Quadratus Lumborum Block Versus Perioperative Intravenous Lidocaine for Postoperative Pain Control in Patients Undergoing Laparoscopic Colorectal Surgery

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A Prospective, Randomized, Double-blind Controlled Clinical Trial

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Objective: To investigate the comparative analgesic efficacy of systemic lidocaine and quadratus lumborum (QL) block in laparoscopic colorectal surgery.

Background: Although epidural analgesia is the standard to control pain in patients undergoing open colorectal surgery, optimal analgesic management in laparoscopic surgery is less well-defined. There is need for effective and efficient alternatives to epidural analgesia for pain management in patients undergoing laparoscopic colorectal surgery.

Methods: A total of 125 patients undergoing laparoscopic colorectal surgery were included in this randomized, double-blind controlled clinical trial. Patients randomly received an intravenous infusion with placebo plus a QL-block with placebo, a QL-block with ropivacaine 0.25% plus intravenous placebo, or intravenous lidocaine plus a QL-block with placebo. Postoperatively, all patients received patient-controlled intravenous anesthesia (PCIA) with morphine. Primary outcome parameter was the opioid consumption during the first 24 hours postoperatively. Secondary endpoints included severity of postoperative pain, time to return of intestinal function, incidence of postoperative nausea and vomiting, and length of hospital stay.

Results: The QL-block was not superior to systemic lidocaine for the reduction of morphine requirements in the first 24 hours postoperatively {QL-group: 37.5 (28.4) mg [mean (standard deviation)] vs lidocaine group: 40.2 (25) mg, $P = 0.15$}. For the majority of secondary outcome parameters, no significant differences were found between the groups. Morphine consumption in the postanesthesia care unit, the number of PCIA-boli demanded by the patient, and the number of PCIA-boli delivered by the PCIA-pump during the first 24 hours postoperatively were lower in the placebo group.

Conclusions: In our trial, the QL-block did not provide superior postoperative analgesia when compared to systemic lidocaine in laparoscopic colorectal surgery.

Trial registration: Eudra CT: 2014-001499-73; 31/7/2014

Keywords: colorectal, laparoscopic, pain, postoperative

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Although epidural anesthesia (EA) remains the standard to control pain after open abdominal surgery, EA has been reported not to facilitate recovery in laparoscopic surgery.[1,2] Modern enhanced recovery protocols for laparoscopic surgery do no longer recommend EA for postoperative pain control.[3]

The QL-block is an abdominal trunk block that controls somatic pain in the upper and lower abdomen.[4,5] The QL-block is an ultrasound-guided block administered to the QL-space posterior to the abdominal wall muscles and lateral to the QL-muscle. In contrast, for the TAP-block, the local anesthetic is injected into the transversus abdominis plane. It has been demonstrated that the QL-block can reduce opioid consumption after laparoscopic colorectal surgery.[6,7] Also the use of systemic lidocaine has been found to reduce postoperative pain scores and opioid consumption.[8–10]

Although both the QL-block and systemic lidocaine have been reported to reduce pain after laparoscopic colorectal surgery when compared to placebo,[6,11–13] the efficacy of these techniques has never been compared head-to-head.

We hypothesized that in laparoscopic colorectal surgery, QL-block would provide superior postoperative analgesia when compared to perioperative systemic lidocaine.

METHODS

A total of 125 patients scheduled for laparoscopic colorectal surgery were included in this double-blind, randomized, placebo-controlled trial. The study protocol was approved by the ethics committee of the University Hospitals Leuven, Belgium (EC OG032, 2014) and the Belgian government (703180, 2014), and has been previously published.[14] The study is registered in the publicly accessible study register of the European Medicines Agency (EUDRACT 2014-001499-73). Patients were enrolled between December 2014 and January 2017. Inclusion criteria were age between 18 and 75 years, and an ASA physical status I–III. Exclusion criteria included refusal of the patient, known hypersensitivity to study medications, chronic opioid use, liver insufficiency (defined as a serum-bilirubin $\geq$2 mg/dL), renal insufficiency, epilepsy, mental retardation, morbid obesity (body mass index >40), obstructive sleep apnea syndrome, and cardiac rhythm disorders.

After written informed consent, patients were randomly allocated to the quadratus lumborum group (QL-group), the lidocaine group (L-group), or the placebo group (P-group), using a computer generated random table (Graphpad Software, Inc, La Jolla, CA) and an allocation ratio of 2:2:1. Blinding of research personal was maintained throughout the whole observation period including all postoperative follow-ups.

The study interventions are schematically displayed in Figure 1.

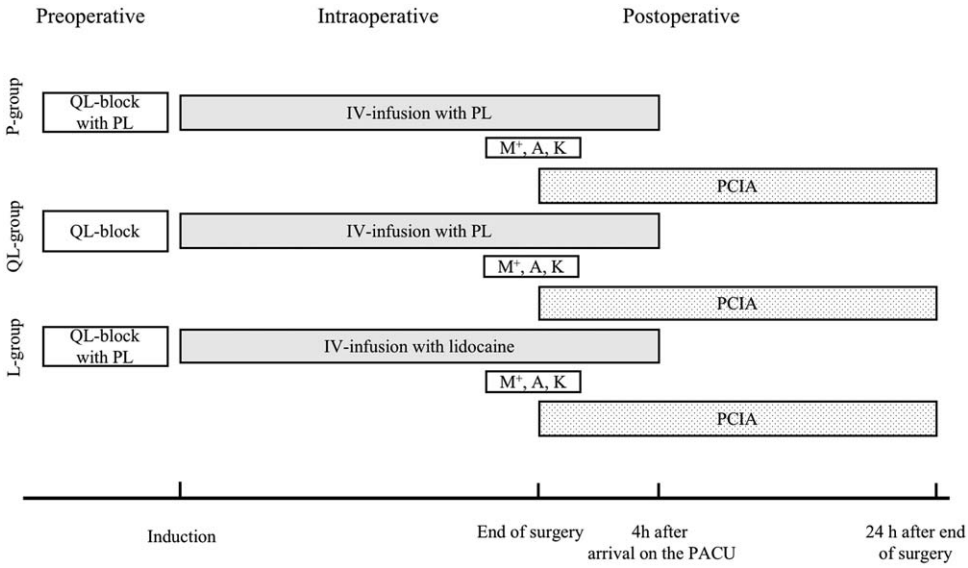

FIGURE 1. Study intervention. A, acetaminophen; K, ketorolac; L, lidocaine; M+, morphine; PL, placebo.

In patients of the QL-group, a bilateral single shot QL-block was applied under ultrasound guidance before induction of anesthesia. At each side, 30 mL (in patients weighing >55 kg) or 20 mL (in patients weighing <55 kg) of ropivacaine 0.25% and clonidine 0.5 μg/kg were injected using a 22 G needle of 50 mm length.

Patients in the L-group received an intravenous (IV) bolus injection of lidocaine 1.5 mg/kg at induction of anesthesia followed by a continuous infusion of $1.5\ mg \cdot kg^{-1} \cdot h^{-1}$ which was continued until 4 hours after arrival at the postoperative anesthesia care unit (PACU).

To attain blinding of the patients and the investigators, patients in the QL-group and the P-group received a perioperative placebo infusion with saline at the same rate as the lidocaine infusion in the L-group. Moreover, the patients of both the L-group and the P-group received also a QL-block with saline.

The anesthesia technique was standardized. Anesthesia was induced with a bolus injection of propofol (2 mg/kg), a target-controlled infusion of remifentanil (plasma level: 5 ng/mL) and a bolus of cisatracurium (0.15 mg/kg). General anesthesia was maintained by inhalation of sevoflurane in an oxygen/air mixture. Perioperative fluid administration was standardized using goal directed fluid therapy based on stroke volume optimization.[15]

Thirty minutes before the end of surgery and irrespective of the group allocation, all patients received a combination of the following IV analgesics: acetaminophen 15 mg/kg, ketorolac 0.5 mg/kg, and morphine 0.2 mg/kg for postoperative pain control. Patients were extubated in the operation theater after completion of the surgical procedure and discharged to the PACU.

Postoperative pain in the PACU and on the ward was treated with acetaminophen (15 mg/kg 4/day) and ketorolac (0.5 mg/kg 3/day) using a fixed scheme. In addition, each patient received patient-controlled IV analgesia (PCIA) with morphine.

If the postoperative numeric rating scale (NRS) for pain exceeded 3, an additional bolus of 1 mg of morphine (IV) was given on the PACU. If pain treatment was still insufficient, a clonidine bolus (1 μg/kg) was given.

Postoperative nausea and vomiting (PONV) prophylaxis was performed with IV-dexamethasone and IV-ondansetron. PONV rescue treatment consisted of IV-droperidol (PACU) or IV-ondansetron (on the ward).

Study Outcomes

Primary outcome of the study was the morphine consumption in the first 24 hours postoperatively.

Secondary outcome parameters included severity of postoperative pain as evaluated with the NRS, both at rest and during coughing; time to recovery of intestinal function; the PONV incidence evaluated on the basis of an NRS for nausea and documenting the presence/absence of vomiting during the first 24 hours; length of hospital stay; perioperative inflammatory response (the serum levels of C-reactive protein and interleukin-6); and lidocaine and ropivacaine concentrations in plasma.

Throughout the whole observational period, all patients were closely monitored for the occurrence of eventual adverse events and for local anesthetic toxicity.

Statistical Analysis

Sample Size Calculation

The study was powered to detect the differences in postoperative morphine consumption between the QL-group and the L-group, and between the QL-group and the P-group. The coefficient of variation (CV) of this endpoint was derived from reported standard deviation or interquartile range in the literature[6,16] and found to be in the range between 0.19 and 0.73. Furthermore, in an unpublished retrospective evaluation of 10 patients in our institution, we observed a CV of 0.35. Hence, a CV equal to 0.5 was assumed in the power calculation. Using a 2-sided test for a ratio of means (with alpha = 5%), 44 patients per group were needed to show a 25% reduction in the 24-hour morphine consumption in the QL- versus L-group when a power of 80% was to be achieved. The assumption that perioperative lidocaine also yields a reduction of 25% compared to PCIA alone implies a ratio of means of $0.75^2 = 0.5625$ for QL versus placebo. Recruiting 22 patients in the P-group yields more than 99% power to detect this difference, with 44 patients included in the QL-group. As such, 110 patients in total were needed. To compensate for possible dropouts, we included 125 patients in total. They were randomized into the QL-group (n = 50), the L-group (n = 50), and the P-group (n = 25), hence with weights equal to 2, 2, and 1, respectively.

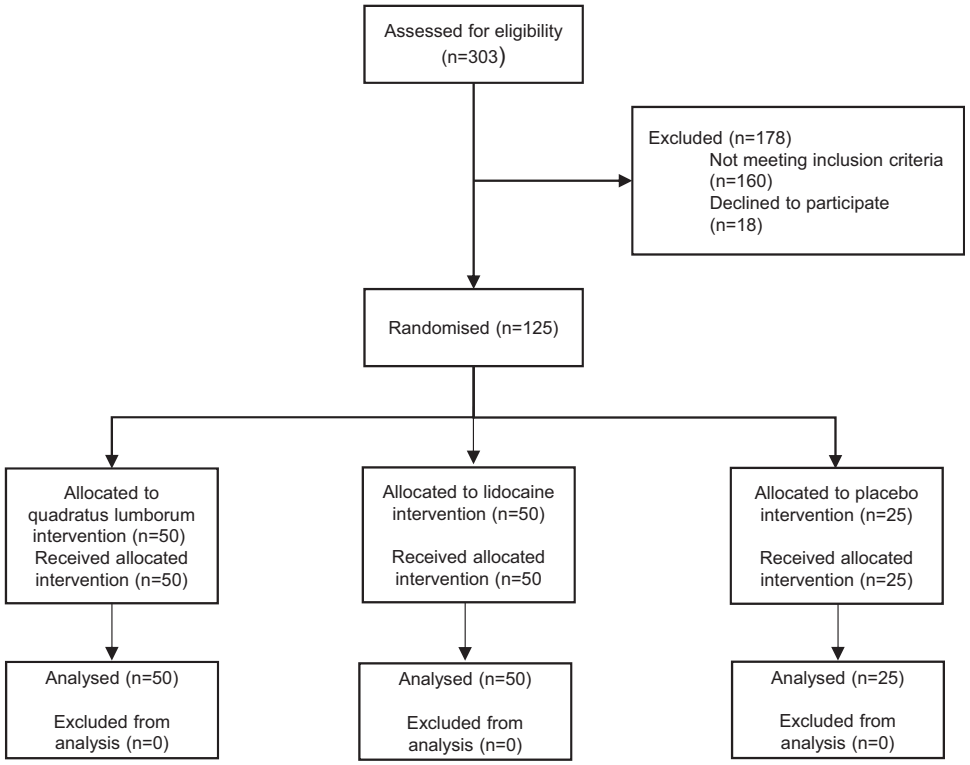

FIGURE 2. Flowchart, CONSORT flow diagram. N = number of patients.

Data Analysis

A 2-sided *t* test for the ratio of means was used to compare the 24-hour cumulative morphine intake between the QL-group and the L-group and between the QL-group and the P-group, respectively, and 95% confidence intervals for the ratio are reported. A Mann-Whitney *U* test was used to test the robustness of the conclusion if the log-transformed data showed a departure from normality based on the Shapiro-Wilk W-test statistic. In addition, a Q-Q plot was used to visually inspect the normality assumption. To enable confirmatory claims about both comparisons (QL vs L and QL vs P) without inflating the type-I error, a hierarchical closed test procedure was used, both comparisons were tested on a 5% level, with however the comparison of QL versus placebo only being tested in case that the comparison of QL versus lidocaine was significant.

Secondary outcomes were compared using Fisher exact test in case proportions had to be analyzed, and Mann-Whitney *U* tests were used when the data were measured on a ratio or ordinal level.

Kaplan-Meier estimates were used to obtain the cumulative distribution curves for the event times, and the treatment groups were compared using the log-rank test. A linear model for longitudinal measurements with a random intercept across patients was used for variables that were measured over time. A linear mixed effect model for repeated measures is used to the compare the evolution over time for the interleukins.

Patients were analyzed according to the intention-to-treat principle. All analyses were performed using R version 3.3.1 (R Foundation for Statistical Computing 2016-06-21, Rstudio, Inc, Boston, MA). In any case, a $P < 0.05$ was considered statistically significant.

RESULTS

The flow chart is shown in Figure 2.

Patients in the 3 groups did not differ with regard to demographic, biometric, and procedure-related data (Table 1).

Primary Outcome

The amount of morphine consumption during the first 24 hours postoperatively was not significantly different between the QL-group and the L-group {37.5 mg [28.4] mg [mean (standard deviation)] vs 40.2 mg [25] mg}, $P = 0.15$ (Fig. 3).

Secondary Outcomes

The mean NRS for pain at rest and coughing did not differ at any timepoint between the 3 groups (electronic supplement, Fig. 4, http://links.lww.com/SLA/B443). Total morphine consumption in the PACU, the number of PCIA-boli demanded by the patients and the number of PCIA-boli delivered by the pump in the first 24 hours postoperatively were significantly lower in the P-group than in the QL- and L-group (Table 2). The incidence of PONV, time to first analgesic request, time to recovery of intestinal function, and length of hospital stay were not significantly different between the 3 groups (Table 2).

The serum levels of IL-6 were not significantly different between the groups (Table 2). There was no significant difference between the serum levels C-reactive protein on day 1 between the groups (Table 2).

Safety Data

The incidence of serious adverse events did not differ significantly between groups (Table 2). The lidocaine and ropivacaine plasma levels we found 4 hours after arrival in the PACU were 1.93 ± 7.6 and 0.6 ± 6.2 μg/mL (mean ± standard deviation), respectively.

In the QL-group, a significantly higher incidence of subjective symptoms for local anesthetic-systemic toxicity was found with significantly more patients reporting a metallic taste (Table 2).

TABLE 1. Patient Characteristics

	Quadratus Lumborum (n = 50)	Lidocaine (n = 50)	Placebo (n = 25)
Age, y	59 (48; 65)	60 (49; 68)	62 (59; 68)
Sex n (%)			
Male	32 (64)	27 (54)	14 (56)
Female	18 (36)	23 (46)	11 (44)
Weight, kg	80 (69; 90)	75 (64; 81)	72 (67; 86)
Height, cm	171 (168; 180)	170 (165; 178)	169 (165; 175)
BMI, kg/m^2	26.4 (23.9; 29.4)	25 (23; 27.2)	25.4 (24.2; 28.4)
ASA n (%)			
I	8 (16)	9 (18)	7 (28)
II	34 (68)	30 (60)	14 (56)
III	8 (16)	11 (22)	4 (16)
PONV history n (%)			
No	36 (72)	34 (68)	20 (80)
Yes	14 (28)	16 (32)	5 (20)
Type of surgery n (%)			
Left-sided colectomy	29 (58)	32 (64)	16 (64)
Right-sided colectomy	21 (42)	18 (36)	9 (36)

Data are given as absolute numbers (n), percentage (%) of the whole population (N), and median (interquartile range), as appropriate.

DISCUSSION

Our study failed to demonstrate superiority of the QL-block compared with systemic lidocaine for postoperative analgesia after laparoscopic colorectal surgery.

The efficacy of both abdominal wall blocks and systemic lidocaine is controversial. Although several studies in laparoscopic colorectal surgery could demonstrate a significant reduction in opioid requirements for systemic lidocaine[13,17] and TAP-block,[6,7,11] other researchers could not confirm these findings.[18–22] The interpretation of these results is further hampered by the fact that the efficacy of systemic lidocaine and abdominal wall blocks has never been directly compared in a randomized controlled trial. We considered it therefore mandatory to perform a study in which the analgesic efficacy of QL-block and systemic lidocaine was not only compared head-to-head, but also to placebo in patients undergoing laparoscopic colorectal surgery. The obtained results are in line with the findings of 1 recently published trial that compared the effect of systemic lidocaine and TAP-block on postoperative pain after open prostate surgery showing no significant differences in postoperative opioid consumption for systemic lidocaine and TAP-block.[23]

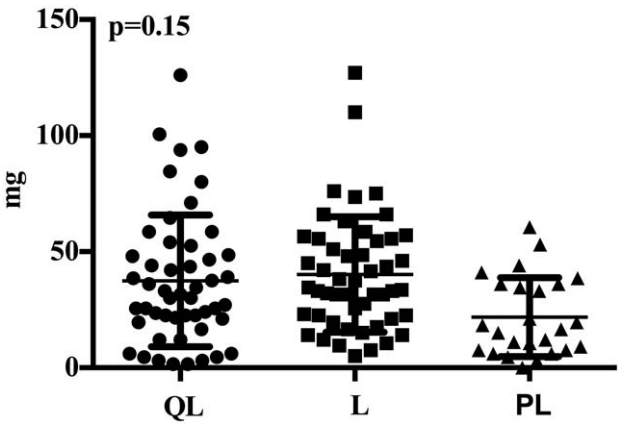

FIGURE 3. Cumulative morphine requirements (mg) in the first 24 postoperative hours for the quadratus lumborum block, the lidocaine, and the placebo group. Data are shown as individual values and as mean ± SD. QL block (closed circles, n = 50); L, lidocaine group (closed squares, n = 50); and P, placebo group (closed triangles, n = 25) ($P = 0.15$).

The reasons why the QL-block and systemic lidocaine had comparative analgesic effects in our study are speculative.

First, we cannot entirely rule out the possibility that the failure of the QL-block to reduce postoperative morphine consumption could be attributed to a failure to sufficiently administer this technique, that is, technical failure. In an attempt to proactively address this caveat, the QL-block was, however, applied in all patients under ultrasound guidance by an anesthetist specialized in locoregional anesthesia and having the experience of several thousand peripheral nerve blocks.

Second, it may be argued that a suboptimal technique was used as abdominal wall block. Amongst the different variants of abdominal truncal blocks, the QL-block is, however, reported to show a particularly high efficacy by blocking the dermatomes T7 to L1, hereby controlling somatic pain in the upper and lower abdomen.[5,24] The QL-block has even been suggested to possibly dampen central visceral pain conduction.[25,26]

Third, dosing issues might have played a role. Although the ropivacaine doses used for the QL-block in our trial have been shown to be effective for postoperative pain relief in other trials,[27,28] the most effective local anesthetic volume is still controversial.[29] In our study, relatively large volumes were used which theoretically might have resulted in insufficient concentrations at the presumed site of action.[5,29] The QL-block is, however, a volume block, and is hence critically dependent upon the administration of large volumes with lower concentrations.[30] Concerning lidocaine, our dosing regimen resulted in plasma concentrations that are similar to those reported in the literature to produce significant postoperative analgesia.[13]

Fourth, it could be argued that giving opioids at the end of surgery might have masked the effect of the QL-block in our study. We considered it, however, unjustifiable not to load our patients with morphine after having received remifentanil perioperatively. Not administering opioids at end of surgery would have left the P-group without any potent analgesic in the immediate postoperative period. Moreover, other authors still demonstrated differences in

TABLE 2. Intraoperative Data and Secondary Outcomes

		Quadratus Lumborum (n = 50)	Lidocaine (n = 50)	Placebo (n = 25)	*P*
Intraoperative data	Duration of surgery, min	135 (123; 160)	146 (131; 182)	130 (120; 160)	0.24
	Cumulative sevoflurane dose, mL	38 (31; 52)	40 (30; 50)	40 (27; 55)	0.90
	Cumulative remifentanil dose, μg	1250 (1000; 1750)	1100 (890; 1370)	1080 (938; 1515)	0.27
	Cumulative fluid therapy, mL				
	Crystalloids	400 (250; 775)	500 (300; 800)	675 (250; 925)	0.42
	Colloids	500 (400; 600)	500 (400; 600)	400 (400; 600)	0.36
	Urinary loss, mL	160 (87; 300)	150 (120; 345)	150 (120; 305)	0.61
	Blood loss, mL	50 (20; 150)	100 (50; 188)	100 (50; 200)	0.56
Secondary outcomes	Total morphine PACU, mg	11 (5; 17)	15 (9; 21)	6 (2; 18)	0.04
	Total number of morphine boli, n				
	Demanded	23 (14; 38)	28 (14; 49)	12 (6; 35)	0.05
	Delivered	20 (13; 31)	22 (13; 32)	11 (5; 22)	0.005
	PONV 24 h, n (%)				
	No	20 (40)	15 (30)	9 (36)	0.58
	Yes	30 (60)	35 (70)	16 (64)	
	Time to first analgesic request, min	15 (15; 41)	15 (15; 30)	15 (15; 30)	0.81
	First solid food, days	1 (1; 1)	1 (1; 2)	1 (1; 2)	0.52
	First flatus, days	2 (1;2)	2 (1; 2)	2 (1; 2)	0.80
	First defecation, days	3 (2; 5)	3 (2; 5)	3 (2; 5)	0.84
	Length of hospital stay, days	4 (3; 5)	4 (4; 5)	4 (3; 5)	0.73
	Serious adverse events, n (%)	5 (10)	7 (14)	4 (16)	0.72
	Anastomosis leak	2	2	2	
	Anaphylaxis	0	0	1	
	Ileus	2	2	0	
	Postoperative bleeding	1	0	0	
	Respiratory depression	0	1	0	
	Inflammation	0	2	1	
	LA toxicity, n (%)				
	Arrhythmias	2 (4)	0 (0)	0 (0)	0.35
	Tinnitus	3 (6)	1 (2)	1 (4)	0.84
	Metallic taste	9 (18)	1 (2)	0 (0)	0.004
	Cytokines, pg/mL				
	IL-6				
	Baseline	3 (1; 4)	2 (0,7; 4)	2 (1; 4)	0.34
	End of surgery	3 (1; 12)	5 (2; 10)	3 (1; 9)	0.61
	POD1	15 (7; 37)	19 (11; 39)	36 (5; 72)	0.52
	CRP, mg/mL				
	POD1	35 (17; 55)	42 (23; 68)	27 (19; 50)	0.31

Data are given as absolute numbers (n), percentage (%) of the whole population (N), and median (interquartile range) as appropriate.
CRP indicates C-reactive protein; LA, local anesthetic toxicity; POD1, postoperative day 1.

postoperative opioid consumption even despite the administration of opioids at the end of surgery in patients receiving remifentanil intraoperatively.[7]

Fifth, cytokines are well-known to play an important role in mechanisms underlying perioperative pain.[31] Lidocaine has been shown in several studies to attenuate the perioperative inflammatory reaction.[32,33] In our study, however, all patients received dexamethasone and a nonsteroidal anti-inflammatory agent (Ketorolac), 2 agents with potent anti-inflammatory properties.[34–36] We suggest that in presence of these 2 anti-inflammatory drugs, systemic lidocaine was unable to further dampen the inflammatory response, which might have resulted in the failure to exert additional analgesic effects.

In our trial, more patients in the QL-group showed subjective symptoms of local anesthetic systemic toxicity. Four hours after arrival in the PACU, plasma ropivacaine-concentrations in the patients suffering from these signs did not exceed the reference value for toxicity of plasma ropivacaine-concentration of 2.2 μg/mL and are in agreement with levels reported in the literature.[37] In any case, caution is warranted when interpreting these findings as the correlation between blood levels and signs of toxicity is multifactorial and determined by anatomical, physiological, and pharmacokinetic factors.[38,39]

Interestingly, the P-group had the lowest postoperative morphine consumption in our study. This finding, however, should be interpreted with caution as the trial was not powered to prove this difference. Moreover, the reduced morphine requirements in the P-group did not translate in an improvement of any clinically relevant outcome parameter.

We acknowledge that our study suffers from several limitations.

First, the variability in morphine consumption was higher than the variability assumed in the sample size calculation (CV = 0.5). The CV equaled 0.757 and 0.622 in the QL- and the L-group, respectively. Based on a pooled estimate for the CV (equaling 0.69) we would have needed 75 patients in each of the 2 groups to have at least 80% to detect a reduction of 25%. With the included 50 patients per group, the study had 62.6% power instead of the desired 80% power. Hence, in hindsight the study was slightly underpowered.

Second, the QL-block was administered using ropivacaine with clonidine as an adjunct, in an attempt to prolong the analgesic

effects of the QL-block. Perineural/intrafascial injection of clonidine is known to result in systemic hemodynamic and coanalgesic effects.[40,41] Moreover, clonidine is known to counteract remifentanil-induced hyperalgesia.[42] All these effects should, however, result in a superior analgesic efficacy of the QL-block rather than in equivalency when compared to systemic lidocaine.

CONCLUSIONS

In patients undergoing laparoscopic colorectal surgery, the QL-block was not superior with respect to postoperative analgesia when compared to perioperative systemic lidocaine. Given its lack of superior efficacy, the technically demanding and time-consuming placement, and the considerable risk of systemic toxicity, we suggest that the QL-block has no value for the pain management in laparoscopic colorectal surgery.

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DISCUSSANTS

Wojciech P. Polkowski (Lublin, Poland):

I congratulate the authors on their excellent work and presentation. I would like to thank the organization for the honor of reviewing this randomized, placebo-controlled analgesic comparison of systemic lidocaine and the QL block (QLB) in laparoscopic colorectal surgery.

I would like to address 4 questions:

First, the ultrasound-guided transversus abdominis plane (TAP) block has become a common analgesic method after surgery involving the abdominal wall. Because this blockade is limited to the somatic anesthesia of the abdominal wall and highly dependent on interfascial spread, variants of QLBs have been proposed as more consistent methods, aiming to accomplish somatic and analgesia of the abdomen. Different variants have different analgesic effects and mechanisms of action. Could you please indicate which of the most popular variants of QLB may have better analgesic effects than the QLB?

Second, could you please describe in detail what the main difference is between the TAP-block and QLB, in terms of where the local anesthetic is injected?

Third, could you explain what the reason was for adding clonidine to ropivacaine?

Fourth, you have concluded that the QLB was not superior, with respect to postoperative analgesia, when compared to perioperative systemic lidocaine. You found that morphine consumption was lowest in the placebo group. Could you please comment on this finding?

Response From André J. D'Hoore (Leuven, Belgium):

Thank you very much for these questions. Regarding your first and second question, for the QL block, the fascia surrounding the transversus abdominis muscle is tracked where the transversus abdominis muscle merges with the thoracolumbar fascia, surrounding the QL muscle, the space posterior to the abdominal wall muscles and lateral to the QL muscle. This posterior ultrasound-guided approach is now referred to as the QL 1 block or the lateral QL-block. In contrast, for the TAP-block, the local anesthetic is injected into the TAP. We have especially chosen the QL-block because this block provides anesthesia from Th5 to L1 (TAP-block: Th10-L1) and might also have the potential to block visceral pain, in addition to the somatic sensory pain.

Regarding your third question, clonidine has been added to prolong the effects. On its own, clonidine has a vasoconstrictive effect, and in the literature, it has been shown to prolong the action of the local anesthetic by 2 hours.

Finally, in regard to the study design, it was powered to show a 25% reduction in morphine requirements in the QL group compared with the lidocaine group. We arbitrarily considered this reduction clinically relevant. So, no conclusions can be drawn on the reduced need of morphine in the placebo group.

Mario Morino (Torino, Italy):

Congratulations on this very interesting study. I just have a short question. Do you have any data, which show whether there is a different course for patients on the second, third, or a later postoperative day?

Response From André J. D'Hoore (Leuven, Belgium):

Median hospital stay was short in this observational study and we observed no differences between the groups. According to our standardized enhanced recovery protocol, the use of morphine was stopped after day 1. We have not recorded the doses of other pain medication (eg, paracetamol, nonsteroidal anti-inflammatory drugs, etc) administered during the rest of hospital stay.