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The Influence of Intravenous Lidocaine Infusion on Postoperative Outcome and Neutrophil-to-Lymphocyte Ratio in Colorectal Cancer Patients. A Pilot Study

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ABSTRACT

Background & Aims: In the last years increasing scientific evidence drew attention on the potential effects of anesthetic drugs on postoperative outcome in cancer patients. Local anesthetics, especially lidocaine, have been intensively studied in relation with postoperative outcome in colorectal cancer patients. Our study objectives were to investigate the effects of perioperative intravenous lidocaine infusion on neutrophil-to-lymphocyte ratio and short-term postoperative outcome. Additionally, we also looked at 1 year outcome after intended radical colorectal cancer surgery.
Methods: 150 patients scheduled for colorectal cancer surgery were randomized to receive sevoflurane anaesthesia with or without 48 hours lidocaine infusion.
Results: 73 patients were included in the group A (sevoflurane) and 77 in the group B (sevoflurane with lidocaine). Lidocaine infusion did not modify neutrophil-to-lymphocyte ratio at 24 hours after surgery (p=0.58). Patients receiving intravenous lidocaine had significantly lower morphine consumption (p=0.04), faster mobilization time (p=0.001) and fewer days spent in the hospital (p=0.04). Moreover, at 1 year follow-up, patients in group B had a significant decreased rate of recurrences (p=0.03). There was no significant difference in 1 year survival (p=0.22).
Conclusions: In our study, intravenous lidocaine infusion hastened the postoperative recovery of patients in terms of mobilization, hospital discharge and opioid consumption and reduced 1 year recurrence rate. Further studies on larger groups of patients are needed.

Key words: colorectal cancer – anaesthesia – sevoflurane – lidocaine – neutrophil-to-lymphocyte ratio.

Abbreviations: CRC: colorectal cancer; LA: local anesthetic; LOS: length of hospital stay; NLR: neutrophil-to-lymphocyte ratio; TIVA: propofol-total intravenous anesthesia; VGSC:voltage-gated sodium channel.

INTRODUCTION

Colorectal cancer (CRC) remains the third as overall cancer incidence and is the second as cancer mortality [1]. The management of a CRC patient, especially in case of metastatic disease, implies a multidisciplinary approach, and may result in a depreciated quality of life [2]. However, for most patients, surgery is still the mainstay of treatment [3]. During surgery, the immune system is influenced by surgical stress and by anesthetics drugs. In addition, during surgery, cancer cells or even minimal residual micro-metastases may spread and proliferate [3-5], facilitated by a modified immune reactivity [3].

It has been shown that anesthesia might influence, directly and indirectly, the immune system perioperatively, thus influencing prognosis of the CRC patients undergoing surgical treatment [6, 7].

Inhalation anesthesia with sevoflurane have been shown to increase the recurrence rate in CRC patients and may be associated with worse survival rate as compared with propofol anesthesia, by promoting proliferation, migration, and angiogenesis of different cancer cells [8 ,9]. Thus, Hasselager et al. [9] in a retrospective study involving CRC patients, reported a reduced risk of recurrence in patients receiving propofol-total intravenous anesthesia (TIVA), similar with other studies reporting a better survival rate in colon cancer surgery associated with TIVA [10]. On the other hand, there

are also studies reporting no difference in the recurrence rate or cancer-related mortality between the two anesthetic techniques [11-13].

More recently, local anesthetics (LAs), especially lidocaine, have been shown to inhibit tumor development and limits the risk of metastatic disease through a number of mechanisms [14, 15]. Potential mechanisms include LAs ability to block voltage-gated sodium channels (VGSCs), especially the expression of the NaV1.5 subunit. It has been shown that cancer cells express NaV1.5 on their surface; their number relates with invasiveness and proliferation. Local anesthetics also have other anti-tumoral effects [14, 16, 17].

In vitro studies on colorectal cancer cell lines have shown that lidocaine may induce apoptosis, inhibits proliferation and suppress the growth of cancer cells, placing lidocaine as a potential therapeutic agent in colorectal cancer [18, 19]. However, *in vivo* studies comparing local anesthetics administered as epidural analgesia in CRC patients have not been able to show clear results on long term outcome [20-22].

There are only two studies investigating the effect of 48 hours intravenous lidocaine infusion on short and long-term prognosis of patients with colorectal cancer, respectively cardiac surgery [23, 24].

The primary endpoints of our preliminary prospective clinical study were to evaluate the clinical effects of 48 hours intravenous infusion of lidocaine on postoperative recovery and on inflammatory response evaluated by neutrophil-to-lymphocyte ratio (NLR) in colorectal surgery. As secondary endpoints, we looked at the outcome at 1 year incidence of recurrences and mortality as an attempt to investigate if lidocaine influenced long-term outcome correlated with NLR changes.

METHODS

The study was approved by the Ethics Committee of Iuliu Haţieganu University of Medicine and Pharmacy Cluj-Napoca, Romania (no. 436/ 26.11.2018) and registered in ClinicalTrials.gov (NCT02786329). Derived from this study, we decided to investigate in a sub-study the effects of lidocaine on short term outcome and NLR which was approved by the Ethics Committee of Prof. Dr. Octavian Fodor Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania (4459/25.03.2020). A total number of 150 patients scheduled for curative resection of CRC were randomized to receive inhalational anaesthesia with sevoflurane with or without intravenous lidocaine infusion. This prospective randomized controlled trial took place at the Regional Institute of Gastroenterology and Hepatology in Cluj-Napoca from November 2019 to December 2021.

Inclusion criteria were patients aged 18-80 years, American Society of Anesthesiology (ASA) score I-III scheduled for elective curative resection of colorectal cancer have been enrolled after written informed consent.

Exclusion criteria included refusal to participate; age <18 years or >80 years; pre-existing chronic pain; chronic medication that may interfere with pain medication (antiepileptics, anti-inflammatory or corticosteroid medication); contraindication to any medication in the study; significant psychiatric disorders (patients with major depressive disorders, bipolar disorders, schizophrenia, etc.); hepatic disfunction (ASAT/ALAT >2 times normal value); renal failure (serum creatinine >2 mg/dL); convulsive conditions that required medication in the last 2 years; planned regional analgesia and/or regional anaesthesia (epidural or spinal); corticoid-dependent diseases; autoimmune disorders; antiarrhythmic drugs (amiodarone, verapamil, propafenone) that may interfere with antiarrhythmic effect of lidocaine; synchronous neoplasms or history of cancer disease.

Drop out criteria included unexpected allergy to one of the medications used, non-curative resection at surgical exploration, intraoperative presence of liver metastasis, patients' decision to withdraw anytime from the study, refusal to give data at postoperative follow-up.

Patients have been allocated using a computer-generated random number table into two study groups: group A (patients undergoing sevoflurane anaesthesia) and group B (patients undergoing sevoflurane anaesthesia and intravenous lidocaine infusion). A statistician ensured the simple randomisation computer-based sequence.

Patients enrolled in the study received a prophylactic dose of low molecular weight heparin 12 hours before surgery. Anesthetic induction was the same in the two groups: fentanyl 2-3 μg/kg, propofol 1.5-2 mg/kg and atracurium or rocuronium for muscle relaxation at anaesthetists' discretion (0.5-0.6 mg/kg). Anesthesia was maintained with sevoflurane at 1 MAC (minimum alveolar concentration) increased/decreased in steps of 0.25-0.5 MAC according to BIS (bispectral index) values (40-59). The patients were ventilated with a lung protective regimen, with a minimal PEEP of 5-6 cm H2O, with a fresh gas flow of 2 litres/minute with a mixture of 45% oxygen and 55% air. Intraoperative analgesia included a multimodal regimen with fentanyl in increments of 1-1.5 μg/kg when necessary (blood pressure and/or heart rate increased with over 20% from baseline, sweating, tears, pupil size) and a dose of 1 g of acetaminophen. A bolus of morphine of 0.1-0.15 mg/kg was administered at least 30 minutes prior to extubation. Postoperative analgesia included intravenous morphine boluses of 0.05 mg/kg when NRS was ≥ 4 (10 points scale, 0 is no pain, 10 is worst pain possible) and 1 g of acetaminophen every 6 hours.

Group B received a perioperative intravenous infusion with 1% lidocaine. A lidocaine bolus of 1.5 mg/kg was administered at induction of anaesthesia (by using a peripheral intravenous catheter), followed by an intravenous infusion of 1.5-2 mg/kg/hour up to a maximum dose of 200 mg/h during anaesthesia. Infusion rate was decreased in post anaesthesia care unit and on surgical ward at 1-1.5 mg/kg/hour (maximum 100 mg/h) for 48 hours. Patients were closely monitored after surgery by a study investigator who checked for local anesthetic toxicity and side-effects. Lidocaine infusion rate was decreased or stopped in case of bradycardia, severe hypotension, or other signs of local anaesthetics toxicity.

Data collection was handled in compliance with EU General Data Protection Regulation legislation.

Statistical analysis was done using the SPSS v26.0 (IBM Corp., Armonk, NY, United States). Sample size calculation was done using reported difference in lengths of hospital stay (LOS) of 1 day in lidocaine group in a previous published study with a power of 80% [25]. Based on time to first mobilization in

the first 5 patients calculated sample size was 96 patients with power 80%, α 0.05. However, we increased the sample size of our study to 75 patients per groups based on our preliminary results on the difference in resumption of bowel function. Categorical values and qualitative variables were analysed using Pearson's chi-squared test. Non-normal distributed data were compared using Mann-Whitney U tests, while normal distributed data were compared using the t-test for independent variables. A p <0.05 was considered significant.

RESULTS

A final number of 150 patients were enrolled in the study (73 patients in group A, and 77 in group B) and completed the study. Demographic data of study groups are shown in Table I.

As can be seen in Table II, there were significant differences in morphine consumption in the first 24 hours after surgery: patients from group B had a significantly decreased morphine consumption as compared with group A (p=0.04). Similarly, group B had a shorter LOS than group A (p=0.04). Lidocaine infusion also significantly reduced the time to first postoperative mobilization (p<0.001). There was no statistically significant difference between the two groups in NLR.

One year after surgery outcome parameters are shown in Table III. While there was no difference in 1 year survival and chronic pain incidence, surprisingly, there were significant differences in the disease progression (p=0.03).

We further wanted to assess if i.v. lidocaine infusion had a different effect depending on tumour classification. We divided patients in 3 groups according to their TNM classification as localized (stage 0 and 1), intermediate (stage 2) and advanced stage (stage 3 and above). As can be seen in Table IV, there were significant differences in morphine consumption in advanced tumours when lidocaine infusion was initiated (p=0.04).

Table I. Demographic and anesthetic data of the study groups

Parameters	Group A (n=73)	Group B (n=77)	p
Age	63.22 (±8.34)	61.97 (±10.63)	0.42
ASA score, n (%)			0.07
I	3 (4.08)	4 (5.16)	
II	55 (74.8)	67 (86.43)	
III	15 (20.4)	6 (7.74)	
Gender, female, n (%)	36 (48.96)	42 (54.18)	0.52
BMI (kg/m^2)	27.77 (±5.07)	26.03 (±4.06)	0.03
Surgery time (minutes)	138.42 (±49.67)	122.34 (±46.05)	0.04
Anaesthesia duration (minutes)	161.10 (±52.63)	150.19 (±52.46)	0.2
Intraoperative Fentanyl (μg/kg)	0.50 (±0.22)	0.54 (±0.22)	0.3
Intraoperative fluids (ml)	1858.22 (±800.19)	1613.12 (±708.95)	0.16
BIS (values)	47.18 (±5.20)	47.68 (±6.21)	0.59
Laparotomy n (%)	58 (79,45)	61 (79,22)	0.97
Laparoscopy n (%)	15 (20,54)	16 (20,78)	
Mean perioperative lidocaine dose (mg)	-	3567.79 (±805,37)	
Mean lidocaine dose post-operative infusion (mg/48 h)	-	1714.77 (±1659,22)	
Mean lidocaine infusion rate post-operative (mg/kg/h)	-	0.46(±2.41)	

ASA: American Society of Anesthesiology; BMI: body mass index

Table II. Data on short-term postoperative outcome

Parameters	Group A (n=73)	Group B (n=77)	p
Morphine over first 24 hours (mg)	26.04 (±9.37)	22.92 (±9.74)	0.04
Mobilisation (time to first stand up)	24.62 (±13.60)	17.75 (±7.35)	0.001
Resumption of bowel function (hours)	48.64 (±25.01)	46.95 (±22.30)	0.66
LOS (days)	10.90 (±5.78)	9.40 (±2.86)	0.04
NLR before surgery	4.68 (±2.55)	4.59 (±3.95)	0.87
NLR 24h after surgery	9.37 (±5.34)	10.03 (±9.04)	0.58

Table III. One-year post-operative outcome in study groups.

Parameters	Group A (n=73)	Group B (n=77)	p
Chronic pain (yes)	11 (15.06%)	9 (11.68%)	0.28
Disease progression at 1 year	10 (12.9%)	3 (3.89%)	0.03
One year survival	68 (93.11%)	75 (97.4%)	0.22

We did not have any case of lidocaine toxicity or side-effects. Lidocaine infusion rate was decreased with different rate intervals (to a minimum of 1 mg/kg/h) during anaesthesia in all patients. Still, in the post-operative period the mean lidocaine infusion rate was 0.46 (±2,41) mg/kg/h (Table I).

DISCUSSION

Our study aimed to investigate the effect of intravenous perioperative lidocaine infusion in patients scheduled for elective colorectal cancer surgery under sevoflurane anaesthesia on short- and long-term outcome. We also aimed to study the effect of lidocaine on inflammatory response evaluated as NLR.

Similar to other studies, we found that the addition of perioperative lidocaine infusion reduced the morphine requirement in the first 24 hours post-operatively, as well as time to first mobilization, resumption of bowel function and LOS [26-28].

The anti-inflammatory effect of lidocaine is well known so far, even though the exact mechanism of action is not very well understood. Inhibition of leucocyte activation, adhesion and migration [29] and other mechanism leading to inhibition of prostaglandin synthesis have been involved [30].

A possible mechanism involved in intravenous lidocaine infusion and its post-operative opioid sparing effect may be a diminished production of both pro- and anti-inflammatory cytokines and a remissive withholding of a lymphocyte proliferative response [31]. Another possible explanation of decreased postoperative opioid consumption after lidocaine infusion could be its central antihyperalgesic effect mediated by mechanoinsensitive nociceptors [32]. Recent literature

Table IV. Results registered on the effect of lidocaine in group B depending on TNM stages at 1-year postoperative follow-up

Parameters	Localized (n=31)		p	Intermediate (n=61)		p	Advanced (n=58)		p
	A (n=18)	B (n=13)		A (n=24)	B (n=37)		A (n=31)	B (n=27)	
Morphine requirement⁺ (mg/24h), mean±SD	23.94 (±10.14)	22.23 (±8.04)	0.61	24.66 (±8.57)	22.93 (±10.03)	0.48	28.32 (±9.30)	23.22 (±10.37)	0.04
Chronic pain at 1 year, n (%)	2 (11.1)	2 (15.3)	0.56	2 (8.33)	6 (16.21)	0.17	5 (16.12)	1 (3.7)	0.28
Disease progression at 1 year, n (%)	1 (5.55)	1 (7.69)	0.67	4 (16.66%)	2 (5.4%)	0.15	5 (16.12)	0 (0)	0.03
1 year survival, n (%)	17 (94.4)	13 (100)	0.38	22 (91.66)	35 (94.59)	0.65	29 (93.5)	27 (100)	0.28

⁺(Data are expressed as mean ±SD), *(no. of patients,%).

linked intravenous lidocaine administration with more than just less opioid consumption, but even lower pain scores, less post-operative nausea and vomiting, reduced duration of ileus and a shorter hospital stay [28, 33, 34]. Our results confirmed the results of a number of studies focusing on early recovery after abdominal surgeries when patients received intravenous lidocaine [34-37]. To the best of our knowledge there are only a couple of studies that investigated continuous i.v. lidocaine infusion postoperatively for different intervals (4, 24 and 48 hours) in colorectal cancer patients [23, 25, 38, 39].

Neutrophil-to-lymphocyte ratio is an easy accessible marker to evaluate inflammation in colorectal cancer surgery as well as in other types of surgery and a marker of prognosis [40]. It is well known by now that general anesthesia increases NLR as compared with spinal anesthesia [41, 42]. Recent studies have focused on comparing the effect of two types of general anaesthesia (propofol-based and sevoflurane-inhalation) on NLR and found that propofol-based anaesthesia may decrease the postoperative increase in NLR [43, 44]. Our study found no difference in changes of NLR (at 24 hours after surgery) between the study groups. Memary et al. [45] study which evaluated NLR at admission, 6, 24, 48 hours and later at 14 days after breast cancer surgery in patients who received intravenous lidocaine during surgery found that changes in NLR were smaller in women who received lidocaine infusion [45]. Our study results could have been influenced by a lower lidocaine dose infusion (due to the fact that we had to lower lidocaine infusion dose during anesthesia as a precaution measure) and the fact that we did not measure lidocaine plasma concentration [25, 38].

We found a significantly reduced number of patients with disease progression at 1 year. In recent years, several animal and *in vitro* studies investigated the effect of lidocaine on apoptosis and proliferation of neoplastic cells [15, 46]. In humans it was also shown that anesthetic technique and LAs (lidocaine) may influence systemic inflammation after surgical resection by mediating circulating cytokines, which were associated with postoperative metastatic disease occurrences [47-49]. The anti-cancer effect of i.v. lidocaine has not been widely investigated in clinical trials, even though *in vitro* trials showed promising results. Lidocaine is strongly recommended as perioperative infusion during colorectal surgery by the Association for the Promotion of Postoperative Recovery, even though it holds a risk of toxicity with a narrow therapeutic index and a therapeutic plasma level of 2.5 to 3.5 μg/mL [14, 50, 51].

This may be a very interesting potential effect of lidocaine derived from its anticancer effects that was not reported before. We can only speculate that intravenous lidocaine reduced the number of patients with regional and distal disease progression taking in consideration the small sample size of our study groups. Another limitation of our study is that we did not measure lidocaine's plasma concentration and it is possible that this concentration to be under clinically effective one due to reduced rate of infusion in case of bradycardia and hypotension as a precaution measure. This also may explain the results on NLR as compared to other study [45].

CONCLUSIONS

In our study, 48 hours intravenous lidocaine infusion reduced significantly postoperative morphine consumption, time to mobilisation and resumption of bowel function. Lidocaine did not reduce NLR at 24 hours postoperatively. Intravenous lidocaine significantly reduced the incidence of disease progression at 1 year without differences in mortality but our study groups are small and we can only speculate this. Further larger studies are required to have more consistent results.

Conflicts of interest: None to declare.

Authors' contribution: A.A.L. and I.D. conceived and designed of the study; A.A.L., C.A., S.S., B.C. and I.D. collected and analyzed the data; V.D. statistical analysis; A.A.L. drafted the manuscript; Z.F., A.H.N. and I.D. critically revised the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agreed to be accountable for all aspects of the work.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424. doi:10.3322/caac.21492
2. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;27:1386-1422. doi:10.1093/annonc/mdw235
3. Lee S, Pyo DH, Sim WS, Lee WY, Park M. Early and long-term outcomes after propofol-and sevoflurane-based anesthesia in colorectal cancer surgery: a retrospective study. J Clin Med 2022;11:2648. doi:10.3390/jcm11092648
4. Yamaguchi K, Takagi Y, Aoki S, Futamura M, Saji S. Significant detection of circulating cancer cells in the blood by reverse transcriptase-

polymerase chain reaction during colorectal cancer resection. Ann Surg 2000;232:58-65. doi:10.1097/00000658-200007000-00009
5. Tedore T. Regional anaesthesia and analgesia: relationship to cancer recurrence and survival. Br J Anaesth 2015;115 Suppl 2:ii34-ii45. doi:10.1093/bja/aev375
6. Dang Y, Shi X, Xu W, Zuo M. The effect of anesthesia on the immune system in colorectal cancer patients. Can J Gastroenterol Hepatol 2018;2018:7940603. doi:10.1155/2018/7940603
7. Baldini G, Fawcett WJ. Anesthesia for colorectal surgery. Anesthesiol Clin 2015;33:93-123. doi:10.1016/j.anclin.2014.11.007
8. Xu J, Gao Z, Coburn M, Ma D, Wang K. Postoperative 5-year survival and related risk factors of colon cancer patients undergoing propofol vs. sevoflurane anesthesia: a retrospective cohort study. Clin Oncol 2022;7:1933.
9. Hasselager RP, Hallas J, Gögenur I. Inhalation or total intravenous anaesthesia and recurrence after colorectal cancer surgery: a propensity score matched Danish registry-based study. Br J Anaesth 2021;126:921-930. doi:10.1016/j.bja.2020.11.019
10. Wu ZF, Lee MS, Wong CS, et al. Propofol-based total intravenous anesthesia is associated with better survival than desflurane anesthesia in colon cancer surgery. Anesthesiology 2018;129:932-941. doi:10.1097/ALN.0000000000002357
11. Yan T, Zhang GH, Wang BN, Sun L, Zheng H. Effects of propofol/remifentanil-based total intravenous anesthesia versus sevoflurane-based inhalational anesthesia on the release of VEGF-C and TGF-β and prognosis after breast cancer surgery: a prospective, randomized and controlled study. BMC Anesthesiol 2018;18:131. doi:10.1186/s12871-018-0588-3
12. Sessler DI, Pei L, Huang Y, et al. Recurrence of breast cancer after regional or general anaesthesia: a randomised controlled trial. Lancet 2019;394:1807-1815. doi:10.1016/S0140-6736(19)32313-X
13. Oh TK, Kim HH, Jeon YT. Retrospective analysis of 1-year mortality after gastric cancer surgery: Total intravenous anesthesia versus volatile anesthesia. Acta Anaesthesiol Scand 2019;63:1169-1177. doi:10.1111/aas.13414
14. Zhang Y, Jing Y, Pan R, Ding K, Chen R, Meng Q. Mechanisms of cancer inhibition by local anesthetics. Front Pharmacol 2021;12:770694. doi:10.3389/fphar.2021.770694
15. Borgeat A, Aguirre J. Impact of local anesthetics on cancer behavior and outcome during the perioperative period: a review. Medicina (Kaunas) 2022;58:882. doi:10.3390/medicina58070882
16. Lirk P, Berger R, Hollmann MW, Fiegl H. Lidocaine time- and dose-dependently demethylates deoxyribonucleic acid in breast cancer cell lines in vitro. Br J Anaesth 2012;109:200-207. doi:10.1093/bja/aes128
17. Baptista-Hon DT, Robertson FM, Robertson GB, et al. Potent inhibition by ropivacaine of metastatic colon cancer SW620 cell invasion and NaV1.5 channel function. Br J Anaesth 2014;113 Suppl 1:i39-i48. doi:10.1093/bja/aeu104
18. Haraguchi-Suzuki K, Kawabata-Iwakawa R, Suzuki T, Suto T, Takazawa T, Saito S. Local anesthetic lidocaine-inducible gene, growth differentiation factor-15 suppresses the growth of cancer cell lines. Sci Rep 2022;12:14520. doi:10.1038/s41598-022-18572-3
19. Qu X, Yang L, Shi Q, Wang X, Wang D, Wu G. Lidocaine inhibits proliferation and induces apoptosis in colorectal cancer cells by upregulating mir-520a-3p and targeting EGFR. Pathol Res Pract 2018;214:1974-1979. doi:10.1016/j.prp.2018.09.012
20. Christopherson R, James KE, Tableman M, Marshall P, Johnson FE. Long-term survival after colon cancer surgery: a variation associated with choice of anesthesia. Anesth Analg 2008;107:325-332. doi:10.1213/ane.0b013e3181770f55
21. Vogelaar FJ, Lips DJ, van Dorsten FR, Lemmens VE, Bosscha K. Impact of anaesthetic technique on survival in colon cancer: a review of the literature. Gastroenterol Rep (Oxf) 2016;4:30-34. doi:10.1093/gastro/gov001
22. Hasselager RP, Hallas J, Gögenur I. Epidural analgesia and recurrence after colorectal cancer surgery: a danish retrospective registry-based cohort study. Anesthesiology 2022;136:459-471. doi:10.1097/ALN.0000000000004132
23. Wongyingsinn M, Baldini G, Charlebois P, Liberman S, Stein B, Carli F. Intravenous lidocaine versus thoracic epidural analgesia: a randomized controlled trial in patients undergoing laparoscopic colorectal surgery using an enhanced recovery program. Reg Anesth Pain Med 2011;36:241-248. doi:10.1097/AAP.0b013e31820d4362
24. Mathew JP, Mackensen GB, Phillips-Bute B, et al. Randomized, double-blinded, placebo controlled study of neuroprotection with lidocaine in cardiac surgery. Stroke 2009;40:880-887. doi:10.1161/STROKEAHA.108.531236
25. Herroeder S, Pecher S, Schönherr ME, et al. Systemic lidocaine shortens length of hospital stay after colorectal surgery: a double-blinded, randomized, placebo-controlled trial. Ann Surg 2007;246:192-200. doi:10.1097/SLA.0b013e31805dac11
26. Lee IW, Schraag S. The use of intravenous lidocaine in perioperative medicine: Anaesthetic, analgesic and immune-modulatory aspects. J Clin Med 2022;11:3543. doi:10.3390/jcm11123543
27. Dunn LK, Durieux ME. Perioperative use of intravenous lidocaine. Anesthesiology 2017;126:729-737. doi:10.1097/ALN.0000000000001527
28. Lovett-Carter D, Kendall MC, Park J, Ibrahim-Hamdan A, Crepet S, De Oliveira G. The effect of systemic lidocaine on post-operative opioid consumption in ambulatory surgical patients: a meta-analysis of randomized controlled trials. Perioper Med (Lond) 2021;10:11. doi:10.1186/s13741-021-00181-9
29. Fischer LG, Bremer M, Coleman EJ, et al. Local anesthetics attenuate lysophosphatidic acid-induced priming in human neutrophils. Anesth Analg 2001;92:1041–1047. doi:10.1097/00000539-200104000-00044
30. Weinberg L, Peake B, Tan C, Nikfarjam M. Pharmacokinetics and pharmacodynamics of lignocaine: A review. World J Anesthesiol 2015;4:17–29. doi:10.5313/wja.v4.i2.17
31. Yardeni IZ, Beilin B, Mayburd E, Levinson Y, Bessler H. The effect of perioperative intravenous lidocaine on postoperative pain and immune function. Anesth Analg 2009;109:1464-1469. doi:10.1213/ANE.0b013e3181bab1bd
32. Koppert W, Weigand M, Neumann F, et al. Perioperative intravenous lidocaine has preventive effects on postoperative pain and morphine consumption after major abdominal surgery. Anesth Analg 2004;98:1050-1055. doi:10.1213/01.ANE.0000104582.71710.EE
33. Sun Y, Li T, Wang N, Yun Y, Gan TJ. Perioperative systemic lidocaine for postoperative analgesia and recovery after abdominal surgery: a meta-analysis of randomized controlled trials. Dis Colon Rectum 2012;55:1183-1194. doi:10.1097/DCR.0b013e318259bcd8
34. Zhao JB, Li YL, Wang YM, et al. Intravenous lidocaine infusion for pain control after laparoscopic cholecystectomy: A meta-analysis of randomized controlled trials. Medicine (Baltimore) 2018;97:e9771. doi:10.1097/MD.0000000000009771
35. Vigneault L, Turgeon AF, Côté D, et al. Perioperative intravenous lidocaine infusion for postoperative pain control: a meta-analysis of randomized controlled trials. Can J Anaesth 2011;58:22-37. doi:10.1007/s12630-010-9407-0

36. Marret E, Rolin M, Beaussier M, Bonnet F. Meta-analysis of intravenous lidocaine and postoperative recovery after abdominal surgery. Br J Surg 2008;95:1331-1338. doi:10.1002/bjs.6375
37. McCarthy GC, Megalla SA, Habib AS. Impact of intravenous lidocaine infusion on postoperative analgesia and recovery from surgery: a systematic review of randomized controlled trials. Drugs 2010;70:1149-1163. doi:10.2165/10898560-000000000-00000
38. Kaba A, Laurent SR, Detroz BJ, et al. Intravenous lidocaine infusion facilitates acute rehabilitation after laparoscopic colectomy. Anesthesiology 2007;106:11-18. doi:10.1097/00000542-200701000-00007
39. Tikuišis R, Miliauskas P, Samalavičius NE, Žurauskas A, Samalavičius R, Zabulis V. Intravenous lidocaine for post-operative pain relief after hand-assisted laparoscopic colon surgery: a randomized, placebo-controlled clinical trial. Tech Coloproctol 2014;18:373-380. doi:10.1007/s10151-013-1065-0
40. Kinoshita T, Goto T. Links between inflammation and postoperative cancer recurrence. J Clin Med 2021;10:228. doi:10.3390/jcm10020228
41. Surhonne N, Hebri C, Kannan S, Duggappa DR, Rs RR, Mapari CG. The effect of anesthetic techniques on neutrophil to lymphocyte ratio in patients undergoing infraumbilical surgeries. Korean J Anesthesiol 2019;72:458-465. doi:10.4097/kja.d.19.00022
42. Erbaş M, Toman H, Gencer M, et al. The effect of general and spinal anesthesia on neutrophil to lymphocyte ratio in patients undergoing cesarian section. Anaesth Pain Intensive Care 2015;19:485-488.
43. Ní Eochagáin A, Burns D, Riedel B, Sessler DI, Buggy DJ. The effect of anaesthetic technique during primary breast cancer surgery on neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and return to intended oncological therapy. Anaesthesia 2018;73:603-611. doi:10.1111/anae.14207
44. Kim WH, Jin HS, Ko JS, et al. The effect of anesthetic techniques on neutrophil-to-lymphocyte ratio after laparoscopy-assisted vaginal hysterectomy. Acta Anaesthesiol Taiwan 2011;49:83-87. doi:10.1016/j.aat.2011.08.004
45. Memary E, Mirkheshti A, Ghasemi M, Taheri M, Arhami Dolatabadi A, Kaboudvand A. The effect of lidocaine infusion during general anesthesia on neutrophil-lymphocyte-ratio in breast cancer patients candidate for mastectomy; a clinical trial. J Cell Mol Anesth 2016;1:146-153. doi:10.22037/jcma.v1i4.13519
46. Du J, Zhang L, Ma H, Wang Y, Wang P. Lidocaine suppresses cell proliferation and aerobic glycolysis by regulating circHOMER1/miR-138-5p/HEY1 axis in colorectal cancer. Cancer Manag Res 2020;12:5009–5022. doi:10.2147/CMAR.S244973
47. Gunawardene A, Dennett E, Larsen P. Prognostic value of multiple cytokine analysis in colorectal cancer: a systematic review. J Gastrointest Oncol 2019;10:134-143. doi:10.21037/jgo.2018.07.11
48. Alhayyan A, McSorley S, Roxburgh C, Kearns R, Horgan P, McMillan D. The effect of anesthesia on the postoperative systemic inflammatory response in patients undergoing surgery: A systematic review and meta-analysis. Surg Open Sci 2019;2:1-21. doi:10.1016/j.sopen.2019.06.001
49. Dai Y, Jiang R, Su W, Wang M, Liu Y, Zuo Y. Impact of perioperative intravenous lidocaine infusion on postoperative pain and rapid recovery of patients undergoing gastrointestinal tumor surgery: a randomized, double-blind trial. J Gastrointest Oncol 2020;11:1274-1282. doi:10.21037/jgo-20-505
50. Gustafsson UO, Scott MJ, Hubner M, et al. Guidelines for perioperative care in elective colorectal surgery: enhanced recovery after surgery (ERAS®) society recommendations: 2018. World J Surg 2019;43:659-695. doi:10.1007/s00268-018-4844-y
51. Eipe N, Gupta S, Penning J. Intravenous lidocaine for acute pain: An evidence-based clinical update. BJA Educ 2016;16:292–298. doi:10.1093/bjaed/mkw008