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Intravenous Lidocaine for Gut Function Recovery in Colonic Surgery
A Randomized Clinical Trial

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IMPORTANCE Despite the recovery advantages of minimally invasive surgical techniques, delayed return of gut function after colectomy is a common barrier to timely discharge from hospital.

OBJECTIVE To evaluate the effect of 2% perioperative intravenous lidocaine infusion on return of gut function after elective minimally invasive colon resection.

DESIGN, SETTING, AND PARTICIPANTS The ALLEGRO trial was a randomized, placebo-controlled, double-blind trial conducted in 27 UK hospitals. A total of 590 adults scheduled for elective minimally invasive colon resection for benign or malignant disease were randomized 1:1 to 2% intravenous lidocaine or saline placebo. Enrollment occurred from August 13, 2018, to April 11, 2023, with a pause in recruitment from March 20, 2020, through July 6, 2020; final follow-up was on August 10, 2023.

INTERVENTIONS The intervention patients received 2% intravenous lidocaine administered as 1.5-mg/kg bolus at induction of anesthesia followed by 1.5 mg/kg/h for 6 or 12 hours. Control patients received 0.9% saline placebo for 6 or 12 hours.

MAIN OUTCOMES AND MEASURES The primary outcome was the proportion of patients with return of gut function at 72 hours after surgery, defined by the GI-3 composite end point of tolerating diet (ingestion of food and drink without significant nausea or vomiting for 3 consecutive meals) and passage of flatus or stool. There were 11 secondary outcomes, including time to GI-3 recovery, time to GI-2 recovery (tolerance of oral diet and passage of stool), prolonged postoperative ileus, postoperative nausea and vomiting score, Overall Benefit of Analgesia Score, postoperative opioid consumption, Quality of Recovery–15, quality of life (EuroQol 5-Dimension 5-Level), enhanced recovery protocol adherence, time to meeting medically defined criteria for discharge, and time to patient self-assessed readiness for discharge.

RESULTS The trial enrolled 590 patients (295 intervention, 295 control); after 33 postrandomization exclusions, 557 patients were included (279 intervention, 278 control; 249 female patients [44.7%]; mean [SD] age, 66 [10.9] years); 532 (96%) received the randomized treatment. Return of gut function as defined by the GI-3 composite outcome was achieved at 72 hours by 160 patients (57.3%) in the intravenous lidocaine group vs 164 patients (59.0%) in the placebo group (adjusted absolute difference, −1.9% [95% CI, −8.0% to 4.2%]; relative risk, 0.97 [95% CI, 0.88 to 1.07]). There was no significant difference between the intervention and control groups in any of the 11 secondary end points.

CONCLUSIONS AND RELEVANCE Among patients undergoing elective minimally invasive colon resection, perioperative administration of 2% intravenous lidocaine did not improve return of gut function at 72 hours.

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Visual Abstract

Supplemental content

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Colonic resection for benign or malignant disease is a common surgical procedure (>20 000 per annum in the UK[1] and >600 000 in the US).[2] Return of gut function is a key component of recovery, indicated by patients being able to eat and drink with bowel propulsive activity (the passage of flatus or feces). Even with minimally invasive surgical techniques and best practice enhanced recovery multimodal perioperative care, absence of gut function recovery is the primary reason for prolonged hospital stay after colon surgery.[3,4] Furthermore, 10% to 15% of colonic resections progress to the clinical syndrome of postoperative ileus (nausea, vomiting, obstipation, and abdominal distension) requiring active inpatient management with analgesia and intravenous (IV) fluid replacement until gut function returns spontaneously, typically several days later. Predictive factors of postoperative ileus include increased surgical complexity, open rather than minimally invasive techniques, higher patient comorbidity, and certain perioperative care practices that are no longer recommended (eg, prolonged fasting, immobilization, and routine use of nasogastric tubes).[5] There are currently no therapeutic interventions to accelerate return of gut function, prevent postoperative ileus, or induce return of gut function after it occurs.

Lidocaine is an inexpensive, commonly used, and widely available local anesthetic medication that has antinociceptive and anti-inflammatory properties.[6] Lidocaine has been used intravenously as an adjunct to general anesthesia during various types of surgery and has been found to reduce early postoperative pain scores and opioid requirements.[7] A meta-analysis of IV lidocaine in laparoscopic abdominal surgery (14 trials, 742 patients) reported reduced incidence of nausea and vomiting (odds ratio, 0.52 [95% CI, 0.35-0.75]; I^2 = 0) and faster resumption of diet (weighted mean difference, −6.2 hours [95% CI, −12.37 to −0.03]; I^2 = 93.8%).[8] Lidocaine's mechanism of action on the gastrointestinal tract is unknown, but may be partly mediated by opiate sparing.[9]

There are currently 3 published randomized clinical trials (RCTs) of IV lidocaine in laparoscopic colectomy, comprising a total of 181 patients. Two of the studies, which were conducted in Europe and had typical postoperative hospital length of stays of 3 to 5 days, found reduced analgesic requirements, faster return of gut function, and a 1-day reduction in median length of stay with IV lidocaine vs placebo.[10,11] The third study, conducted in South Korea, reported reduced analgesic consumption and reduced incidence of nausea, but had a median length of stay of 8 to 9 days, which is inconsistent with current perioperative care practices and makes this study difficult to interpret.[12] No lidocaine-related adverse events were reported in these studies. The quality of evidence for reporting adverse events in 50 trials of perioperative IV lidocaine was graded very low in Cochrane analysis.[6] IV lidocaine has a 10- to 20-minute half-life and infusions up to 12 hours have linear pharmacokinetics; thereafter, pharmacokinetics become time-dependent.[6] Local anesthetic systemic toxicity is defined as seizure and cardiac arrest; the risk of local anesthetic systemic toxicity rises with IV infusion duration longer than 12 hours, where large doses of local anesthetic are used (eg, peripheral nerve blocks),[13] or from dosage or administration errors.[14]

Key Points

Question Does perioperative administration of 2% intravenous (IV) lidocaine affect postoperative return of gut function in adult patients undergoing elective minimally invasive colonic surgery?

Findings In this randomized clinical trial that included 557 adults, perioperative 2% IV lidocaine bolus plus infusion for 6 or 12 hours did not significantly improve return of gut function at 72 hours after operation (57.3% with IV lidocaine vs 59.0% with placebo).

Meaning Among adults undergoing elective minimally invasive colonic surgery, perioperative administration of 2% IV lidocaine did not improve return of gut function.

At the inception of the current trial, there was growing interest in use of perioperative IV lidocaine infusion in colorectal surgery for its perceived benefits on acute pain, opioid sparing, and gut function return.[9,15,16]

The primary aim of the trial was to determine the clinical effectiveness of perioperative IV lidocaine infusion on return of gut function after elective minimally invasive colonic resection.

Methods

Overview

The ALLEGRO trial (A Placebo-Controlled Randomised Trial of Intravenous Lidocaine in Accelerating Gastrointestinal Recovery After Colorectal Surgery) was an investigator-led, masked, placebo-controlled RCT comparing the effect of IV lidocaine infusion vs placebo on return of gut function for adult patients undergoing elective minimally invasive colonic resection. Twenty-seven UK National Health Service hospitals participated in the study. The trial protocol[17] and statistical analysis plan are available in Supplement 1 and Supplement 2, respectively. This trial report follows the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines and checklist.

Supervision

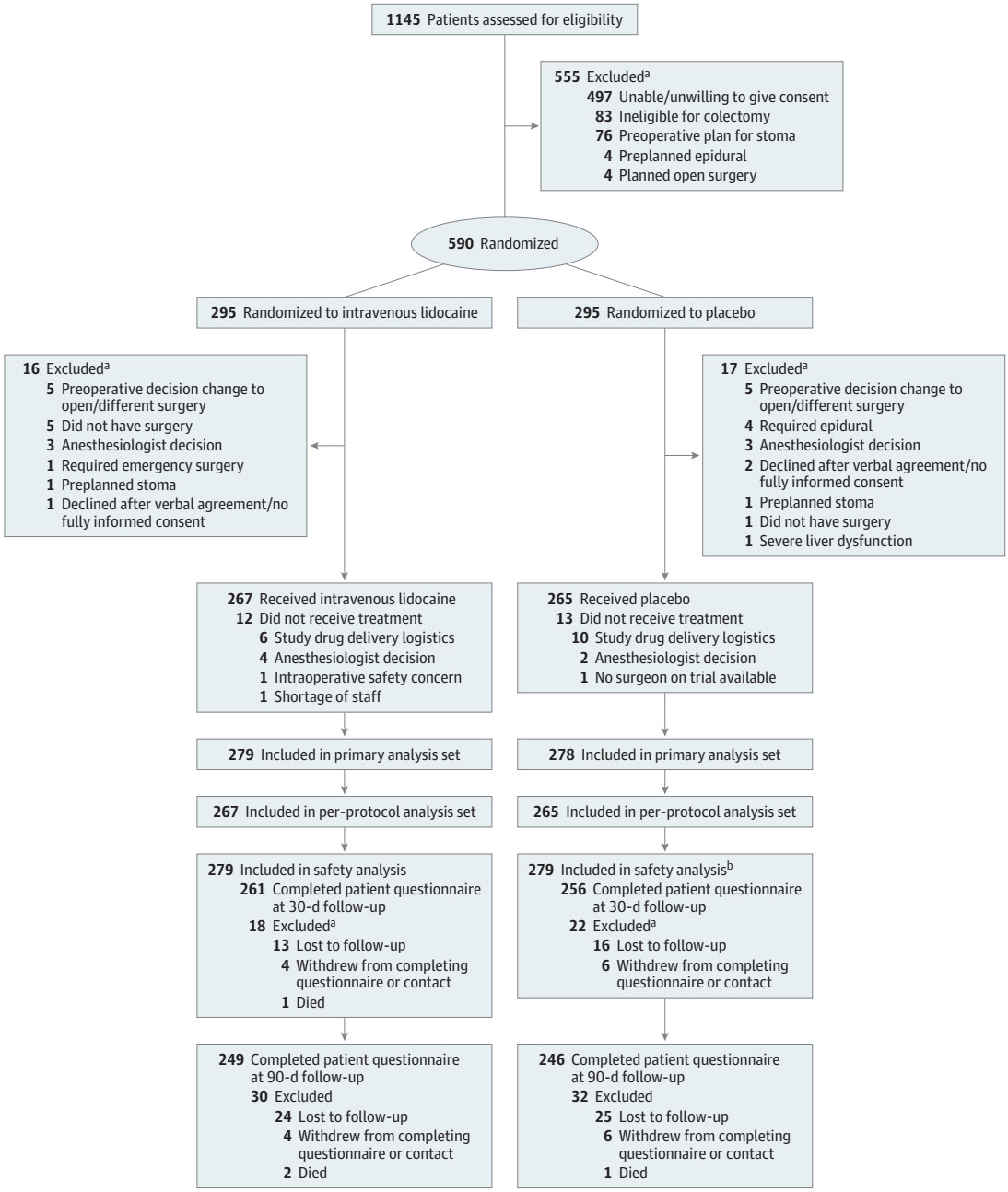
Independent data monitoring and trial steering committees approved the final protocol and provided ongoing oversight for the duration of the study. All participants provided written informed consent.

Ethics approval was obtained from the West of Scotland Research Ethics Committee 1 (17/WS/0210) and the UK Medicines and Healthcare products Regulation Agency (CT 01384/0255/001).

Randomization and Masking

After obtaining written informed consent, participants were randomized in a 1:1 ratio to 2% lidocaine or saline placebo using a web-based portal, stratified by sex, age (<50 years, 50-74 years, ≥75 years), and trial site (**Figure 1**). The web-based application allocated a unique participant study number and assigned a numbered participant study drug pack. The trial was designed to achieve allocation concealment with IV lidocaine appearing identical to placebo, both as clear colorless

Figure 1. Recruitment, Randomization, and Follow-Up in the ALLEGRO Trial



[a]Participants might have more than 1 reason to be excluded.

[b]One additional participant who was a postrandomization exclusion in the placebo group was added to the safety analysis because the participant received the randomized drug.

liquids. All study outcome data were recorded by participating site research staff masked to treatment allocation.

Study Population

Eligible participants were adult patients (aged ≥18 years) scheduled to undergo elective minimally invasive (laparoscopic or robotic) colonic resection with primary anastomosis for colon cancer, benign polyps, benign stricture, or diverticular disease (**Table 1**). Exclusion criteria included lidocaine intolerance, complete heart block, severe liver dysfunction (Child A or greater), kidney impairment (estimated glomerular filtration rate <30 mL/min/1.73 m^2), inflammatory bowel disease, planned use of other continuous local anesthetic infusions (eg, epidural anesthesia), certain surgical procedures (planned new stoma formation, low rectal cancer surgery), and patients currently pregnant or breastfeeding.

Table 1. Key Baseline Characteristics in the ALLEGRO Trial

Characteristic	No. (%) IV lidocaine (n = 279)	Placebo (n = 278)
Age, y		
<50	18 (6.5)	19 (6.8)
50-74	198 (71.0)	198 (71.2)
≥75	63 (22.6)	61 (21.9)
Mean (SD)	65.9 (11.0)	66.5 (10.7)
Sex		
Male	157 (56.3)	151 (54.3)
Female	122 (43.7)	127(45.7)
Currently smokes	24/279 (8.6)	26/277 (9.4)
BMI, mean (SD)	28.0 (5.6)	28.0 (5.4)
EQ-5D-5L[a]		
Total score, mean (SD) [No.]	0.833 (0.146) [n = 270]	0.825 (0.168) [n = 266]
Visual analog scale, mean (SD)	77.7 (18.3) [n = 269]	78.1 (18.1) [n = 266]
Operation performed		
Right hemicolectomy	137 (49.1)	135 (48.6)
High anterior resection	88 (31.5)	86 (30.9)
Sigmoid colectomy	22 (7.9)	15 (5.4)
Extended right hemicolectomy	10 (3.6)	19 (6.8)
Left hemicolectomy	9 (3.2)	8 (2.9)
Subtotal colectomy (ileosigmoid/ileorectal anastomosis)	2 (0.7)	4 (1.4)
Other	11 (3.9)	11 (4.0)
Unplanned stoma	12 (4.3)	8 (2.9)
Conversion to open surgery	30 (10.8)	38 (13.7)
Intraoperative blood loss recorded, median (IQR), mL	100 (30-200) [n = 244]	100 (25-200) [n = 246]

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); EQ-5D-5L, EuroQol 5-Dimension 5-Level; IV, intravenous.

[a] EQ-5D-5L score ranges from −0.59 to 1. Higher values represent a better quality of life. In comparison with the population in England where the mean score for males and females in the age range 65 to 69 years was 0.775 (95% CI, 0.770-0.795) and 0.797 (95% CI, 0.792-0.818), respectively,[18] the ALLEGRO trial population showed slightly better quality of life.

Complete inclusion and exclusion criteria are listed in the protocol (Supplement 1).[17]

Treatments

Patients received usual anesthetic protocols and perioperative care at each center. In addition, patients received an IV bolus of study drug (1.5 mg/kg [ideal body weight]) of 2% lidocaine made isotonic with 0.9% sodium chloride), placebo (0.9% sodium chloride) given over 20 minutes at induction of anesthesia followed by IV infusion of 2% lidocaine dosed at 1.5 mg/kg/h [ideal body weight] with a maximum rate of 120 mg/h (6 mL/h), or placebo. Continuous cardiac monitoring was mandatory during study drug infusion. The intended minimum duration of infusion was 6 hours. At centers without continuous cardiac monitoring on surgical wards, the infusion was continued in the postanesthesia care unit to complete a total duration of 6 hours and stopped prior to ward transfer. At hospitals that provided continuous cardiac monitoring on surgical wards, the infusion was continued for a total duration of 12 hours.

Follow-Up and Safety Monitoring

Patients were asked to complete outcome questionnaires daily from the day after surgery until the day of discharge from hospital or until hospital day 7. After discharge, patients were contacted by telephone at postoperative days 7 and 30. For patients who could not be contacted or who declined to complete questionnaires by telephone, safety data were recorded from hospital records at days 30 and 90 (readmission, complications, death).

Adverse events (AEs) and serious adverse events (SAEs) were collected from inpatient medical records from the time of patient enrollment to postoperative day 30. Severity, causality, and expectedness of AEs and SAEs were assessed by a clinician at each center and SAEs were reported to the sponsor for independent adjudication. Complications of surgery of Clavien-Dindo[19] grade 3 and above were reported as outcome data rather than as SAEs.

Outcomes

The primary outcome of the ALLEGRO trial was rate of return of gut function at 72 hours after surgery measured by GI-3 recovery, a composite outcome defined as tolerating diet (ingestion of food and drink without significant nausea or vomiting for 3 consecutive meals) and passage of flatus or stool. The GI-3 end point was originally derived in a series of RCTs of alvimopan (a peripherally acting opioid antagonist) in preventing postoperative ileus[20] and validated in a previous study by the authors.[21] There were 11 secondary outcomes: time to GI-3 recovery, time to GI-2 recovery (tolerance of oral diet and passage of stool), rate of prolonged postoperative ileus (failure to achieve GI-3 by 120 hours after surgery), postoperative nausea and vomiting, Overall Benefit of Analgesia Score,[22] postoperative opioid consumption (up to 24 hours), Quality of Recovery-15 score,[23] quality of life (EuroQol 5-Dimension 5-Level),[18] enhanced recovery protocol adherence, time to meeting medically defined criteria for discharge, and time to patient self-assessed readiness for discharge. There were 5 tertiary objectives: total length of hospital stay up to 30 days after surgery, unplanned readmission within 30 days of surgery, major surgical complications (Clavien-Dindo grade ≥3), 30-day mortality, and 90-day mortality. Data validation checks within the database flagged missing or erroneous data. The trial office undertook regular manual checks of data and raised data queries with individual sites.

The preplanned subgroups were intended infusion duration (6 vs 12 hours), operation type (right colectomy vs nonright colectomy), sex, age group (<50 years, 50-74 years, ≥75 years), and high vs low enhanced recovery protocol adherence.

Statistical Analysis

Sample Size and Statistical Power

Based on data from a previous feasibility study[21] and evaluation of effect sizes reported in other small studies, it was estimated that a sample size of 562 patients had 90% power at

a 2-sided 5% level of significance to detect a relative increase of 22% from 60% to 73.2% (absolute increase of 13.2%) in return of gut function at 72 hours after surgery with use of IV lidocaine vs placebo. This sample size also had similar power to detect a reduction of 10% (from 20% to 10%) in the secondary outcome of prolonged postoperative ileus (failure to achieve GI-3 5 days after surgery).

Analysis Methods

The primary outcome was analyzed using a generalized linear model with a log-link function adjusted for the minimization factors using fixed effects for sex (male, female), age group (<50 years, 50-74 years, ≥75 years), and a random effect for trial site. Secondary outcomes were analyzed using a similar approach with the appropriate link function for the outcome. Cox regression was used to analyze time-to-event outcomes and the empirical survival distribution was plotted using Kaplan-Meier plots. Proportional hazards assumptions were assessed using proportional hazard test. There was no evidence that the proportional hazards assumption was violated. A per-protocol analysis on primary outcome excluded those who did not receive IV lidocaine/placebo. There was no missing data for primary outcome and secondary outcomes were analyzed on observed data. All treatment effect estimates are presented with 95% confidence intervals (CIs). We performed planned subgroup analysis for the primary outcome exploring possible treatment effect modification by including treatment-by-subgroup interactions in the primary outcome analysis model above, using a stricter 2-sided 1% level of statistical significance. The preplanned subgroups were intended infusion duration (6 vs 12 hours), operation type (right colectomy vs nonright colectomy), sex, age group (<50 years, 50-74 years, ≥75 years), and high vs low enhanced recovery protocol adherence (eFigure in Supplement 3). All analysis was carried out by the authors (T.V., L.A.) according to the statistics analysis plan using Stata version 17 (StataCorp).

Impact of COVID-19

Recruitment to ALLEGRO was paused on March 20, 2020, at the start of the COVID-19 pandemic and restarted on July 7, 2020. No change of trial design was required to mitigate the impact of COVID-19. However, an amendment was approved to permit verbal agreement prior to written informed consent to permit randomization in advance of hospital admission.

Results

Patients

Between August 13, 2018, and April 11, 2023, 1145 patients were assessed for eligibility, and 590 patients were randomly assigned either to IV lidocaine (295 patients) or placebo (295 patients). There were 33 postrandomization exclusions, and no crossovers (Figure 1). The last date of follow-up was August 10, 2023.

Baseline Characteristics

The mean (SD) age of the population was 66 (10.9) years and 44.7% were female. Baseline characteristics and surgical procedures were well balanced between the groups (Table 1). Almost half of the patients underwent right hemicolectomy, and approximately 12% of operations were converted intraoperatively from minimally invasive to open surgery.

The primary analysis set included 557 patients (279 in the IV lidocaine group and 278 in the placebo group). Of these, 532 received the randomized treatment (267 in the IV lidocaine group and 265 in the placebo group in the per-protocol analysis).

Primary Outcome

The primary outcome of return of gut function (by GI-3 definition) at 72 hours after operation was met by 160 participants (57.3%) in the IV lidocaine group vs 164 patients (59.0%) in the placebo group. Primary outcome data were reported in 100% of participants. The absolute difference between IV lidocaine and placebo was −1.9% (95% CI, −8.0% to 4.2%) (relative risk [adjusted for minimization variables], 0.97 [95% CI, 0.88 to 1.07]; $P = .54$) (**Table 2**). On the basis of per-protocol analysis, the absolute percentage difference between IV lidocaine and placebo was −2.3 (95% CI, −8.9 to 4.3) and relative risk was 0.96 (95% CI, 0.86 to 1.07) ($P = .49$).

Secondary Outcomes

Results of secondary outcomes are presented in **Figure 2** and Table 2. There was no statistically significant difference between the groups in time to GI-3 outcome, time to GI-2 recovery, or incidence of prolonged postoperative ileus. There was no significant difference in postoperative nausea and vomiting assessments, intraoperative or postoperative opioid analgesia consumption (up to 24 hours), patient-reported pain (Overall Benefit of Analgesia Score), Quality of Recovery-15 score, quality of life (EuroQol 5-Dimension 5-Level), enhanced recovery perioperative practice, time to meet clinician-assessed medical criteria for discharge from hospital, or patient-assessed fitness for discharge from hospital.

In prespecified subgroup analysis, there was no evidence of any treatment effect moderation by 6- vs 12-hour duration of lidocaine infusion, operation type, sex, age group, or enhanced recovery protocol adherence (eFigure in Supplement 3). We found no evidence of any treatment effect in post hoc subgroup analysis considering actual (rather than intended) duration of lidocaine infusion.

Adverse Effects and Safety

Thirty- and 90-day mortality and surgical complication rates were low (**Table 3**).[1,24] Length of hospital stay, adverse events, and safety outcomes were similar between the groups; most adverse events were mild or moderate in severity and most were assessed as unrelated to the study drug (ie, were complications related to surgery) (Table 3).

Discussion

In this large, pragmatic RCT, compared with placebo, 2% IV lidocaine, administered as a 1.5-mg/kg bolus followed by a 1.5-mg/kg/h infusion for 6 or 12 hours had no significant effect

Table 2. Primary and Secondary Clinical Outcomes

	IV lidocaine (n = 279)		Placebo (n = 278)		Absolute % difference (95% CI)	Relative risk (95% CI)[b]	*P* value
	No.	No. (%)[a]	No.	No. (%)[a]			
Primary outcome: achieved GI-3 recovery by 72 h after operation							
Primary analysis set[b,c]		160 (57.3)		164 (59.0)	−1.9 (−8.0 to 4.2)	0.97 (0.88 to 1.07)	.54
Per protocol[b,c]		154/267 (57.7)		158/265 (59.6)	−2.3 (−8.9 to 4.3)	0.96 (0.86 to 1.07)	.49
Secondary outcomes							
Time to GI-3 recovery[c,d]		275 (98.6)		275 (98.9)		HR, 0.98 (0.83 to 1.17)	
Time to GI-2 recovery[c,d]		261 (93.5)		256 (92.1)		HR, 1.03 (0.86 to 1.23)	
Prolonged postoperative ileus[b,c]		44 (15.8)		39 (14.0)	1.8 (−3.3 to 6.8)	IRR, 1.13 (0.80 to 1.61)	
Clinically important nausea and vomiting[e]							
Day 1		7/237 (2.9)		16/238 (6.7)			
Day 2		5/223 (2.2)		19/226 (8.4)			
Day 3		5/202 (2.5)		5/189 (2.6)			
OBAS score, mean (SD)[c,f]							
Baseline	238	2.62 (2.87)	240	2.53 (2.69)			
Postoperative day 1	235	4.57 (3.11)	241	4.55 (3.41)		0.086 (−0.505 to 0.678)	.78
Postoperative day 2	232	4.07 (3.41)	228	4.44 (3.65)		−0.574 (−1.176 to 0.027)	.06
Postoperative day 3	210	3.33 (3.07)	199	3.51 (3.16)		−0.296 (−0.924 to 0.332)	.36
Postoperative day 4	147	3.56 (3.48)	149	2.89 (3.41)		0.565 (−0.148 to 1.279)	.12
Postoperative day 5	87	3.30 (3.36)	98	2.91 (3.50)		0.231 (−0.641 to 1.102)	.60
Postoperative day 6	69	3.41 (3.41)	63	2.76 (3.16)		0.696 (−0.328 to 1.720)	.18
Postoperative day 7	244	2.19 (2.55)	241	1.96 (2.52)		0.278 (−0.300 to 0.856)	.35
Intraoperative opioid analgesia, median (IQR), OME mg	249	63.3 (29.3 to 213.3)	256	60.0 (29.3 to 201.9)			
Postoperative opioid analgesia up to 24 h, median (IQR), OME mg	210	70.6 (30.0 to 150.0)	210	45.0 (17.1 to 98.6)			
Quality of Recovery-15, mean (SD)[c,f]							
Baseline	263	96.67 (11.09)	258	96.11 (12.15)			
Postoperative day 1	220	74.29 (15.37)	229	73.12 (13.56)		1.22 (−1.27 to 3.70)	.34
Postoperative day 2	215	78.89 (15.30)	209	80.08 (13.62)		−1.22 (−3.77 to 1.33)	.35
Postoperative day 3	198	81.43 (14.00)	190	80.01 (15.43)		1.17 (−1.46 to 3.80)	.38
Postoperative day 4	133	79.92 (15.30)	133	82.41 (15.24)		−2.28 (−5.38 to 0.81)	.15
Postoperative day 5	81	78.58 (14.85)	94	79.19 (15.36)		0.23 (−3.47 to 3.93)	.90
Postoperative day 6	64	78.86 (12.20)	59	79.54 (14.53)		1.75 (−2.60 to 6.09)	.43
Postoperative day 7	236	87.15 (12.86)	226	87.49 (11.08)		0.21 (−2.24 to 2.66)	.86
Postoperative day 30	238	93.34 (9.64)	240	92.91 (9.43)		0.31 (−2.11 to 2.73)	.80
Quality of life (EQ-5D-5L), mean (SD)[c,f]							
Baseline	270	0.833 (0.146)	266	0.825 (0.168)			
Postoperative day 1	237	0.398 (0.301)	237	0.393 (0.286)		−0.005 (−0.042 to 0.032)	.78
Postoperative day 2	227	0.529 (0.253)	226	0.523 (0.252)		0.005 (−0.033 to 0.042)	.81
Postoperative day 3	204	0.583 (0.243)	197	0.594 (0.217)		−0.018 (−0.057 to 0.021)	.37
Postoperative day 4	144	0.598 (0.235)	142	0.619 (0.241)		−0.011 (−0.055 to 0.034)	.64
Postoperative day 5	89	0.555 (0.257)	96	0.621 (0.247)		−0.057 (−0.111 to −0.003)	.04
Postoperative day 6	69	0.603 (0.249)	60	0.615 (0.263)		−0.013 (−0.076 to 0.050)	.69
Postoperative day 7	246	0.700 (0.187)	240	0.718 (0.165)		−0.017 (−0.054 to 0.019)	.35
Postoperative day 30	260	0.819 (0.137)	256	0.831 (0.129)		−0.011 (−0.047 to 0.024)	.54
Postoperative day 90	249	0.869 (0.149)	246	0.871 (0.138)		−0.002 (−0.038 to 0.034)	.92

(continued)

Table 2. Primary and Secondary Clinical Outcomes (continued)

	IV lidocaine (n = 279)		Placebo (n = 278)		Absolute % difference (95% CI)	Relative risk (95% CI)[b]	*P* value
	No.	No. (%)[a]	No.	No. (%)[a]			
Enhanced recovery perioperative procedures							
IV dexamethasone at anesthesia induction		179 (64.2)		176 (63.3)			
Intrathecal (spinal) diamorphine		181 (64.9)		194 (69.8)			
PONV prophylaxis prescribed regularly for first 48 h		161 (57.7)		155 (55.8)			
Laxative prescribed after surgery		45 (16.1)		45 (16.2)			
Nasogastric tube placed intraoperatively and still in situ when patient woke up		8 (2.9)		6 (2.2)			
Chewing gum prescribed		9 (3.2)		3 (1.1)			
Preoperative carbohydrate loading on day of surgery		171 (61.3)		183 (65.8)			
Mobilization target achieved on day 1[g]		93 (33.3)		91 (32.7)			
Patient offered food on day 1		218 (78.1)		221 (79.5)			
Received postoperative supplement drinks on day of surgery		69 (24.7)		69 (24.8)			
Total IV fluids in first 24 h from start of anesthesia, median (IQR), mL	279	3000 (2000 to 4000)	278	3000 (2000 to 4000)			
IV fluids discontinued within 48 h of start of operation		213 (76.3)		214 (77.0)			
Urinary catheter removed within 48 h of start of operation		185 (66.3)		186 (66.9)			
Mobilization target achieved on day 2[h]		221 (79.2)		219 (78.8)			
Time to meet clinician-assessed medical criteria for discharge from hospital[c,d]		278 (99.6)		277 (99.6)		HR, 0.99 (0.84 to 1.17)	
Time to patient-assessed fitness for discharge from hospital[c,d]		278 (99.6)		277 (99.6)		HR, 0.99 (0.83 to 1.17)	

Abbreviations: EQ-5D-5L, EuroQol 5-Dimension 5-Level; GI-2, tolerating diet and first passage of stool; GI-3, tolerating diet and passage of flatus or stool (whichever comes first); HR, hazard ratio; IRR, incidence rate ratio; IV, intravenous; OBAS, Overall Benefit of Analgesia Score; OME, oral morphine equivalents; PONV, postoperative nausea and vomiting.

[a] Numbers in cells are No. (%) except where indicated.

[b] Analyzed using a generalized linear model with a log-link function except where otherwise noted.

[c] Adjusted for minimization variables, age, sex, and center.

[d] Analyzed using Cox regression model; estimate is hazard ratio.

[e] PONV score ≥5 defines clinically important postoperative nausea and vomiting.

[f] Analyzed using linear mixed model and treatment effects at each time were derived from the interaction term for time by treatment.

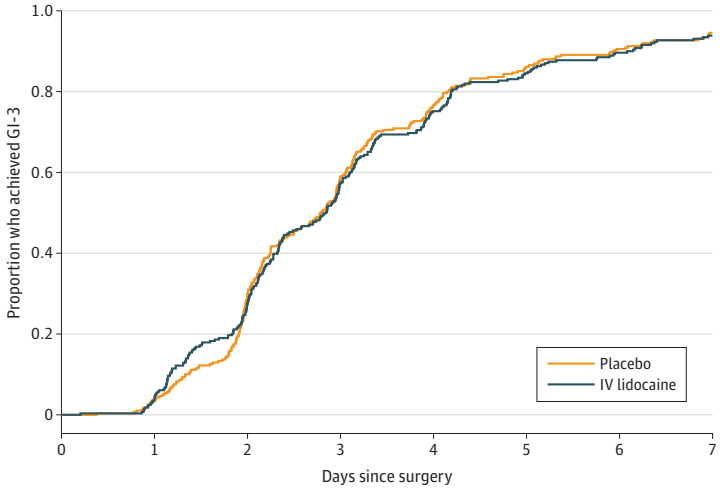
[g] Mobilization target: 2 hours out of bed on day of surgery and 4-6 hours on day 1.

[h] Mobilization target: out of bed for at least 4 hours on day 2.

on the primary outcome of postoperative return of gut function at 72 hours after elective minimally invasive colonic surgery. This study also showed no benefit of lidocaine on any of the 11 secondary end points including postoperative pain, quality of recovery, quality of life, and total length of hospital stay. The result was robust across prespecified subgroup analysis for age group, sex, right vs nonright colectomy, 6- vs 12-hour infusion duration, and enhanced recovery protocol adherence. The current trial also confirms that delayed return of gut function affects a substantial proportion of patients undergoing minimally invasive colonic resection.[3,4]

Prior individual RCTs reporting a benefit of IV lidocaine as a perioperative adjunct for return of gut function have been limited by inconsistent end points, small size, and variation in IV lidocaine infusion duration, although meta-analyses appeared to support the benefit of lidocaine.[8,25] Two European single-center RCTs found faster return of gut function, improved analgesia, and reduced length of stay with use of

Figure 2. Postoperative Return of Gut Function by the GI-3 Definition



No. at risk (No. of events)														
Placebo	278	(10)	268	(71)	197	(82)	115	(49)	65	(27)	38	(12)	26	(11)	15
IV lidocaine	279	(10)	269	(66)	202	(83)	119	(50)	69	(26)	43	(14)	28	(11)	16

Kaplan-Meier curves show the proportion of patients who received intravenous (IV) lidocaine and placebo who achieved GI-3. The table below the figure shows the number of participants at risk and number of events in parentheses at each time point. GI-3 definition of return of gut function is a composite outcome: tolerating diet (ingestion of food and drink without significant nausea or vomiting for 3 consecutive meals) and passage of flatus or stool (whichever comes first).

Table 3. Tertiary/Safety Outcomes

	IV lidocaine (n = 279)[a]	Placebo (n = 278)[a]	Incidence rate ratio
Total length of hospital stay within 30 d after surgery, mean (SD), d[b,c,d]	6.0 (5.9)	5.8 (4.5)[b]	1.03 (0.92-1.14)
Serious adverse events[e]			
No. of participants (%)	4 (1.4)	9 (3.2)	
No. of events	4	9[f]	
Adverse events[e]			
No. of participants (%)	40 (14.3)	37(13.3)	
No. of events	75	65	
30-d Mortality	1 (0.4)	2 (0.7)	
90-d Mortality	2 (0.7)	3 (1.1)	
Unplanned readmission after discharge and within 90 d of operation[c]	31 (11.1)	34 (12.2)	
Clavien-Dindo grade ≥3 perioperative complication[g]	13 (4.7)	12 (4.3)	

Abbreviation: IV, intravenous.

[a] Data are numbers of participants who had 1 or more of the listed events (%), unless otherwise specified.

[b] Adjusted for minimization variables, age, sex, and center.

[c] One participant in the placebo group did not contribute to this analysis because date of discharge was unknown as participant was moved to another hospital prior to discharge.

[d] Analyzed using negative binomial regression; estimate is incidence rate ratio.

[e] One additional participant who was a postrandomization exclusion in the placebo group was added to the safety analysis because the participant received the randomized drug.

[f] One event was initially assessed as a possible suspected unexpected serious adverse reaction; on unmasking, the patient was in the placebo group and so was reported as a serious adverse event.

[g] The Clavien-Dindo classification is a widely used method of grouping complications based on the level of intervention required to resolve them: grade 1, deviation from normal postoperative course not requiring pharmacological, surgical, radiological, or endoscopic intervention; grade 2, requiring pharmacological treatment; grade 3, requiring surgical, endoscopic, or radiological intervention; grade 4, life-threatening, requiring intermediate/intensive care; grade 5, death of the patient.

perioperative IV lidocaine after colon resection.[10,11] In contrast to these studies, the current trial found no beneficial effect in any primary or secondary end points, with a patient cohort that was older, had more comorbidities, and were more likely to be undergoing surgery for colorectal cancer than benign disease.

The surgical outcomes in both groups in this study were similar, with low rates of complications, few conversions to open surgery, and a low 30-day mortality rate (with no deaths within 72 hours of surgery). Most patients had an uncomplicated recovery (Table 3) after minimally invasive colectomy, yet 40% had not recovered gut function at 72 hours after surgery.

Although this study reported no adverse events attributable to lidocaine using this administration schedule, there is ongoing concern that its use carries a risk of systemic toxicity and death.[26,27]

Strengths of this study include the large sample size of 557 patients, who were representative of the population undergoing colonic resection in the UK (where the majority

of colonic resections are performed for colon cancer) from a large number of hospitals. The primary outcome was recorded in all participants and more than 95% received their allocated intervention. Perioperative care information was recorded. The trial's pragmatic design allowed continuation of the study with only a 3-month hiatus during the COVID-19 pandemic with minimal change to study procedures and included allocation concealment and masking. The sample size was large enough for treatment effect estimates with adequate precision to rule out any meaningful benefit from IV lidocaine on the primary and secondary outcomes.

Limitations

There are limitations to this study. First, this study did not include information about participant race or ethnicity or socioeconomic status. Second, more complex colorectal operations (eg, low rectal cancer) were excluded. Third, a strict protocol for anesthetic or surgical technique was not provided. Fourth, although it cannot be discounted that there is the possibility that longer duration of administration of IV lidocaine might have been effective, there was no difference between lidocaine and placebo in the 6-hour vs 12-hour subgroup analysis. Longer durations of infusion, therefore, seem unlikely to have achieved different outcomes, and increase the likelihood of systemic lidocaine toxicity.

Conclusions

Among adults undergoing elective minimally invasive colon resection, perioperative administration of 2% IV lidocaine infusion did not improve return of gut function at 72 hours.

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Concept and design: Paterson, Innes, Balfour, Stoddart, Cotton, Arnott, Foo, Nimmo, Speake, Norrie.
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Supervision: Paterson, Cotton, Aucott, Foo, MacLennan, Nimmo, Norrie.
Other - senior trial management support for the project: Cotton.
Other - health economic analysis: Atter.
Other - health economic evaluation: Stoddart.

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