Original Research

The clinical effects of an intravenous perioperative lidocaine infusion during hepatectomy: a pilot study

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Abstract

Background. Intravenous (i.v.) lidocaine exhibits multimodal analgesic, anti-inflammatory, and anticancer properties. However, concerns regarding systemic toxicity and impaired hepatic drug clearance during liver resection necessitate caution in perioperative dosing protocols. This study aimed to evaluate the clinical recovery parameters and systemic inflammatory markers following continuous perioperative i.v. lidocaine infusion in patients undergoing elective hepatectomy for hepatocellular carcinoma (HCC).

Methods. In this prospective, randomized controlled trial, 60 patients undergoing elective surgical resection for HCC were assigned (1:1 ratio) to either a lidocaine group (n=30) or a control group (n=30). The lidocaine group received an intraoperative IV bolus (1.5 mg/kg) followed by a continuous infusion (1 mg/kg/h), maintained throughout surgery and for 24 hours postoperatively. Primary endpoints evaluated 24 hour opioid consumption, Numeric Rating Scale pain scores, return of bowel function, length of hospital stay, and perioperative inflammatory response.

Results. No statistically significant differences were observed between the lidocaine and control groups across clinical recovery outcomes. Intraoperative fentanyl consumption was identical between groups 0.8±0.1 mg (vs. 0.8±0.2 mg; p=0.957). The lidocaine group demonstrated a non-significant trends toward reduced 24-hour postoperative morphine consumption (13.5±13.3 mg vs. 19.5±15.8 mg; p=0.224), lower mean 24-hour NRS pain scores (3.36±1.77 vs. 3.80±1.85; p=0.275), and faster recovery of bowel motility (3.0±0.9 vs. 3.4±1.5 days; p=0.215). Length of hospital stay was comparable (9.46±3.15 vs. 8.47±3.09 days; p=0.340). Both groups exhibited significant postoperative increases in CRP and leukocyte levels ($p<0.05$), with no significant between-group differences postoperatively.

Conclusion. A modified, lower-dose perioperative i.v. lidocaine regimen tailored for toxicity safety in patients with liver resection is well-tolerated but does not yield statistically significant reductions in postoperative opioid consumption, pain scores, bowel recovery time, systemic inflammatory markers, or hospital stay following open hepatectomy. Further, adequately powered studies are needed.

Keywords: hepatocellular carcinoma, surgery, lidocaine, pain

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Introduction

Liver cancer is the third leading cause of cancer-related death worldwide and the sixth most commonly diagnosed cancer [1]. Although surgical resection is an effective treatment, postoperative recurrence remains a major clinical challenge [2]. Emerging evidence suggests that anesthetic management may influence oncological outcomes, and perioperative analgesia can influence the postoperative recovery [3].

Intravenous lidocaine administration during major surgery, including hepatectomy is considered to decrease postoperative pain and the dose of opioids [4]. Protocols recommend the administration of a bolus dose of 1-2 mg/kg intraoperative i.v. lidocaine at anesthetic induction, followed by a continuous infusion of 1-2 mg/kg/h throughout the surgical procedure [5]. Systemic toxicity is typically associated with plasma concentrations above 5 μg/mL, whereas concentrations exceeding 10 μg/mL may precipitate seizures [6].

Beyond its effects of decreasing postoperative pain, opioid consumption, speeding resumption of normal bowel function, and a reduced hospital length of stay [7], lidocaine exhibits anti-inflammatory and antitumor effects, including inhibition of hepatocellular carcinoma cell proliferation [8,9]. Lidocaine blocks voltage-gated sodium channels, particularly Nav1.5, thereby reducing cancer-cell proliferation, migration, invasion, as well as inhibition of angiogenesis and DNA damage repair [8,10]. It may also enhance apoptosis and chemotherapy response, although a clear survival benefit in patients has not yet been demonstrated [10].

Beyond hepatocellular carcinoma, lidocaine has demonstrated antitumoral activity in breast, endometrial and bladder cancer cells [11-13]. Chen et al showed that at a molecular level lidocaine increased the levels of autophagy-related marker microtubule-associated protein light chain 3BII (LC3BII) while decreasing the levels of autophagic marker p62 suggesting an enhancement of the autophagy process [14]. A number of mechanisms support cytotoxic effects of lidocaine, such as the induction of mitochondrial membrane depolarization, lipid peroxidation, apoptosis, as well as suppression of cellular proliferation in both HepG2 and Hep3Bcells [14-18]. These effects increase with lidocaine concentration. Preclinical studies have demonstrated its anticancer activity both in vitro and in vivo, while retrospective clinical data indicate that intraoperative i.v. lidocaine may be associated with improved overall survival in patients undergoing cancer surgery [19,20]. Overall, these findings support the potential repurposing of lidocaine as an adjunct anticancer agent and its antitumoral activity appears to result from the simultaneous disruption of cancer-cell survival, metabolism, stress regulation, and proliferation [14,21,22].

Lidocaine-related systemic toxicity may develop as a consequence of excessive accumulation of the parent compound and its pharmacologically active metabolites, monoethylglycinexylidide (MEGX) and glycinexylidide (GX) [4]. Because lidocaine undergoes extensive hepatic biotransformation via the cytochrome P450 system, while its metabolites are subsequently cleared predominantly through renal excretion, patients with hepatic or renal dysfunction are particularly susceptible to impaired drug elimination and toxic plasma concentrations, considered clinically significant at plasma concentrations higher than 6.0 mg/L [23]. The risk may be further increased during hepatic resection, especially when the Pringle maneuver is employed [4]. Hepatic inflow occlusion, ischemia–reperfusion injury, and perioperative hemodynamic instability may compromise hepatic perfusion and functional capacity, thereby reducing the systemic clearance of lidocaine and MEGX [2]. Given that lidocaine is a high-extraction-ratio drug, its clearance is highly dependent on hepatic blood flow [24]. Accordingly, perioperative monitoring of plasma lidocaine and active metabolite concentrations should be considered in patients with impaired liver or kidney function and in those exposed to major alterations in hepatic hemodynamics [2].

Methods

Following Institutional Review Board approval (DEP 45/22.11.2021), Ethics Committee of the University of Medicine and Pharmacy Cluj approval (AVZ12/03.02.2022) and the acquisition of written informed consent, 60 patients diagnosed with hepatocellular carcinoma scheduled for elective surgical resection were enrolled in the study. Eligible participants were required to be between 18 and 80 years of age and classified under American Society of Anesthesiologists physical status 1 to 3. The exclusion criteria comprised several clinical, oncological, pharmacological, and administrative parameters to ensure patient safety and prevent confounding factors. Emergency surgical procedures were excluded, as were patients with advanced oncological or hepatic impairment. Specifically, exclusions comprised patients with Barcelona Clinic Liver Cancer (BCLC) stage B disease receiving non-surgical management, BCLC stages C and D, Child-Pugh class C cirrhosis, or those scheduled for transcatheter arterial chemoembolization (TACE), systemic therapy, or palliative care. Patients with underlying immunological or inflammatory dysregulation were also excluded—since baseline immune alterations could interfere with pre- and post-procedural assays. Patients with concurrent antiarrhythmic therapy with verapamil, propafenone, or amiodarone were excluded due to potential interference with the antiarrhythmic effects of lidocaine. Additionally, exclusion applied to pregnant women and individuals with known contraindications to any study medication. Finally, patients were excluded if they presented with psychiatric disorders that impaired their capacity to understand the study protocol or provide informed consent, as well as those who refused participation.

Randomization

The patients were assigned to one of the two groups using a computer generated randomisation process in a 1:1 ratio. The group allocation and patient study number were concealed in a sealed opaque envelope, which was opened after the patient had given their written, informed consent before surgery. The trial groups were: Lidocaine and non-Lidocaine. While the involved anesthesiologists were not masked to study group allocation, investigators involved in data analysis, and interpretation were unaware of the group allocation.

Clinical protocol

During anesthesia, all patients were monitored according to the Standards for Basic Anesthetic Monitoring of the American Society of Anesthesiologists. Low molecular weight heparin was administered 12 hours prior to surgery. Induction consisted of fentanyl 2–3 mcg/kg, propofol 1–1.5 mg/kg, and rocuronium 0.5–0.6 mg/kg for muscle relaxation. Anesthesia in Sevoflurane group was maintained with Sevoflurane (EtSevo of 1–1.5 MAC), adjusted in steps of 0.25–0.5 MAC depending on BIS levels (target 40–59). In case of TIVA anesthesia, propofol was administered using TCI-technique (Schneider model), starting with an effect-site concentration of 4 µg/ml, adjusted according to BIS (target 40–59). All patients received protective mechanical ventilation, FiO_2 of 40–60% to maintain $SpO_2 \geq 94\%$, in a semi-closed circuit, with a fresh gas flow of 1.8–2.0 L/min. For intraoperative analgesia, fentanyl 1-2 µg/kg was injected as needed (e.g., if blood pressure or heart rate increased > 20% from baseline, or there were signs of sympathetic activation such as mydriasis, lacrimation, sweating). Thirty minutes before the end of surgery, morphine 0.1–0.2 mg/kg IV was administered. In lidocaine groups, a bolus of lidocaine 1% (1.5 mg/kg) was administered during induction followed by a continuous infusion of lidocaine 1 mg/kg/h up to a maximum of 200 mg/hour during surgery, and for 24 h after operation. Lidocaine dose was lower compared with recommendations and that used in other studies due to concerns regarding a reduced hepatic metabolism. In addition, the dose was temporarily reduced in cases of severe hypotension or bradycardia. Postoperative analgesia included nefopam hydrochloride 40 mg every 8 hours, with the first doses administered intraoperatively. Rescue analgesia consisted of i.v. morphine 2 mg every 5 minutes, (with a maximum total hourly dose of 10 mg), if the NRS score was ≥ 4. We did not use NSAID for postoperative analgesia because of their potential interference with lidocaine's anti-inflammatory effects [25].

Postoperatively, patient pain intensity was monitored using the Numeric Rating Scale (NRS) at least twice per hour. Pain scores were documented in the monitoring flow sheet, and the mean pain score over the first 24 hours was calculated. Additionally, total 24-hour cumulative consumption of fentanyl and morphine was quantified. To evaluate the level of systemic inflammation, leukocyte counts and C-reactive protein (CRP) levels were measured pre- and postoperatively.

Data management and statistics

Data were handled throughout in compliance with EU General Data Protection Regulations legislation, and uploaded onto an Excel file and imported into Graph Pad Prism TM v8 for analysis. All data were inspected for distribution. Normally distributed data were compared using analysis of variance with post hoc Bonferroni correction for differences between independent groups. Differences in serum marker values before and after anesthesia and surgery within groups was undertaken using paired Student's t-tests. Values of $p < 0.05$ were deemed statistically significant.

Results

A total of 60 patients were enrolled and randomly assigned in a 1:1 ratio to two study groups: 30 patients to the Lidocaine group and 30 patients to the non-Lidocaine group. There were no major differences regarding the baseline subject characteristics, the classification of ASA physical status, the Barcelona and the Child Pugh classifications between study groups. We only found a difference in the case of arterial hypertension between groups (Table I).

We found no significant differences in opioid consumption between the groups. The intraoperative Fentanyl dose was comparable in both groups (0.8 mg in each group, $p = 0.957$). Although the non-Lidocaine group received a higher cumulative morphine dose during the first 24 postoperative hours (19.5 mg vs 13.5 mg), this difference did not reach statistical significance ($p = 0.224$).

Recovery of normal gastrointestinal motility was also similar between the groups, with no statistically significant difference (3 days vs 3.4 days, $p = 0.215$), however, it was slightly lower in the lidocaine group.

Patients in the non-Lidocaine group reported higher pain scores on the NRS during the first 24 postoperative hours compared with those in the lidocaine group (3.8 vs 3.36), however this difference was not statistically significant.

The effects of lidocaine on inflammatory markers were also evaluated. In both groups, CRP levels increased significantly after surgery compared with preoperative values (lidocaine group: 1.03 mg/dL preoperatively vs. 4.1 mg/dL postoperatively, $p = 0.04$; non-Lidocaine group: 0.45 mg/dL preoperatively vs. 2.95 mg/dL postoperatively, $p = 0.01$). However, no statistically significant differences in CRP levels were observed between the groups either preoperatively (1.03 mg/dL vs. 0.45 mg/dL, $p = 0.225$) or postoperatively (4.1 mg/dL vs. 2.95 mg/dL, $p = 0.376$).

Table I. Baseline characteristics of the study patients. Data are expressed as mean (standard deviation) or n (%). BMI, body mass index; ASA, American Society of Anesthesiologists; TIVA, total intravenous anesthesia.

Study groups		Lidocaine	Non-Lidocaine	P between
Age (yr)		67.4 (56-76)	63.2 (51-74)	0.12
BMI (kg/m²)		26.8 (1.9)	26.9 (1.6)	0.78
ASA physical status (n, %)				
II		10 (33.3%)	11 (36.6%)	1.00
III		20 (66.6%)	19 (63.3%)	
Barcelona classification (n, %)				
A		10 (33.3%)	8 (26.6%)	0.77
B		20 (66.6%)	22 (73.3%)	
Diabetes mellitus (n, %)		9 (30%)	14 (46.66%)	0.28
Arterial hypertension (n, %)		18 (60%)	7 (23%)	0.008
Pulmonary disease (n, %)		5 (16.6%)	3 (10%)	0.70
Anesthesia duration (min)		165.43 (63.75)	158.73 (60.61)	0.74
Surgery duration (min)		165.4 (63.7)	158.7 (60.6)	0.75
Type of surgery (n, %)	Right hepatectomy	3 (10%)	4 (13.33%)	0.712
	Left hepatectomy	6 (20%)	8 (26.67%)	
	Segmentectomy	21 (70%)	18 (60%)	
Type of anesthesia (TIVA n, %)		6 (20%)	4 (13.3%)	0.73

Table II. Effect of intravenous lidocaine infusion. All data shown are mean (standard deviation) or n (%). CRP, C-reactive protein.

Study groups		Lidocaine	Non-Lidocaine	P between
Fentanyl (mg)		0.8 (0.1)	0.8 (0.2)	0.95
Morphine 24h (mg)		13.5 (13.3)	19.5 (15.8)	0.22
Return of bowel function (days)		3.0 (0.9)	3.4 (1.5)	0.22
Pain numeric scale in 24h (0-10)		3.36 (1.77)	3.8 (1.85)	0.27
CRP (mg/dl)	Preoperative	1.03 (1.58)	0.45 (0.70)	0.23
	Postoperative	4.10 (4.54)	2.95 (2.82)	0.38
	Intra-Group P-value	0.041	0.011	
Leucocytes (/µl)	Preoperative	7302.61 (1877.14)	5462.00 (1841.25)	0.005
	Postoperative	13930 (1305.00)	10550.00 (6488.05)	0.35
	Intra-Group P-value	0.0001	0.005	
Length of Hospital Stay (days)		9.46 (3.15)	8.47 (3.09)	0.34

A similar pattern was observed for leukocyte counts. Both groups exhibited a significant postoperative increase compared with baseline (lidocaine group: 7.302/µL vs. 13.930/µL, $p < 0.0001$; non-Lidocaine group: 5.462/µL vs. 10.550/µL, $p = 0.0056$). However, no statistically significant difference was found between the groups in postoperative leukocyte counts (13.930/µL vs. 10.550/µL, $p = 0.359$). The only significant between-group difference was observed at baseline, with the non-lidocaine group demonstrating significantly lower preoperative leukocyte counts than the lidocaine group (5.462/µL vs. 7.302/µL, $p = 0.005$) despite the randomization (Table II).

Regarding the length of hospital stay, no statistically significant difference was observed between the study groups.

No systemic toxicity or local anesthetic-related adverse events were recorded in patients who received i.v. lidocaine throughout the perioperative period.

Discussion

While local anesthetics are predominantly utilized in regional techniques to attenuate the surgical stress response, preserve cellular immune function (such as NK cell activity and T-helper cell populations), and reduce opioid dependence, i.v. lidocaine stands out as the sole local anesthetic indicated for systemic perioperative administration as an adjunctive analgesic [26]. Numerous clinical studies have demonstrated that systemic lidocaine infusion effectively alleviates postoperative pain, decreases perioperative opioid consumption, exerts anti-inflammatory

activity, and promotes early gastrointestinal recovery [27]. In contrast to these findings, the clinical endpoints evaluated in our study did not reach statistical significance. Nevertheless, our data revealed a consistent, favorable trend in the lidocaine cohort, characterized by a lower overall requirement for postoperative opioids alongside lower persistent NRS pain scores compared to the control group.

While systemic lidocaine significantly accelerated bowel recovery and reduced intraoperative anesthetic consumption in extra-abdominal procedures like lumbar spine surgery [28], our trial in patients undergoing elective liver resection demonstrated only a non-significant trend toward earlier return of bowel function (3.0±0.9 vs. 3.4±1.5 days; p=0.215). This disparity likely stems from our reduced maintenance dosing 1 mg/kg/h, used to prevent systemic toxicity in the setting of hepatic resection and transient surgical ischemia (Pringle maneuver), as well as the more pronounced surgical trauma and visceral handling inherent to open hepatectomy, which may attenuate subtle pro-peristaltic effects.

Regarding perioperative opioid administration, our study found identical intraoperative fentanyl consumption between the lidocaine and control groups (0.8±0.1 mg vs. 0.8±0.2 mg; p=0.957), alongside a reduction in 24-hour cumulative postoperative morphine requirements in the lidocaine group (13.5±13.3 mg vs. 19.5±15.8 mg) that did not reach statistical significance (p=0.224). These results do not reach statistical significance, as in the evidence-based synthesis by Eipe et al. (2016), which highlights that while i.v. lidocaine can effectively blunt central sensitization and decrease opioid consumption as a multimodal analgesic adjunct, its clinical opioid-sparing magnitude varies considerably depending on the surgical model, tissue trauma intensity, and total dose administered [29].

Regarding inflammatory markers, the difference between groups was not statistically significant. Leukocyte counts increased significantly after surgery in both groups, without a statistically significant postoperative difference between groups. Interpretation is limited by the significant baseline imbalance.

Several limitations of the present study warrant consideration. First, to mitigate the heightened risk of systemic toxicity—driven by impaired hepatic drug clearance, altered parenchyma, and transient ischemia during potential Pringle maneuvers—we administered a reduced lidocaine maintenance infusion rate of 1 mg/kg/h, up to a maximum dose of 200 mg/h. Consequently, systemic plasma concentrations may have fallen near the lower threshold needed to elicit significant analgesic, pro-motility, or anti-inflammatory effects. Additionally, systemic plasma levels of lidocaine and its active hepatic metabolites (MEGX and GX) were not routinely measured, precluding direct correlation between individual plasma concentrations and observed clinical or biological outcomes. Furthermore, despite computer-generated randomisation, a statistically significant baseline difference was present between cohorts regarding the baseline leukocyte counts (7302/μL vs. 5462/μL, p=0.0055), which may have introduced subtle confounding in inflammatory trajectories. Finally, the single-center design and relatively modest sample size (N=60) may limit the statistical power required to detect subtle biomarker shifts or minor reductions in opioid consumption, while the extensive visceral manipulation and robust surgical stress response inherent to open hepatectomy may have masked low-dose pro-peristaltic or anti-inflammatory benefits.

Conclusion

A modified, lower-dose perioperative i.v. lidocaine regimen during major hepatectomy is well-tolerated but does not yield statistically significant reductions in postoperative opioid consumption, pain scores, bowel recovery time, systemic inflammatory markers, or hospital stay following open hepatectomy. Further, larger RCTs are needed for a more accurate quantification of the clinical benefits of perioperative i.v. lidocaine during major hepatectomy and for an eventual dedicated administration protocol.

Author Contributions

Conceptualization: S.S., D.I. and A.A; methodology: S.S., D.I. and A.A.; software: I.R.; validation: S.S., A.A., I.R. and D.I.; formal analysis: S.S and D.I.; investigation: S.S.; data curation: S.S., V.D. and A.A. All authors have read and agreed to the published version of the manuscript.

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