Does hyperthermic preconditioning affect the rate of surgical site infection rate and inflammatory reaction in colorectal cancer patients? A prospective randomized clinical trial

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ABSTRACT

Objective: Hyperthermic preconditioning has been shown to protect against different insults in experimental studies. However, clinical studies assessing its effects remain limited. The aim of this study was to investigate the effects of hyperthermic preconditioning on the rate of surgical site infection and inflammatory reaction in patients undergoing elective colorectal cancer surgery.

Material and methods: Patients with colorectal cancer, scheduled to undergo elective surgery were enrolled in this prospective randomized study. Patients were randomly assigned to either the hyperthermic preconditioning group or control group. Postoperative superficial and deep surgical site infection were recorded. Blood samples were collected from all the patients in the hyperthermic preconditioning group prior to the application of hyperthermia 12 h before surgery, immediately prior to surgery, and 4 h and 24 h postoperatively. For the control group, blood samples were obtained within the same periods without the application of hyperthermia. Levels of interleukin-1, IL-6, and tumor necrosis factor-α were measured from blood samples.

Results: Twenty patients were randomized to the hyperthermic preconditioning group and 21 to the control group. No significant difference was found in deep or superficial surgical site infection between the groups. No significant difference in the tumor necrosis factor-α, interleukin-1, and IL-6 levels was found in serum samples collected before hyperthermia, during the operation, and postoperatively.

Conclusion: This study showed that hyperthermic preconditioning has no effect on the surgical site infection and cytokine response in patients undergoing elective surgical intervention for colorectal cancer.

Keywords: Colorectal cancer, hyperthermic preconditioning, inflammatory reaction, surgical infection

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INTRODUCTION

Hyperthermic preconditioning (HP) has been shown to be protective against different insults in experimental studies. HP protects against stress conditions in the small intestine, liver, kidney, hippocampus, forebrain, and heart (1, 2). Animal studies have shown that hyperthermia protects against intestinal ischemia/reperfusion injury and the lethal effects of endotoxin (3, 4) and decreases intestinal permeability in septic mice (5). HP can improve the immune response and subsequently might play a protective role in reducing the severity of fecal peritonitis and sepsis in rats (6, 7).

Hyperthermia (HT) induces heat-shock protein (HSP) expression and decreases pancreatic injury. It has also been shown to improve survival in cases of necrotizing pancreatitis (8). The protective effect of HT has been commonly related to the induction of HSPs. Systemic HT is currently used in the treatment of certain malignant diseases (9-11). The positive effect of fever on survival during infections has been well known for several years (12-14). However, despite positive results of experimental studies, the effectiveness of HP in clinical studies remains limited. This prospective randomized study aimed to investigate the effects of HP on surgical site infection (SSI) rates and inflammatory reaction in colorectal cancer patients.

MATERIAL AND METHODS

Colorectal cancer patients undergoing elective surgery with a curative intent were enrolled in this prospective randomized study at Marmara University Hospital between May 2007 and February 2009. The Marmara University Research Ethics Committee approved the study, and all the subjects provided informed consent before participating in the study.

Patients with colorectal cancer, scheduled to undergo elective surgery with a curative intent, having American Society of Anesthesiologists (ASA) I-II scores were included in the study. Patients with metastatic or disseminated disease, obstruction, and perforation were excluded. Patients not tolerating HT, having ASA scores above II, and those who did not give informed consent were also excluded. The sample size was determined by a power analysis owing to the assumption that HP will decrease infection rate.

By using an internet randomization table, patients were randomly assigned to either of these groups:

1. HP group: Patients were exposed to heat for 1 h using a heating blanket (39°C) 12 h before surgery. After the heating procedure was completed, patients were followed until surgery at normal room temperature.

2. Control group: Patients were kept at room temperature.

Patients were randomized according to their application dates to our clinic. One of the authors (AC) enrolled participants and assigned them to interventions after generating the random allocation sequence. The participants were blinded after being assigned to interventions according to the randomization table. Duration of postoperative stay in the hospital, number of blood transfusions, and SSI rates were recorded for all the participants. Postoperative complications, including superficial and deep SSI and anastomotic leaks, were also noted. Patients were followed for 30 days after surgery for SSIs. Low molecular weight heparin was administered to all patients for deep venous thrombosis prophylaxis, and its dose was ad-

justed according to body weight. The antibiotics cefazolin and metronidazole were also routinely administered.

Blood samples were collected from all the patients in the HP group prior to the application of hyperthermia 12 h before surgery, immediately prior to surgery, and 4 h and 24 h postoperatively. In the control group, blood samples were obtained within the same periods without the application of hyperthermia. Collected blood samples were centrifuged, and serum samples were stored at −200°C and were later used to measure isnterleukin-1 (IL-1), Interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) levels.

Isnterleukin-1 and IL-6 enzyme-linked immunosorbent assay kits were used according to the manufacturer's recommendations without any modification. A plate reader set at 450 nm was used to measure optical densities. IL-1, IL-6, and TNF-α levels in the samples were calculated from the standard curve and were multiplied by the dilution factor (expressed as pg/mL).

The trial was completed after all randomized patients finished the study protocol.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS; version 17.0) statistical software (SPSS, Inc., Chicago, IL, USA). Fisher's exact test and two-tailed chi-square test were used to compare categorical variables (e.g., surgical side infection and gender), whereas the independent two-sample t-test and the Mann–Whitney U test were used to analyze con-

Table 1. Patient characteristics and study results

	Hyperthermic preconditioning group n=20	Control group n=21	p[a]
Age (years)[b]	59 (30–88)	69 (36–81)	0.074[c]
Gender*			
Male	10 (50)	9 (43)	0.65[d]
Female	10 (50)	12 (57)	
ASA*			
I	14 (70)	13 (62)	0.6[d]
II	6 (30)	8 (38)	
BMI (mean)	26±2	28±5	0,012[d]
SSI*	6 (30)	5 (24)	0,87[d]
COmorbid disease*	4 (6)	1 (5)	0,83
Smoking*	4 (20)	1 (5)	0,19[f]
Alcohol*	1 (5)	2 (10)	1.0[f]
Postoperative stay in hospital[#]	5.6±2.7	6±3	0,66[d]
Anastomosis leak*	0 (0)	1 (5)	1.0[f]
Postoperative complications	45 (35–240)	59 (55–270)	0.07[c]
Tumor distance from anal verge*			
≤6 cm	24 (38)	6 (30)	0.3[d]
>6 cm	40 (62)	14 (70)	
Blood transfusion*	21 (33)	1 (5)	0,014[d]
SSI risk*	30 (47)	5 (25)	0.083[d]
Follow-up period[b]	11 (1–20)	6 (2–19)	0.21[c]

[a]Comparison between two groups
[b]Values are medians (range)
[c]Mann–Whitney U test
[d]Chi-square test
[e]t test for independent samples
[f]Fisher's exact test
*; n (%), [#]; mean±SD

ASA: American Society of Anesthesiologists; BMI: body mass index; HP: hyperthermic preconditioning; SSI: surgical site infection

Table 2. TNFα, IL1, and IL6 values in the study groups

	Hyperthermic preconditioning group n=20	Control group n=21	p[a]
TNF levels			
Prior to hyperthermia	5.76 (0.086–727)	6.72 (0–68.9)	0.9[a]
Prior to start operation	5.85 (0.05–497)	5.79 (0–154)	1.0[a]
Postoperative 4 h	7.0 (0.06–727)	6.0 (0–136)	0.7[a]
Postoperative 24 h	5.0 (0.05–417)	5.645 (0–96.3)	0.8[a]
IL-1 levels			
Prior to hyperthermia	0.60 (0.27–2.46)	0.68 (0.18–67)	0.18[a]
Prior to start operation	0.49 (0.17–2.07)	0.52 (0.09–26)	0.38[a]
Postoperative 4 h	0.66 (0.18–45.6)	0.61 (0.16–9.8)	0.67[a]
Postoperative 24 h	1.12 (0.13–3.0)	0.57 (0.14–4.05)	0.40[a]
IL-6 levels			
Prior to hyperthermia	1.94 (0.05–11.2)	6.7 (0.3–238)	0.075[a]
Prior to start operation	2.0 (0.05–21.5)	6.0 (0.05–59.8)	0.06[a]
Postoperative 4 h	104.0 (6.49–238)	10.65 (4.06–238)	0.16[a]
Postoperative 24 h	46.95 (6.9–97)	13.2 (4.06–238)	0.087[a]

[a]Mann–Whitney U Test
TNF-α: tumor necrosis factor-α; IL-1: interleukin-1; IL-6: interleukin-6

tinuous variables (e.g., age). All statistical tests were two-sided, and p-value <0.05 was considered to be significant.

RESULTS

Forty-one patients with colorectal carcinoma were randomized for this study. Twenty patients were randomized to the HP group and 21 to the control group. Age, gender, ASA scores, presence of comorbid disease, alcohol and cigarette consumption, and number of blood transfusions were similar in both groups, while the body mass index was higher in the control group (26±2 vs 28±5, p=0.012). Patient demographics are given in Table 1.

Superficial SSI was detected in six patients in the HP group (30%). In the control group, superficial SSI was noted in five patients (24%) at the postoperative 30-day follow-up (p=0.87). An anastomotic leak was noted in one patient in the control group, while none were detected in the HP group. Duration of the postoperative stay showed similar results (p=0.66).

The median TNF-α levels were 5.76 (0.08–727), 5.85 (0.05–497), 7.0 (0.06–727), and 5.0 (0.05–417) pg/mL prior to HT, prior to surgery, and at postoperative 4 and 24 hours, respectively. In the control group, the corresponding values were 6.72 (0–68.9), 5.79 (0–154), 6.0 (0–136), and 5.65 (0–96.3) respectively. No statistically significant difference was found among the groups.

The median IL-1 levels were 0.6 (0.27–2.46), 0.49 (0.17–2.07), 0.66 (0.18–45.6), and 1.12 (0.13–3.0) prior to HT, prior to surgery, and at 4 h and 24 h postoperatively, respectively. In the control group, the corresponding values were 0.68 (018–67.0), 0.52 (0.09–26.0), 0.61 (0.16–9.8), and 0.57 (0.14–4.0), respectively. No statistically significant difference was noted.

The median IL-6 levels were 1.94 (0.05–11.2), 2.0 (0.05–21.5), 104.0 (6.49–238), and 46.95 (6.9–97) prior to HT, prior to surgery, and at 4 h and 24 h postoperatively, respectively. In the control group, the corresponding values were 6.7 (0.3–238), 6.0 (0.05–59.8), 10.65 (4.06–238), and 13.2 (4.06–238), respectively. No statistically significant difference was found (Table 2). There was no complication or any unintended effect in each group.

DISCUSSION

In this prospective randomized study, the effect of HP was investigated in patients with colorectal carcinoma treated with a curative intent. No significant difference was found in the rate of SSI among the control and HP groups. In addition, no significant difference was found in TNF-α, IL-1, and IL-6 levels among the groups.

Most of the studies reporting the protective effect of HP in various stress states are experimental studies performed in animals, and clinical studies remain limited. However, HT has been more widely used in humans. Systemic HT is currently used in the treatment of certain malignant diseases (9-11), and the positive effect of fever on survival in infections has been well known for several years (12-14). Fever-range hyperthermia has been shown to improve the outcome of serious infections in several animal models (7, 15-17). It was suggested that fever may enhance polymorphonuclear leucocyte (PMNL) function, which is the most important defense mechanism against acute bacterial infections. In one rat model, HT was found to increase PMNL counts via the attenuation of apoptosis (18). Furthermore, better leukocyte trafficking was found, which was also associated with tumor regression (19). Therefore, despite insufficient evidence of benefit in humans, HT has been increasingly used in not only complementary or alternative medicine, but also some clinical oncology centers, as an adjunctive treatment to chemoradiotherapy and for the treatment of certain inflammatory diseases.

Previously, induction of heat-shock response was found to preserve organ function and reduce cell injury in myocardial and renal ischemia (20, 21). It has been suggested that heat therapy administered before the onset of sepsis may decrease the production of IL-1 and TNF-α and thus might reduce the harmful effects endotoxin release (22). All these positive results were obtained in experimental studies. In contrast to other studies (7, 15-17), an animal study performed by our group failed to demonstrate improvement in the rate of survival at 120 h of intra-abdominal sepsis using HP alone.

Cytokines mediate local inflammatory responses at the site of injury and infection. An exaggerated pro-inflammatory cytokine response to infectious stimuli may result in severe hemodynamic effects (i.e., septic shock) and alteration in the metabolic equilibrium (i.e., increased muscle catabolism and wasting) (23). In this clinical study, no significant difference among the groups in TNF-α, IL-1, and IL-6 levels was found in all the serum samples collected before HP, during the operation, and postoperatively (at 4 h and the 24 h).

The small number of patients is the most important limitation of this study that needs to be acknowledged. Moreover, different temperatures and different preconditioning models may leasd to different results. The duration of HT (39℃) (1 h and 12 h) before surgery, may not have been the best model. Recent research has shown that HSPs can protect isolated cells from the cytotoxic effects of IL-1 and TNF-α, which are considered to be the chief mediators of sepsis (24-26). In this study, HSPs were not investigated. However, IL-1, IL-6, and TNF-α levels were not significantly different in the control and HP groups, which provides indirect effect on the HSP response.

The pro-inflammatory cytokine response was not different among the groups and at the same time the values obtained varied widely in both groups, contributing to statistical indifference. Superficial SSI was detected in six patients in the HP group (30%) and in five patients in the control group (24%) during the postoperative 30-day follow-up. Also, one anastomotic leak was noted. The presence of infection increases pro-inflammatory cytokines, and high infection rate is probably responsible for the broad variation in cytokine values.

CONCLUSION

This study showed that HP has no effect on SSI and cytokine response in patients undergoing elective surgical intervention for colorectal cancer.

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