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A randomised controlled trial of lidocaine infusion on post-operative opioid consumption in patients undergoing robotic colorectal surgery

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ABSTRACT

INTRODUCTION: Intravenous lidocaine has been shown to have analgesic effects leading to a reduced post-operative opiate need, but this effect is still debated in various surgical populations. We investigated whether this effect could be demonstrated in robot-assisted colorectal surgery.

METHODS: A total of 60 adult patients undergoing robot-assisted colorectal surgery were randomly assigned to two groups in this prospective, double-blinded trial. The lidocaine group was treated with intravenous lidocaine. Treatment was initiated before induction of anaesthesia with a bolus of 1.5 mg/kg and immediately followed by infusion of 1.5 mg/kg/h continued until 2 h after end of surgery. The control group received placebo treatment with an equal volume and a dosing of 0.9% saline. The follow-up period was 72 h.

RESULTS: No significant difference between groups in the median cumulated morphine consumption at 24 and 72 h was observed. Nor were there any differences in pain score, use of antiemetics, time until flatus and/or defecation or length of hospital stay.

CONCLUSIONS: In this randomised, double-blinded, prospective study using intravenous lidocaine versus 0.9% saline in robot-assisted colorectal surgery, we found no significant difference in post-operative cumulated morphine consumption at 24 or at 72 h.

FUNDING: The study received funding from DASAIMs Forskningsinitiativ (2016) and DASAIMs Smerteforskningspris (2016).

TRIAL REGISTRATION: The trial is registered with EudraCT (2014-003466-25) and ClinicalTrials.gov (ID: NCT03044808).

Patients undergoing surgery regularly experience post-operative pain, ileus, nausea and vomiting. Opioid-related side effects further increase patient discomfort. Alleviation of these side effects by reducing the use of opiates is thought to enhance post-operative recovery.

An increasing number of patients receive anticoagulant therapy and therefore neuraxial analgesia is often contraindicated. Hence, safe and effective alternatives for post-operative pain treatment are needed, preferably alternatives with a very low rate of side effects. In their systematic review from 2017, MacFater et al [1] found that two of five small studies showed a significant reduction in morphine consumption at 24 h when using lidocaine infusion compared with placebo in patients undergoing colorectal surgery.

Lidocaine has been shown to have anti-inflammatory [2] and analgesic properties [3]. Furthermore, lidocaine has been shown to reduce the duration of post-operative ileus [4] and to reduce the length of hospital stay [5]. Recently, Weibel et al [6] updated their Cochrane systematic meta-analysis on intravenous lidocaine. They found an uncertain effect on the reduction of post-operative morphine consumption overall in the range of 4.52 mg in all studies (not divided into laparoscopic or open procedures).

We hypothesised that lidocaine given intravenously, initiated before induction of anaesthesia and continued until the post-operative period would reduce post-operative opioid consumption in long-duration robot-assisted laparoscopic colorectal surger

METHODS

After approval from the review board from the Department of Anaesthesiology and Intensive Care at Odense University Hospital, the study obtained ethical approval from The Regional Committee on Health Research Ethics for Southern Denmark on 18 December 2014 (Regionshuset, Damhaven 12, 7100 Vejle. Project ID: S-20140174. Chair J. M. Hertz), the Danish Medicines Agency (Alex Heides Gade 1, 2300 Copenhagen S. Record number: 2015110368. Approval: 17 December 2015) as well as the Danish Data Protection Agency (Sdr. Boulevard 29, 5000 Odense C. Record number: 15/5789. Approval: 18 December 2015). The study was monitored by the Good Clinical Practice Unit for Region of Southern Denmark. The trial is registered with EudraCT (2014-003466-25) and ClinicalTrials.gov (ID: NCT03044808).

The inclusion criteria were adult Danish-speaking patients undergoing elective robot-assisted laparo-

ORIGINAL ARTICLE

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scopic colorectal surgery. The exclusion criteria were allergy to amide local analgesics, atrioventricular blocks, hepatic or renal failure, chronic use of opioids or nonsteroidal anti-inflammatory drugs (NSAIDS), pregnant or lactating women and treatment with beta-blockers and porphyria.

Patients' written informed consent was obtained after giving verbal and written information and allowing 24 h for consideration.

Premedication consisted of ranitidine 150 mg, dexamethasone 8 mg and paracetamol 1 g, orally. Standard monitoring at the department was used. All patients were given intravenous antibiotic prophylaxis before surgery.

Anaesthesia was induced with sufentanil, propofol and rocuronium and maintained with titrated doses of sufentanil and desflurane aiming for a stable circulation and bispectral index of 40-60. Sufentanil was administered per local guideline at the discretion of the anaesthetist. Train of four count was not allowed above 0. At the end of surgery, the patient was given 4 mg of intravenous ondansetron and the neuromuscular blockade was reverted with neostigmine and glycopyrrone. Restrictive fluid therapy with a background infusion of 100 ml/h of Ringer's acetate was kept throughout the procedure. The patients' fluid losses were corrected by additional infusion of crystalloid.

The hospital pharmacy was responsible for the randomisation in blocks of four and preparation of the study medication. To keep track of the randomisation number, we used sequentially numbered containers containing six ampules with 50 ml of either 0.9% saline or 0.5% lidocaine together with stickers for the syringes for the infusions. No randomisation code was broken during the study. The investigators, patients, nurses, surgeons and the statistician were unaware of the group allocation until the end of the statistical analysis.

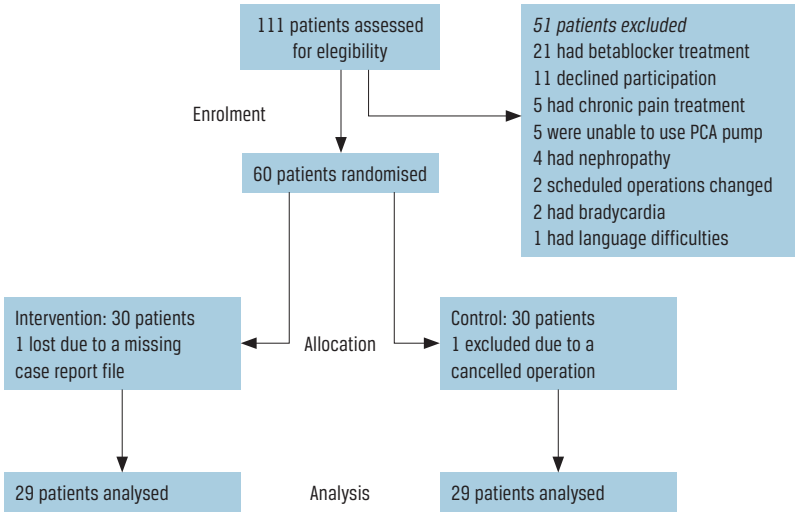
Before inducing anaesthesia, we gave an equal volume of blinded study medication according to 1.5 mg/kg bolus from a solution of 5 mg/ml lidocaine at a rate of 300 ml/h. Thereafter, we initiated the continuous infusion of the same volume per hour throughout the surgery and ended in the post-anaesthesia care unit (PACU) 2 h after the end of surgery. Throughout the study, we used simplified normal weight calculation according to Broca's Index (height in cm's minus 100). Upon arrival to the PACU, the patient was connected to a morphine intravenous pump without background infusion and patient-controlled bolus doses of 0.04 mg/kg were possible every 7 min.

The follow-up times were 30 min. and 1 h after end of surgery and every 30 min. throughout the patient's stay at the PACU. At the ward, data were collected upon arrival and every 8 h until 72 h after end of surgery. The patients were treated with paracetamol and NSAID post-operatively at the surgeon's discretion. No local analgesics were injected by the surgeons.

We collected data on cumulative morphine consumption, numerical pain score (NRS), use of antiemetics and time to flatus and defecation.

The primary outcome was cumulated morphine consumption at 24 h after end of surgery. The secondary outcomes were cumulated morphine consumption at 72 h, NRS at 24 and 72 h, time until first flatus/defecation, use of antiemetics and time until discharge.

FIGURE 1 / Flow diagram.



PCA = patient-controlled bolus.

Data sharing statement

The trial data are not publicly available owing to data privacy considerations, but access to the anonymised dataset can be obtained from the corresponding author on reasonable request.

Statistics

A power calculation was done in advance, assuming a 30% reduction in morphine consumption in the lidocaine group based on available studies at the drafting of the protocol [3, 7]. Furthermore, we considered that a 30% reduction would be clinically relevant. We needed a power of 80% to detect a difference defined by a $p < 0.05$. According to this calculation, we needed 49 patients and decided to include 60 considering that there might be dropouts. The data were analysed according to the intention-to-treat principle.

Given the limited number of observations and some outliers, we relied on comparison of medians. A non-parametric test was applied for comparison of medians from two independent groups. A test for comparison of proportions from two independent groups was used for percentages.

TABLE 1 / Baseline characteristics.

	Intervention group (N = 29)	Control group (N = 29)	p-value
Age, yrs, median (IQR)	69 (61-74)	68 (59-74)	0.57
Female gender, n (%)	9 (31)	9 (31)	1.00
ASA score 1/2/3, n (%)	13 (44.8)/15 (51.7)/1 (3.4)	8 (27.6)/19 (65.5)/2 (6.9)	0.18/0.29/0.55
BMI, kg/m^2, median (IQR)	26.5 (24.5-31)	27 (25.5-30)	0.73
Weight, kg, median (IQR)	83 (73.9-94.5)	87 (74.6-90)	0.40
Surgery duration, min., median (IQR)	310 (248-364)	330 (290-375)	0.45
Cancer/non-cancer, n (%)	28 (96.6)/1 (3.4)	26 (89.7)/3 (10.3)	0.3/0.3
Rectum cancer, n (%)	17 (58.6)	16 (55.2)	0.80
Perioperative blood loss, ml, median (IQR)	100 (0-100)	50 (0-100)	0.06
Converted to open surgery, n (%)	1 (3.4)	1 (3.4)	1.00
Study medicine, bolus, ml, median (IQR)	22.8 (20.1-24)	22 (19.5-24.3)	0.48
Study medicine, total, ml, median (IQR)	180 (149-205.2)	180 (163.2-216)	1.00
Perioperative sufentanil, µg, median (IQR)	100 (80-110)	100 (86.25-120)	1.00
Post-operative paracetamol, any, n (%)	28 (96.6)	29 (100)	1.00
Post-operative NSAID, any, n (%)	11 (37.9)	13 (44.8)	0.60

ASA = American Society of Anesthesiologists; IQR = interquartile range; NSAID = nonsteroidal anti-inflammatory drug.

Trial registration: The trial is registered with EudraCT (2014-003466-25) and ClinicalTrials.gov (ID: NCT03044808).

RESULTS

From February 2016 to May 2017, we included 60 patients in the study. We could use data from 29 patients in each group. **Figure 1** provides a flow diagram. The baseline characteristics were comparable in the two groups (**Table 1**). **Figure 2** presents the data distribution for the primary outcome.

Table 2 shows the results for outcomes as median values. For the primary outcome, we found a median cumulative opioid consumption of 43.3 (range: 35-70.6) mg in the lidocaine group versus 41.3 (25-63.8) mg in the control group. This difference was not significant (p = 0.78). No data were missing for the primary outcome besides one patient per group, as mentioned in Figure 1. For NRS at 24 and 72 h, no significant difference in outcomes between groups was found. In line herewith, we observed no significant difference between the groups for the other secondary outcomes. For NRS at 24 h, we were unable to retrieve data for four patients in the lidocaine group and for five patients in the control group. At 72 h, the corresponding numbers were 17 and 22, respectively.

In the lidocaine group, the reasons for reoperation were two anastomotic leakages, one perineal wound infection and one small bowel perforation with abscess. In the control group, the reasons were five patients with anastomotic leakages, one ischaemia of the stoma and one perforation of the small bowel from the primary operation.

DISCUSSION

In this randomised, double-blinded, placebo-controlled trial of intravenous lidocaine compared with 0.9% saline, we found no significant difference in morphine consumption during the first 24 or 72 h. In line herewith, we observed no between-group differences for the remaining secondary outcomes.

The strength of our study was thorough blinding and randomisation, and comparable groups. No allocation assignment was broken. No patients experienced side effects endangering the blinding of the personnel. We lost one patient from each group. This did not affect the baseline characteristics.

One reason why we failed to detect any difference between the groups may be that we studied patients who did not experience enough pain for detection of a

FIGURE 2 / Data distribution for the primary outcome: cumulated morphine consumption.

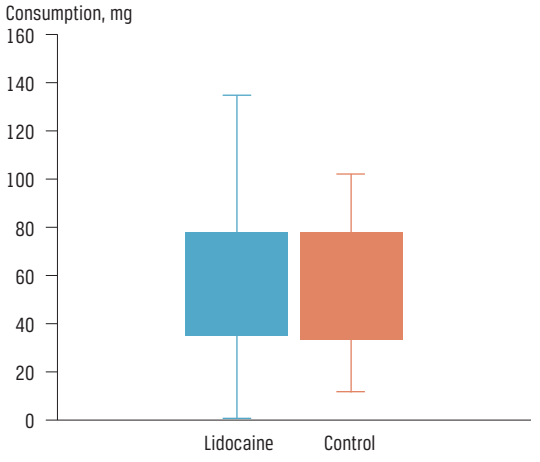


TABLE 2 / Primary and secondary outcomes.

Results	Control group (N = 29)	Lidocaine group (N = 29)	p-value
Cumulative opioid consumption, mg, median (IQR)[a]			
At 24 h	41.3 (25-63.8)	43.3 (35-70.6)	0.78
At 72 h	78.7 (36-125)	77 (46.6-105)	0.78
NRS, median (IQR)			
At 24 h	2 (0-3)	2 (1-3)	0.99
At 72 h	0 (0-1.5)	1 (0-2)	0.37
Antiemetic doses until 72 h, n, median (IQR)	2 (2-3)	3 (2-4)	0.21
Time to 1st flatus/defaecation, h, median (IQR)[b]	34 (26-48)	32 (24-40)	0.99
Time to discharge, days, median (IQR)	5 (4-9)	5 (4-7)	0.99
Complicated surgery, n (%)[c]	7 (24.1)	4 (13.8)	0.32

IQR = interquartile range; NRS = numerical pain score.
a) Calculated morphine equivalents according to www.medicin.dk.
b) 3 patients in each group did not have flatus/defaecation at 72 h and were not included.
c) The patients in need of any kind of reoperation, specified in the text.

clinically significant difference. Even so, in the systematic review by Weibel et al [8], lidocaine infusion was followed by a reduction in opiate consumption in laparoscopic abdominal operations. The patients in our study were given relatively high doses of morphine on top of a multimodal analgesics regime. Hence, we are convinced the dose would be adequate for detecting a difference, if such a difference existed.

Patients were treated with the opioid analgesic sufentanil during the operation. This may explain why we detected no difference in post-operative morphine consumption. However, the median total dose was 100 µg (range: 80-110 µg) per patient in the lidocaine group versus 100 µg (86.25-120 µg) per patient in the control group. It therefore seems unlikely that the effect of this opioid should have influenced our results. No other opioids were administered at the end of surgery. The need for re-operation might have influenced our primary and secondary outcomes. No patients were re-operated during the first 24 h, but data for the secondary outcomes might have been influenced by other surgery. However, randomisation should eliminate this issue.

The patients were also treated with non-opioid analgesics as NSAID and paracetamol after surgery. This could normally mask an effect of opioid consumption, but consumption was evenly distributed among the groups and we therefore find it unlikely that this affected the study results.

All patients received a standard two-drug antiemetic therapy including ondansetron and dexamethasone which might mask any effect of lidocaine on the incidence of PONV. Furthermore, dexamethasone might also mask the effect on reduction of the opioid consumption. Nevertheless, the doses of anti-emetics were similar in the groups, so we are convinced that this regime has not influenced our results.

The optimal dosing range, timing and duration of the infusion of lidocaine remain unknown [9]. This study probably falls in the low dosing range regarding bolus and continuous infusion as other studies have used 2 mg/kg/h for infusion. We chose the lower dosing for the continuous infusion because this study included robot-assisted operations with a mean surgery time of over 5 h and hence approx. 7 h of lidocaine infusion. We registered no side effects from intravenous lidocaine administration. For future research, it would be interesting to study a higher dosing range.

The adequate lidocaine concentration in the blood remains unknown. We measured neither serum nor plasma concentrations of lidocaine, but even if we had, this would not have helped us determine if we used a sufficient dosing regimen. Koppert et al [3] used a regime very similar regime to the one used in the present study and found a reduction in morphine consumption with a measured serum lidocaine of 1.9 µg/l (range: 1-5 µg/l).

Both during anaesthesia and in the PACU, there were no clinical signs of lidocaine toxicity. These symptoms or findings would have led to breaking of the randomisation code.

We were unable to demonstrate differences or advantages of lidocaine as previously described in the literature in our setting. Given the power calculation, the number of patients included should have been enough to detect a difference. We performed our power calculation on the basis of previously published studies. We anticipated that we would find a reduction in morphine consumption at 24 h of no less than 30%.

Our power calculation for the study was based on earlier studies by Koppert et al [3] and McKay et al [7]; the first showing a decrease in morphine consumption of 30% at 72 h with a similar setup; the second showing a 50% reduction in the PACU and 40% reduction for the total study period. Additionally, a 30% reduction in opiate consumption would be a clinically important finding. Comparing the results from these two studies with the newer pooled literature from Weibel et al, we may have an underpowered study and a much more modest effect of lidocaine.

CONCLUSIONS

In this randomised, double-blinded, placebo-controlled trial of intravenous lidocaine compared with 0.9% saline in robot-assisted colorectal surgery, we found no significant difference in morphine consumption during the first 24 h and also failed to detect a difference in consumption at 72 h. In line herewith, we also failed to demonstrate any difference on the secondary outcomes. Based on the lack of effects in this study and the

literature in the field, we do not find that intravenous lidocaine is adequate for reducing pain in laparoscopic operations for colorectal cancer.

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CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at Ugeskriftet.dk/dmj

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