medical records, patients or their families were contacted to determine their current health status.

Data analysis

Our primary outcomes were tumor recurrence and all-cause mortality. These outcomes were compared for normothermic and hypothermic patients with Log rank test and Kaplan-Meier curves. All other data were compared with unpaired, 2-sided Student *t*, Chi-squared, Fisher's Exact, or Wilcoxon ranked sum tests as appropriate. Results are presented as medians, means (95% confidence intervals), or number of patients (%); percentages in each category are based on the number of patients for whom data are available.

Results

Patients in the original study were accrued between July 1993 and March 1995. Among the 200 patients enrolled, 140 carried a diagnosis of cancer. Patient outcome was evaluated between August 2001 and June 2002, thus providing between five and nine years of follow-up. Our analysis was restricted to 124 cancer patients (86%) in whom follow-up data were available.

Core temperature at the end of surgery averaged 36.6°C (95% confidence interval 36.5–36.7) in the normothermic patients and 34.5°C (95% confidence interval 34.4–34.6) in the hypothermic patients. Morphometric and demographic characteristics in the 2 treatment groups were similar as were surgical and anesthetic characteristics (Table 1). Tumor status—including Duke's and TNM classifications, preoperative serum carcinoembryonic antigen concentration, histologic differentiation, number of nodes biopsied and number positive, blood vessel invasion, and adhesion of the tumor to adjacent organs—was also similar in the 2 groups (Table 2).

The number of patients who developed recurrent tumor and their cancer-free intervals were similar in the 2 temperature groups (Table 3). In addition, there were no statistically significant differences in cancer-related mortality or total mortality between the normothermia and hypothermic groups (Table 4).

Cancer-free survival in the patients who were kept normothermic during surgery did not differ from those kept hypothermic ($P = .498$). These data provide an 80% power