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Comparison of immunologic and physiologic effects of CO_2 pneumoperitoneum at room and body temperatures

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Abstract
Background: Prolonged and complex laparoscopic procedures expose patients to large volumes of cool insufflation gas. The aim of this study was to compare the effects of a conventional room temperature carbon dioxide (CO_2) pneumoperitoneum with those of a body temperature pneumoperitoneum.
Methods: Patients were randomized to undergo laparoscopic cholecystectomy with a CO_2 pneumoperitoneum warmed to either body temperature ($n = 15$) or room temperature ($n = 15$). The physiologic and immunologic effects of warming the gas were examined by measuring peroperative core and intraperitoneal temperatures, peritoneal fluid cytokine concentrations, and postoperative pain.
Results: The mean duration of surgery was 32 min in both groups. Core temperature was reduced in the room temperature group (mean, 0.42°C; $p < 0.05$). No reduction in temperature occurred when the gas was warmed. Greater levels of cytokines were detected in peritoneal fluid from the room temperature insufflation group tumor necrosis factor alpha (TNF-α): mean, 10.9 pg/ml vs. 0.42, $p < 0.05$; interleukin 1 beta (IL-1β): mean, 44.8 pg/ml vs. 15.5, $p < 0.05$; and IL-6: mean, 60.4 ng/ml vs. 47.2. There was no difference in postoperative pain scores or analgesia consumption between the two groups.
Conclusions: The authors conclude that intraoperative cooling can be prevented by warming the insufflation gas, even in short laparoscopic procedures. In addition, warming the insufflation gas leads to a reduced postoperative intraperitoneal cytokine response.

Key words: Laparoscopic cholecystectomy — Mild hypothermia — Pneumoperitoneum

Advances in technology and modern surgery have meant that laparoscopic procedures are becoming more widespread, complicated, and longer in duration. During an advanced laparoscopic operation, many hundred liters of carbon dioxide (CO_2) may be insufflated into the abdomen to create and maintain the pneumoperitoneum. However, modern insufflators do not allow for the fact that gas cooler than body temperature is being insufflated into a cavity with a large surface area.

Carbon dioxide is supplied in a liquid form in cylinders at a pressure approximately 40 times greater than atmospheric pressure. Sudden evaporation produces the so-called ''carbon dioxide snow'' at a temperature of −90°C. Passage of the gas through the insufflator and tubing raises its temperature to almost room temperature, or approximately +20°C [14].

Prolonged CO_2 insufflation with gas 15° below normal core temperature is associated with a visible hyperemia of the peritoneum and peritoneal exudation [14]. Acute-phase cytokines, including tumor necrosis factor alpha (TNF-α) as well as interleukins 1 (IL-1β) and 6 (IL-6), have been measured in peritoneal fluid after laparotomy [1]. Semm et al. [14] postulated that warming the insufflation gas to body

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Table 1. Comparison of two patient groups

Variable	Group 1 Mean (SD)	Group 2 Mean (SD)
Age (years)	53.73 (18.34)	46.2 (21.2)
Operation time (min)	31.53 (11.40)	32.13 (9.75)
Gas flow (liters)	92.05 (47.27)	85.52 (25.53)
Starting core temperature (°C)	36.09 (0.42)	36.13 (0.41)
Starting peritoneal temperature (°C)	35.43 (0.48)	35.57 (0.41)
Volume of fluid in drain at 24 h (ml)	191.54 (184.03)	156.43 (101.25)

temperature reduces the peritoneal inflammation and improves patient well-being. To test this hypothesis, the authors conducted a randomized prospective study that compared the physiologic responses to normothermic (37°C) and room temperature CO_2 insufflation by measuring peroperative core and intraperitoneal temperatures, cytokine concentrations in peritoneal fluid, and postoperative pain.

Methods

The trial was approved by the local hospital ethics committees, and all patients gave informed, written consent. Patients eligible for this study were those undergoing elective laparoscopic cholecystectomy for symptomatic cholelithiasis classified as ASA class I and II, who otherwise were well at the time of operation. Patients with acute cholecystitis were excluded from the study. A standard anesthetic regimen, including standardized on-demand postoperative analgesia, was used in all patients. Patients were randomized by sealed envelopes to receive either a hypothermic room temperature or a normothermic body temperature CO_2 pneumoperitoneum. The gas was warmed using the WISAP Flow Therme (WISAP, Germany).

Patients underwent a modified standard laparoscopic cholecystectomy, with temperature probes placed in the esophagus to record core temperature and through a fifth 5-mm port situated in the left hypochondrium (remote from the surgical field and the camera light) to record intraperitoneal temperature. Temperature was monitored continuously and recorded every 5 min. Peritoneal fluid was collected after surgery for 24 h in a closed vacuum drain (Redivac UK Ltd.). The duration of the pneumoperitoneum and volume of CO_2 used was recorded. Twenty-four hours post after surgery the patients completed a visual analogue pain chart, and their drains were removed. Postoperative analgesia consumption was recorded. The volume of fluid in the suction drain was recorded and the fluid assayed for concentrations of the proinflammatory cytokines TNF-α, IL-1β, and IL-6 in duplicate by enzyme-linked immunoadsorbent assay (ELISA) technique (Quantikine Assay kits, R&D Systems Europe Ltd., Abingdon, UK).

Data was analyzed by the use of paired and unpaired *t*-tests as appropriate. Results were expressed as means (+/− SD), and a p value less than 0.05 was considered significant.

Results

The two groups were comparable with respect to age, surgery time, volume of gas insufflated, and starting core and intraperitoneal temperatures (Table 1). In all patients, recorded temperatures decreased peroperatively. There was a statistically significant difference in the reduction of core temperature between the two groups ($p = 0.033$, *t*-test of independent samples). In the normothermic group (group 2) there was a mean reduction of 0.24 ± 0.21°C, which was not a significant change from the mean starting temperature of 36.13 ± 0.41°C. This compared with a mean reduction of 0.42 ± 0.231°C in those with hypothermic insufflation (group 1) who started at 36.09 ± 0.42°C ($p < 0.05$). Analysis of correlation coefficients showed no correlation between the decrease in temperature and the volume of gas used, nor between the decrease in temperature and the duration of surgery ($p = 0.30$ and 0.51, respectively).

Table 2. Results of cytokine assays

	Group 1 Mean (SD)	Group 2 Mean (SD)	p value
TNF-α (pg/ml)	10.93 (16.38)	0.42 (3.02)	0.036 Welch's *t*-test
IL-1β (pg/ml)	44.76 (52.25)	15.54 (11.49)	0.002 Welch's *t*-test
IL-6 (ng/ml)	60.44 (49.26)	47.17 (28.30)	0.15 Welch's *t*-test

Intraperitoneal temperatures decreased peroperatively. In the hypothermic group, there was a mean decrease of 0.46 ± 0.34°C from a starting temperature of 35.43 ± 0.48°C, compared with a mean decrease of 0.15 ± 0.52°C from a starting temperature of 35.57 ± 0.41°C in the normothermic group. These differences did not reach statistical significance.

The results of the cytokine assays are summarized in Table 2. There was a significantly larger production of TNF-α and IL-1β after hypothermic pneumoperitoneum. No difference was noted between the visual analogue pain scores for the two groups ($p = 0.34$), nor any postoperation analgesia consumption (Table 3).

Discussion

Advances in technology and modern surgery have resulted in more complex and prolonged laparoscopic procedures. Due to the sizeable peritoneal surface area, insufflating large volumes of room temperature CO_2 into the peritoneal cavity can result in cooling of the peritoneum and a reduction in core temperature. Modern electronic insufflator units are able to maintain the pneumoperitoneum at a constant pressure by continuous insufflation of gas to replace losses caused by leaks and dissolution of CO_2 in the blood. This means that during a complex or advanced operation, hundreds of liters of CO_2 gas may be insufflated into the abdomen.

In this study, patients whose pneumoperitoneum was created with gas at room temperature had a statistically significant peroperative reduction in core temperature. These results are consistent with those of Monagle and colleagues [8] who also reported a statistically significant core temperature reduction in a group of patients undergoing laparoscopic cholecystectomy. Although in a short operation such as laparoscopic cholecystectomy the temperature reductions may not be clinically significant, in this study, there was no correlation between the temperature reduction and the total volume of gas used. In a study on pigs, Bessell et al. [2] demonstrated a reduction in core temperature as a result of CO_2 insufflation. Their failure to attenuate the fall in core temperature using warm CO_2 was due to the fact that by the time the gas had reached the abdomen from the gas warmer, its temperature had fallen to 0.7°C above room temperature.

There is a significant postoperation mortality and morbidity associated with prolonged hypothermia. In a study of patients admitted to I.T.U., prolonged hypothermia was

Table 3. Visual analogue pain scores and analgesic consumption

Variable	Group 1 Mean (SD)	Group 2 Mean (SD)
Codydramol consumption (tablets in 24 h)	2.71 (2.55)	3.69 (2.93)
Omnopon (ml IM injection)	2.2 (1.75)	3.13 (1.48)
Visual analogue pain score (mm)	46.17 (16.36)	53.33 (19.68)

shown to increase postoperation mortality with greater postoperation fluid requirements for those who were hypothermic on admission [15]. Those patients who remained hypothermic 2, 4, and 8 after surgery had significantly greater mortality. Hypothermia also is associated with higher rates of postoperation wound infection [7], more cardiac events [4], and greater transfusion requirements [12].

Another concern regarding postoperation hypothermia is in the immediate postanesthetic period when thermoregulatory responses reappear. During anesthesia, shivering and peripheral vasoconstriction are suppressed, but as the neuromuscular block wears off, a shivering response occurs. Shivering can suddenly increase oxygen consumption several-fold [3], placing elderly patients or those with pulmonary or cardiovascular disease at risk. To counteract this effect, some authors recommend routine oxygen therapy for hypothermic patients during the early postoperation period [6] to ameliorate the severe reductions in oxygen saturation associated with shivering. Others recommend the administration of neuromuscular blocking agents to reduce myocardial work and reduce metabolic demands [11].

Some controversy exists regarding the influence of CO_2 insufflation on intraperitoneal thermoregulation. On the one hand, Ott [10] reported that the vasodilatory effects of CO_2 are not important to thermal consequences. Semm [13], however, proposed that insufflation of CO_2 warmed to body temperature has two advantages: (a) It is more ''physiologic'' and less traumatic, resulting in a reduction of peritoneal hyperemia and exudation, and (b) there is a reduction in postoperation pain scores and consequently greater patient well-being.

Ott [10] was the first to quantify the degree of hypothermia resulting from laparoscopy and insufflation of cool gas. He reported a decrease in core temperature of 0.3°C for each 50 liters of CO_2 delivered. Unfortunately, this study was nonrandomized, and the groups differed within and across study arms in terms of the operations performed. Furthermore, the duration of pneumoperitoneum was not reported. In a follow-up study, Ott [9] evaluated the effect of warming the CO_2 to between 35.0 and 35.5°C. In patients receiving warmed gas, the thermal losses were less marked and more stable during the postoperation period. Ott concluded that gas should be warmed to counteract hypothermia.

Semm [13] observed a peritoneal hyperemia and exudation in response to CO_2 insufflation. However, hyperemia is difficult to determine and quantify because it is observed on a television monitor and may be dependent on the color settings. This study detected TNF-α, IL-1β, and IL-6 in peritoneal fluid 24 h after surgery. This finding is consistent with those of previous studies on the cytokine content of postoperation peritoneal exudate. Badia et al. [1] demonstrated a sequential cytokine response to surgery whereby peak levels of TNF-α, IL-1β, and IL-6 occurred at 1, 3, and 5 h, respectively. The early peak may explain why TNF was detected at low concentrations in the current study. Because the peritoneal fluid was sampled only once, only one view of the dynamic process was seen. In this study, the concentrations of all cytokines were lower than in other studies [1, 16], as might be expected when cytokine levels in open and laparoscopic surgery are compared [5]. Significantly lower concentrations of TNF and IL-1 were present in the warmed gas group, suggesting that reduced intraperitoneal temperature may exaggerate the inflammatory response. Although the absolute differences between the two groups are quite large, the *p* value is quite high due to the distribution of the figures and the fact that Welch's *t*-test was used because the variances were not equal. These findings therefore support Semm's [13] hypothesis that a warmed pneumoperitoneum is more ''physiological.''

The authors' assessment of postoperation pain found no difference between the two groups, a finding that contrasts with Semm's [14] finding of a 31% decrease in postoperation analgesia consumption when CO_2 is warmed in patients undergoing a range of laparoscopic procedures. An explanation of this difference notes that the temperature of the CO_2 affects only one component of the postoperation pain arising from the operation site and surgical wounds in addition to peritoneal inflammation. Also, the current study did not look at possible negative effects of warming CO_2. Theoretically, warm CO_2 could diffuse more rapidly into the blood stream, having an effect on arterial pCO_2 or endtidal CO_2. However, the diffusion rate of a gas is proportional to the gas temperature in degrees Kelvin, and the gas in this study was warmed by approximately 15 to 17°C. On the Kelvin scale this equates with a temperature rise, and therefore a diffusion rate increase of only 0.5%, but endtidal CO_2 and biochemical outcome were not recorded in this study.

Conclusions

The immunologic and physiologic effects of a pneumoperitoneum warmed to body temperature were compared with those of the more usual room temperature pneumoperitoneum by randomizing patients to receive either a warmed or room temperature pneumoperitoneum. Although there was no difference in the postoperation pain experienced by patients in the two groups, there was a statistically significant core temperature reduction in the group receiving a room temperature, hypothermic pneumoperitoneum. Furthermore, lower concentrations of acute-phase cytokines were detected in patients receiving a normothermic pneumoperitoneum. Although the temperature reductions were not clinically significant, insufflation of cold gas was associated with an increased production of acute-phase proinflammatory cytokines. The philosophy underlying the introduction of laparoscopic surgery is one of minimizing trauma to the patient. Therefore, routine warming of insufflation gas may cause an attenuated peritoneal inflammatory response and less patient trauma.

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