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Five Year Follow-Up of a Randomized Controlled Trial on Warming and Humidification of Insufflation Gas in Laparoscopic Colonic Surgery—Impact on Small Bowel Obstruction and Oncologic Outcomes

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Warming and humidification of insufflation gas has been shown to reduce adhesion formation and tumor implantation in the laboratory setting, but clinical evidence is lacking. We aimed to test the hypothesis that warming and humidification of insufflation CO_2 would lead to reduced adhesion formation, and improve oncologic outcomes in laparoscopic colonic surgery. This was a 5-year follow-up of a multicenter, double-blinded, randomized, controlled trial investigating warming and humidification of insufflation gas. The study group received warmed (37°C), humidified (98%) insufflation carbon dioxide, and the control group received standard gas (19°C, 0%). All other aspects of patient care were standardized. Admissions for small bowel obstruction were recorded, as well as whether management was operative or nonoperative. Local and systemic cancer recurrence, 5-year overall survival, and cancer specific survival rates were also recorded. Eighty two patients were randomized, with 41 in each arm. Groups were well matched at baseline. There was no difference between the study and control groups in the rate of clinical small bowel obstruction (5.7% versus 0%, *P* 0.226); local recurrence (6.5% versus 6.1%, *P* 1.000);

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overall survival (85.7% versus 82.1%, *P* 0.759); or cancer-specific survival (90.3% versus 87.9%, *P* 1.000). Warming and humidification of insufflation CO_2 in laparoscopic colonic surgery does not appear to confer a clinically significant long term benefit in terms of adhesion reduction or oncological outcomes, although a much larger randomized controlled trial (RCT) would be required to confirm this. ClinicalTrials.gov Trial identifier: NCT00642005; US National Library of Medicine, 8600 Rockville Pike, Bethesda, MD 20894, USA.

Key words: Adhesions – Small bowel obstruction – Laparoscopy – humidification – colectomy – Colorectal

In laparoscopic surgery, the abdominal wall is commonly distended using carbon dioxide (CO_2) insufflation to provide pneumoperitoneum.[1] The gas is delivered at room temperature (19–21°C) with a relative humidity approaching 0% at the point of entry into the peritoneal cavity.[2] Early data suggested that unconditioned gas can cause structural and biochemical injury to the peritoneal mesothelium, and that warming and humidification of the insufflation CO_2 resulted in reduced postoperative pain after laparoscopic procedures.[3–7] However, more recent evidence from high quality, randomized controlled trials and a Cochrane meta-analysis have shown this not to be the case, with no difference in postoperative pain scores or opiate use with warming and humidification.[8–10]

With no demonstrable difference in short-term clinical outcomes, attention has now shifted toward long-term outcomes, namely adhesion formation and oncological response. There is now laboratory evidence to suggest that conditioning of insufflation gas may in fact reduce postoperative adhesion formation,[11,12] and peritoneal tumor implantation.[13] It is thought that this is because conditioning insufflation gas reduces the peritoneal inflammatory response. However, clinical evidence to confirm these findings has been lacking.

We previously published a multicenter, double-blinded, randomized controlled trial investigating warming and humidification of insufflation gas in laparoscopic colonic surgery.[8] This study showed that warming and humidification did not confer any clinically significant short-term recovery benefit in laparoscopic colonic surgery. In light of the recent laboratory study findings mentioned above, we aimed to test the hypothesis that warming and humidification of insufflation CO_2 leads to reduced adhesion formation, and improved oncologic outcomes in laparoscopic colonic surgery.

Materials and Methods

Participants

The study population included all people residing within the catchment area of the three district health boards serving Auckland city (Auckland District Health Board [DHB], Waitemata DHB, and Counties Manukau DHB). All patients undergoing elective laparoscopic colonic resection for any indication and at any of the three public hospitals between April 2008 and June 2009 were screened for inclusion. Exclusion criteria were: patients aged 15 years or younger, acute colonic resection, hand-assisted laparoscopic colonic resection, decision to perform open surgery preoperatively (intraoperative conversions were included as intention to treat), surgery for rectal lesions defined as within 15 cm of the anal verge on sigmoidoscopy/colonoscopy, stoma formation (preoperative or intraoperative decision), patients who did not have colon resection despite initial surgical plan, preoperative steroid dependence, inability to consent or complete visual analogue scores in study questionnaires due to cognitive impairment or language barrier, patients with ASA >4, and deviation from anesthetic protocol (as defined below). Conversion to open colectomy was at the discretion of the individual surgeon for concerns of patient safety, technical difficulties, or associated unexpected conditions requiring treatment by laparotomy. Conversions were recorded and analyzed in the allocated group on an intention-to-treat basis.

Interventions

Surgery

All patients underwent routine laparoscopic-assisted colonic resection either by, or under the supervision of, consultant colorectal specialists employed by the three district health boards. Technical aspects of the surgical procedure, and postoperative care not related to analgesia protocol (see below) were left up to the discretion of the surgical team.

Anesthesia and analgesia

All patients were administered standardized intraoperative and postoperative analgesia as per a protocol designed in conjunction with the Department of Anaesthesia at Auckland City Hospital (details can be found in the original publication).[8] All patients received dexamethasone 8 mg intravenously after induction (DBL dexamethasone sodium phosphate injection, Hospira NZ Limited, Wellington, New Zealand), and no nonsteroidal anti-inflammatories were given. Epidural, spinal, and intrathecal analgesia/anesthesia were not used.[14] Room temperature was set at 19°C before the start of the case, and all patients were covered with a forced-air-rewarming blanket (the Original Bair Hugger Forced Air Warming Temperature Management Units, Arizant Healthcare Inc, Eden Prairie, Minnesota). Choice, volume, and temperature of intravenous fluid given intraoperatively were left up to the discretion of the anesthetic team.

Study Group

The study group received warm, humidified insufflation gas. Insufflation pressure was set at 12 to 15 mmHg with a variable flow rate. The gas used was carbon dioxide (carbon dioxide medical gas, BOC Ltd, Auckland, New Zealand), and this was warmed to 37°C and humidified to 98% RH using a laparoscopic humidification system (Fisher & Paykel MR860, Fisher & Paykel Healthcare, Auckland, New Zealand). This humidification system is specifically designed to deliver warm, humidified CO_2 to patients undergoing laparoscopic surgery, and has previously undergone independent testing by our group to confirm the effectiveness of gas conditioning.[15] The gas is passed from the insufflator through a chamber which is filled with 30 mL of sterile water and sits on a heater plate. Water evaporates from the chamber into the gas that flows over it. The temperature of the gas is maintained as it travels along a heated tube to the laparoscopic port and into the patient's abdomen. The humidifier monitors the temperature and flow rate of the gas at the chamber outlet with a probe attachment, controlling the amount of power delivered to the heater plate to maintain the chamber set point temperature.[16]

Control Group

The control group received standard dry carbon dioxide for insufflation (carbon dioxide medical gas; BOC Ltd) delivered at room temperature (19°C) and 0% RH. Insufflation pressure was set at 12 to 15 mm Hg with a variable flow rate.

Objectives

The objective of this study was to test the hypothesis that warming and humidification of insufflation CO_2 would lead to reduced adhesion formation, and improve oncologic outcomes in laparoscopic colonic surgery.

Outcomes

All data were collected by a single, blinded investigator (TS) to ensure standardization of data collection.

Baseline data

Patient data

Baseline patient data recorded included: National Health Index (NHI) number, the hospital that the patient was treated at, patient surname, age, sex, ethnicity as coded in hospital electronic records (self-identified), weight in kilograms, height in centimeters, past medical history, past surgical history, American Society of Anesthesiologists (ASA) score, and colorectal physiological and operative severity score (Cr Possum).

Operative data

Operative data recorded included: preoperative diagnosis; postoperative diagnosis on histology (including full TNM staging for neoplastic lesions); lesion location; date of surgery; operation performed; approach (laparoscopic, laparoscopic-assisted, conversion to open); operation start time (scalpel to skin); gas insufflation start time; gas insufflation end time; operation end time (all wound dressings applied); volume of gas used for insufflation; use of intraperitoneal fluid washout; and contamination with pus or feces. Core temperature was measured with an esophageal probe, (intra-abdominal temperature was not measured, as this would have required insertion of a separate port).

Postoperative complications up to 30 days after surgery were recorded prospectively using predefined criteria. Complications were defined using the standardized "definitions of operation and/or disease-related complications" proposed by Buzby *et*

al.[17] In addition to this, ileus was defined as postoperative obstipation and vomiting requiring nasogastric tube insertion, but without radiological evidence of bowel obstruction. All complications were recorded per patient and graded by the Clavien-Dindo classification.[18]

Primary Outcomes

Patients were followed up for 5 years from the date of their surgery. Electronic patient records were reviewed, and admissions for small bowel obstruction were recorded, as well as whether management was operative or nonoperative. Local and systemic cancer recurrence as detected on cross-sectional imaging using CT, MRI, or PET scanning was recorded. Histological confirmation was required for local recurrence, but not for systemic recurrence, as biopsy may not have been clinically indicated if the management of metastatic disease was non-interventional. Five-year overall survival and cancer-specific survival rates were also measured.

Sample size

The *a priori* power calculation was based on the primary outcome of the original study, which was total opiate analgesia use during the index inpatient stay.[8] Using a two-tailed Mann-Whitney *U* test for difference between two independent groups, 37 patients were required in each arm to detect a difference of 20% between groups with an alpha of 0.05 and power of 0.8.[19]

Randomization

Sequence generation

Randomization was conducted using random numbers obtained from an open source computer-based random number generator (www.random.org). Randomization was stratified by hospital to ensure equal distribution of intervention and control group patients between these, and minimize bias due to differences in pre, intra and post-operative protocols between sites.

Allocation concealment

Allocations were concealed in opaque numbered envelopes. There were kept in a central location and not used until interventions were assigned on the day of surgery.

Implementation

The randomization sequence was generated by a third party not involved in the study. Patients were recruited on the day of surgery. All patients were seen on a one-to-one basis preoperatively by TS, and the trial rationale and procedure were explained verbally. Patients were then given a participant information sheet, after which written informed consent was obtained prior to randomization. Allocation of each individual patient into either study or control group was performed intraoperatively by an unblinded research assistant (see below), after the patient was anesthetized and before the insufflation was started.

Blinding

The patient, study investigators, surgeon, and medical staff responsible for patient care were all blinded to patient allocation. This was achieved by having the humidifier connected to the insufflation apparatus and power supply regardless of allocation, and covered with a specially designed plastic casing which concealed its LCD screen and water chamber. This was to ensure that none of the theatre occupants were able to tell if the humidifier was switched on or not. A research assistant not involved in patient management, study design, data collection, data analysis or results write-up was responsible for setting up the humidifier. After the patient was asleep, the assistant opened an opaque envelope with allocation instructions and set up the humidifier away from view of the theatre staff and investigator. If the patient was in the study group, 30 mL of sterile water was added to the chamber and the humidifier was switched on and muted so that it did not make any noise. If the patient was in the control group, water was not added and humidifier was not switched on.

The blinding protocol was practiced in simulation several times and tested in March 2008 (prior to study commencement) on a consented patient undergoing a laparoscopic colonic resection at the Counties Manukau DHB. The patient, study investigators, surgeon, and all medical staff responsible for patient care were blinded successfully.

Data analysis was also blinded. The investigator undertaking statistical analysis on study completion was only allowed access to modified data tables with the allocation concealed. These specified patients as being allocated to "group 1" and "group 2."

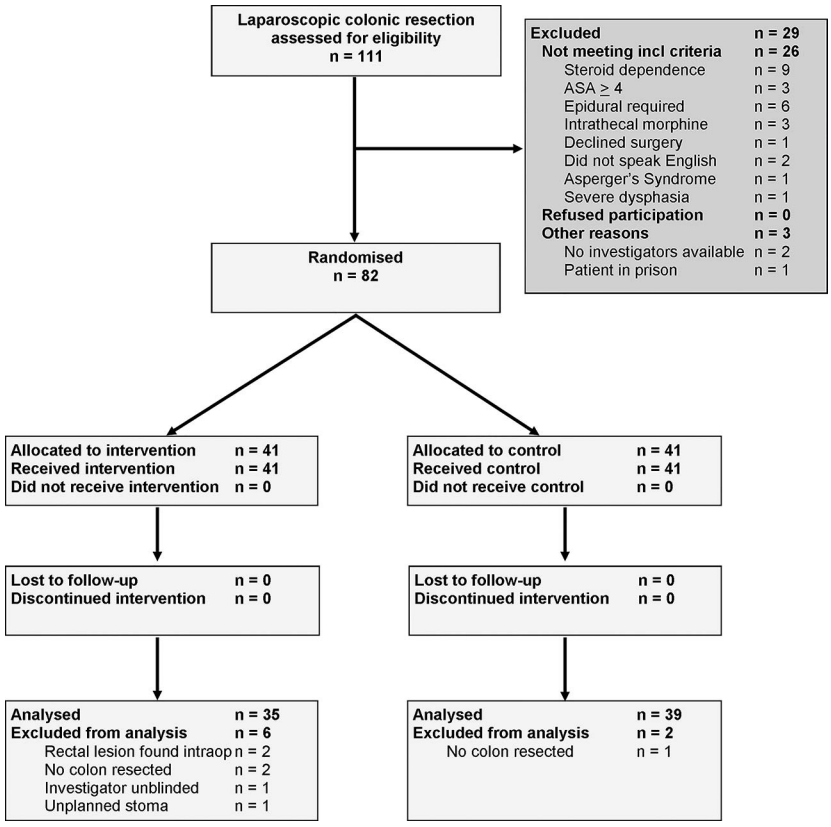

Fig. 1 CONSORT diagram documenting patient flow.[20] n, number of patients; incl, inclusion.

Statistical Methods

Results were analyzed using statistical software (SPSS for Windows, version 22.0, IBM Corp, Armonk, New York). Continuous variable parametricity was tested using the Shapiro-Wilk test. Results are presented as mean (standard deviation) for parametric data and median (interquartile range) for nonparametric data. Groups were compared using the Fisher's exact or χ^2 test for categorical variables, the Mann-Whitney *U* test for nonparametric continuous variables, and the *t*-test for parametric continuous variables. Statistical significance was accepted at the 0.05 level.

Ethics Approval and Trial Registration

Ethics approval was granted by the Ministry of Health, Northern X Regional Ethics Committee. Approval was also granted by the clinical boards of all three DHBs. The trial was prospectively registered with ClinicalTrials.gov (trial identifier: NCT00642005, US National Library of Medicine, 8600 Rockville Pike, Bethesda, MD 20894, USA).

Results

Participant recruitment and flow

Detailed patient flow is shown in the CONSORT diagram (Fig. 1).[20] Between April 2008 and June 2009, 111 patients were screened for inclusion. Of these, 82 patients were randomized equally between the study and control groups. Six patients in the study group were excluded after randomization: 2 patients had a rectal lesion below 15 cm found intraoperatively, 2 patients did not have any colon resected despite initial plan, 1 patient had an unplanned diverting ileostomy performed due to a positive anastomotic air-leak test, and in 1 case the investigator was unblinded when a nurse inadvertently lifted the plastic cover off the humidifier during surgery. Two patients in the control group were excluded after randomization: 1 patient did not have any colon resected despite initial plan, and 1 patient suffered a severe anaphylactic reaction on induction of anesthesia, and the procedure was abandoned.

Number analyzed

Seventy-four patients were analyzed: 35 in the study group and 39 in the control group. All patients had

Table 1 Baseline characteristics

	Study group (n = 35)	Control (n = 39)	*P* value
Age (median in years, IQR)	71 (29)	69 (22)	0.959[a]
Sex			1.000[b]
Male	15 (42.9%)	16 (41.0%)	
Female	20 (57.1%)	23 (59.0%)	
BMI (mean in kg/m^2, SD)	26.5 (4.8)	25.5 (5.4)	0.401[c]
ASA score			0.355[d]
I	6 (17.1%)	3 (7.7%)	
II	21 (60.0%)	23 (59.0%)	
III	8 (22.9%)	13 (33.3%)	
CR-POSSUM (median, IQR)	17 (5)	19 (5)	0.178[a]
Previous abdominal surgery	15 (42.9%)	13 (33.3%)	0.475[b]
Operation			0.073[d]
Ileocolic resection	5 (14.3%)	0 (0%)	
R hemicolectomy	14 (40.0%)	11 (28.2%)	
Extended R hemicolectomy	5 (14.3%)	3 (7.7%)	
Transverse colectomy	1 (2.9%)	1 (2.6%)	
L hemicolectomy	2 (5.7%)	6 (15.4%)	
Sigmoid colectomy	1 (2.9%)	2 (5.1%)	
High anterior resection	7 (20.0%)	16 (41.0%)	
Diagnosis			0.587[d]
Adenocarcinoma	21 (60.0%)	27 (69.2%)	
Adenoma	6 (17.1%)	3 (7.7%)	
Diverticulitis	3 (8.6%)	3 (7.7%)	
Inflammatory bowel disease	3 (8.6%)	2 (5.1%)	
Carcinoid	2 (5.7%)	2 (5.1%)	
Other benign	0 (0%)	2 (5.1%)	
AJCC staging			0.316[d]
I	6 (26.1%)	5 (17.2%)	
II	11 (47.8%)	9 (31.0%)	
III	5 (21.7%)	13 (44.8%)	
IV	1 (4.3%)	2 (6.9%)	

n, number of patients; IQR, interquartile range; SD, standard deviation; r, right; l, left.
[a]Mann-Whitney *U* test.
[b]Fisher's Exact test.
[c]*t* test.
[d]χ^2 test.

complete data collected for the primary outcome and for all variables measured during the index hospital stay. Complete follow-up data for the primary outcomes of adhesive small bowel obstruction and survival were obtained for 74 patients (100%).

Baseline characteristics

Groups were well matched at baseline, with no significant differences in age, sex, BMI, ASA, Cr Possum, previous abdominal surgery, operation performed, diagnosis, or histological stage (Table 1).

The operative time, pneumoperitoneum time and volume of CO_2 used were similar between groups (Table 2). There was a higher conversion rate in the control group (15.4 versus 5.7%), but this was not statistically significant. Out of 6 conversions in the control group, 2 were due to extensive intraoperative adhesions preventing dissection, 1 due to invasive disease requiring en-bloc resection, 1 due to intraoperative bleeding from inadvertent injury to a gonadal vessel, 1 due to inability to localize the lesion tattoo, and 1 due to failure of the bean bag used to secure the patient to the operating table. The first conversion in the study group was due to difficulty extracting a large specimen, and the second due to invasive disease requiring partial bladder resection. The total wound size was similar in both groups despite this. Complication rates and grades were equivalent.

Small bowel obstruction

There was no statistically significant difference in the rate of admission for small bowel obstruction between the two groups (Table 3). Only 2 patients were admitted with a small bowel obstruction, and both of these were in the study group. Both patients were given gastrografin but proceeded to open adhesiolysis as the obstruction did not resolve with nonoperative management.

Oncologic outcomes and survival

There was no statistically significant difference in the local recurrence rate or in the overall or cancer specific survival between the two groups (Table 3).

Ancillary analyses and adverse events

No unplanned subgroup or adjusted analyses were performed, and no other adverse events specific to the intervention or control are reported.

Discussion

We conducted a 5-year follow-up of a multicenter, double-blinded, randomized controlled trial investigating warming and humidification of insufflation carbon dioxide in laparoscopic colonic surgery. There was no statistically significant difference in rates of admission for small bowel obstruction, oncological outcome, or survival between groups.

There are no other published randomized trials investigating long-term outcomes of warming and humidification of insufflation gases in laparoscopic surgery. There is only one published clinical trial evaluating conditioning insufflation gas and postoperative adhesions in laparoscopic endometriosis surgery. However, comparisons with this study

Table 2 Intraoperative parameters and post-operative complications

	Study group (n = 35)	Control (n = 39)	*P* value
Operating time (mean in min, SD)			
Total operating time	176.3 (48.8)	184.7 (57.5)	0.504[a]
Pneumoperitoneum time	105.1 (39.0)	116.9 (55.0)	0.295[a]
Volume CO_2 used (mean in L, SD)	113.9 (110.1)	178.4 (170.4)	0.057[a]
Conversion to laparotomy			0.267[b]
Converted	2 (5.7%)	6 (15.4%)	
Not converted	33 (94.3%)	33 (84.6%)	
Total wound size (median in cm, IQR)	10.0 (5.0)	11.3 (6.0)	0.451[c]
Complication			0.650[b]
Yes	19 (54.3%)	19 (48.7%)	
No	16 (45.7%)	20 (51.3%)	
Complication grade			0.543[d]
I	1 (5.3%)	1 (5.3%)	
II	15 (78.9%)	13 (68.4%)	
III	3 (15.8%)	3 (15.8%)	
IV	0 (0%)	2 (10.5%)	

n, number of patients; IQR, interquartile range; SD, standard deviation.

[a] *t* test.

[b] Fisher's Exact test.

[c] Mann-Whitney *U* test.

[d] χ^2 test.

cannot be made as there was significant cointervention in the treatment group with humidification, cooling, addition of other gases, intravenous steroid administration, and pharmacological barrier application all administered simultaneously.[21] It is therefore unclear which of these interventions led to the reported reduction in adhesion scoring at second look laparoscopy. In addition, the clinical relevance of the adhesion reduction with this strategy was not evaluated with long-term follow-up.

Early data suggested that cold, dry gas can cause structural and biochemical injury to the peritoneal mesothelium, which results in a local inflammatory and cytokine response that increases postoperative pain, and potentially contributes to adhesion formation tumor seeding or systemic progression.[3–7]

Table 3 Five-year follow-up

	Study group (n = 35)	Control (n = 39)	*P* value
Small bowel obstruction			0.226[a]
Admission	2 (5.7%)	0 (0%)	
Gastrograffin	2 (5.7%)	0 (0%)	
Adhesiolysis	2 (5.7%)	0 (0%)	
Cancer local recurrence [b]	2 (6.5%)	2 (6.1%)	1.000[a]
Survival			
Overall	30 (85.7%)	32 (82.1%)	0.759[a]
Cancer specific [b]	28 (90.3%)	29 (87.9%)	1.000[a]

[a] Fisher's Exact test.

[b] n = 31 in study, and 33 in control.

Animal models have actually demonstrated a reduction in peritoneal adhesion formation with humidification of insufflation gas which is at odds with our study findings.[11,22,23] There may be several reasons for this disparity. First, several animal models have not accurately emulated the clinical situation with insufflation flow rates and pressures that are exaggerated.[24] Furthermore, in most animal models, no intraoperative surgery is actually performed, and it may be that the peritoneal inflammatory response after colonic surgery is so extensive, that it overshadows any immunological effects caused by the insufflation gas per se.[25–29] This is supported by the finding in our original RCT that the inflammatory response as measured by local and systemic cytokine concentrations was equivalent in both groups,[8] and by the fact that the difference in the inflammatory response between laparoscopic and open surgery (particularly in colonic resections) is minimal.[30] Another important consideration is that adhesion scores in animal models are notoriously unreliable, and do not necessarily correlate with adhesions that manifest as clinically significant (*i.e.*, cause a small bowel obstruction).[31,32]

There is also laboratory evidence that conditioning of insufflation gas reduces tumor implantation.[13] Once again, translation of these findings to the bedside is difficult because of inherent limitations of the animal model. However, this and other studies

by Binda *et al*. have shown that there may be additional benefit with cooling and supplementation with oxygen and nitrous oxide (which also reduce adhesion formation). It may be that this method should be further investigated in the setting of a clinical trial.[23,33,34]

We note some weaknesses of our study. There was a nonsignificant trend toward more right sided cases in the study group, and more left-sided cases and conversions in the control group. Importantly, there were no resulting differences in operating time, pneumoperitoneum time or volume of gas used, and had these seemingly random differences been important, they would all have actually favored the study group in terms of adhesions and recurrence. Another weakness is that this study was plainly not powered for the endpoints measured at 5 years and given the very low rate of bowel obstruction and recurrence in this group of patients it is likely that the study is significantly underpowered. A retrospective power calculation suggests that 750 patients would have been required in each arm to have an 80% power to detect a 50% decline in adhesion or recurrence from 6 to 3%. However, it must also be noted that there was not even a trend in favor of gas conditioning. In fact, the reverse is true, with a trend favoring unconditioned insufflation gas for both primary outcomes. Even if this is taken as a pilot study in this context (which is probably appropriate), it is unlikely that this trend justifies a large multicenter RCT given the numbers and resources that would be required to achieve this. A third weakness is that we were not able to assess intra-abdominal adhesions visually in this context, but relied instead on the surrogate measure of adhesive small bowel obstruction. Arguably, however, adhesions in the absence of small bowel obstruction are not necessarily clinically relevant.

Conclusion

Warming and humidification of insufflation CO_2 in laparoscopic colonic surgery does not appear to confer a clinically significant long term benefit in terms of adhesion reduction or oncological outcomes, although a much larger RCT would be require to confirm this.

Acknowledgments

Both authors made substantial contribution to conception and design, drafting the article, and final approval for publication. Tarik Sammour collected the data and analyzed it.

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