Original Article

Safety of perioperative intravenous lidocaine in liver surgery – A pilot study

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Abstract

Background and Aims: Perioperative lidocaine infusion has many interesting properties such as analgesic effects in the context of enhanced recovery after surgery. However, its use is limited in liver surgery due to its hepatic metabolism.
Material and Methods: This prospective, monocentric study was conducted from 2020 to 2021. Patients undergoing liver surgery were included. They received a lidocaine infusion protocol until the beginning of hepatic transection (bolus dose of 1.5 mg kg^{-1}, then a continuous infusion of 2 mg kg^{-1} h^{-1}). Plasma concentrations of lidocaine were measured four times during and after lidocaine infusion.
Results: Twenty subjects who underwent liver resection were analyzed. There was 35% of preexisting liver disease before tumor diagnosis, and 75% of liver resection was defined as "major hepatectomy." Plasmatic levels of lidocaine were in the therapeutic range. No blood sample showed a concentration above the toxicity threshold: 1.6 (1.3–2.1) μg ml^{-1} one hour after the start of infusion, 2.5 (1.7–2.8) μg ml^{-1} at the end of hepatic transection, 1.7 (1.3–2.0) μg ml^{-1} one hour after the end of infusion, and 1.2 (0.8–1.4) μg ml^{-1} at the end of surgery. Comparative analysis between the presence of a preexisting liver disease or not and the association of intraoperative vascular clamping or not did not show significant difference concerning lidocaine blood levels.
Conclusion: Perioperative lidocaine infusion seems safe in the field of liver surgery. Nevertheless, additional prospective studies need to assess the clinical usefulness in terms of analgesia and antitumoral effects.

Keywords: Analgesia, lidocaine, liver surgery, pain, pharmacokinetics

Introduction

Enhanced recovery after surgery (ERAS) aims to shorten length of stay and to improve patient's outcome. One part of ERAS consists in multimodal pain control strategy using analgesic drugs with different mechanisms of action to potentiate their analgesic effects.

Intraoperative intravenous lidocaine administration during abdominal surgery with laparotomy is known to decrease postoperative pain, opioid consumption, delay of resumption of normal bowel function, and hospital length of stay.[1-3] These effects are related to the inhibition of the depolarization of A-delta and C fiber sensory nerve and to the anti-inflammatory properties.[4,5] Thus, guidelines of the French Society of Anesthesia and Intensive Care Medicine (Société Française d'Anesthésie-Réanimation [SFAR]) recommend intravenous lidocaine infusion during major surgery (abdominal, pelvic, or spinal surgery), to decrease the level of postoperative pain and to improve recovery.[6]

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Moreover, preclinical studies suggested a proapoptotic effect of lidocaine on cancer cells,[7-10] including hepatocarcinoma cells.[11]

Lidocaine is mainly metabolized by the liver through cytochrome P450 3A4 (CYP3A4) into an active metabolite (monoethylglycinexylidide [MEGX]), and thereafter into ineffective metabolites.[12] Protocols for intraoperative infusion of lidocaine advocate a bolus of 1–2 mg kg^{-1} at the induction of anesthesia, followed by 1–2 mg $kg^{-1} \cdot h^{-1}$ during surgery. These doses result in mean plasmatic concentration of lidocaine of 1.9 ± 0.7 μg ml^{-1}, encompassing (or twice above) the concentration required for analgesia.[12,13] Toxicity occurs when the plasmatic concentration of lidocaine rises above the threshold of 5 μg ml^{-1}, and seizures can occur with concentrations above 10 μg ml^{-1}.[14]

During liver surgery, the metabolism of lidocaine can be modified for the following reasons. First, patients scheduled for liver surgery may have a history of liver disease, which can impair the liver function.[15] Second, intraoperative vascular clamping (Pringle maneuver) may compromise hepatocytes' blood supply. Nevertheless, international guidelines on ERAS in the field of liver surgery recommend a multimodal analgesia,[16] and so, intravenous lidocaine in this setting must be evaluated.

The primary objective was to evaluate the lidocaine pharmacokinetics during hepatic surgery to verify that effective concentrations are reached throughout the surgery and the absence of toxic concentration. The secondary objectives were to compare plasmatic concentrations of lidocaine according to the presence of a liver disease and intraoperative hepatic vascular clamping.

Material and Methods

The HEPATOLIDO study (*HEPATectOmy and LIDOcaine infusion*) was a prospective, single-center study. We received authorization from our local ethics committee in November 2020 (*Comité Local d'Ethique et de Recherche en Santé* [CLERS], number 1831). The study did not imply deviation from the standard care, and all patients signed informed consent before inclusion. Enrollment began in December 2020 and ended in August 2021.

Inclusion criteria were patients aged 18 years or older and scheduled for a liver resection. Exclusion criteria were contraindication to lidocaine (allergy to lidocaine, porphyria, high-degree atrioventricular block) and patient's refusal to participate.

Patients received a bolus of 1.5 mg kg^{-1} of intravenous lidocaine during induction of anesthesia, followed by a continuous infusion of 2 mg kg^{-1} h^{-1}, until the beginning of hepatic transection. For obese patients (body mass index [BMI] >30 kg m^{-2}), lidocaine dosage was calculated using estimated adjusted body weight (ideal body weight + 0.4 [actual weight − ideal body weight]), and ideal body weight was calculated using the formula 50+ (0.91× [height in centimeters − 152.4]) for men and 45.5+ (0.91× [height in centimeters − 152.4]) for women. For each patient, blood samples for plasmatic lidocaine measurements were collected at four different time periods as follows: T0: 1 h after the initial bolus, T1: beginning of hepatic transection, T2: 1 h after the end of lidocaine infusion, and T3: end of surgery (defined as the skin closure) [Figure 1] Plasma lidocaine concentration was determined after liquid/liquid extraction in basic buffered medium with gas chromatography coupled with mass spectrometry (GC–MS/MS; Thermo Scientific® TSQ Duo). Results were expressed in μg ml^{-1}.

Patients' preoperative clinical characteristics (age, gender, height, weight, BMI, preexisting chronic diseases) and biological characteristics (prothrombin ratio [PR], serum creatinine, liver enzymes like alanine aminotransferase [ALT] and aspartate aminotransferase [AST], bilirubin, and albumin) were analyzed. The presence of a preexisting liver disease was defined by a diagnosis of cirrhosis regardless of its etiology (alcoholic, hemochromatosis, nonalcoholic fatty liver disease). We collected intraoperative data such as surgical indication, type of surgical approach (laparotomy or laparoscopy), use of a vascular clamping and its duration, length of surgery and anesthesia, hemodynamic parameters such as invasive arterial pressure, and cardiac frequency at the four predefined surgical steps. Vascular clamping was defined as a Pringle maneuver (clamping of the hepatic hilum) or a partial hepatic clamp (lobar or segmental) during the intervention. Major hepatectomy was defined in our center as the resection of more than three liver segments.

Statistical analysis

Being a pilot study, no sample size calculation was done, and the sample size was arbitrarily set at 20. Data are presented as the mean ± standard deviation for normally distributed continuous variables and medians (25^{th}–75^{th} percentile) for non-normally distributed continuous variables. The normality of continuous variables was tested with the Shapiro–Wilk Kolmogorov–Smirnov test and visual analysis of quantiles–quantile plots. Categorical variables are presented as numbers (percentages). Comparisons between two groups for continuous and categorical variables were performed by Student *t*-test and Fisher's exact test, respectively. Comparison of concentrations of plasmatic lidocaine between groups was performed using two-way analysis of variance with

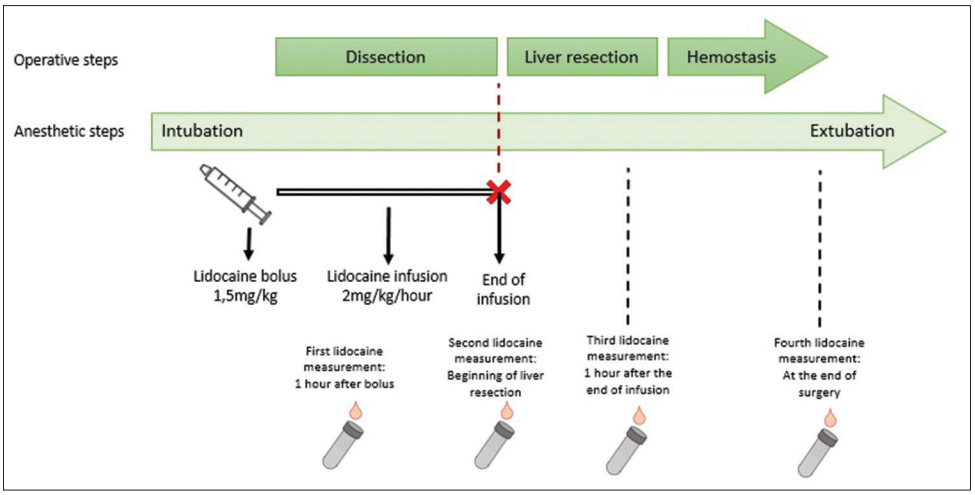

Figure 1: Operative course and different times of lidocaine measurement

plasmatic concentrations of lidocaine as the dependent variable and groups (liver disease or vascular clamping) as a factor. Significance was set to $P < 0.05$. Statistical analyses were conducted using JASP - Jeffreys's Amazing Statistics Program (JASP Team, 2020, Version 0.14.1).

Results

Twenty patients scheduled for liver surgery during the study period (9 months) were included in the study [Figure 2]. Table 1 presents the baseline characteristics of the patients.

Fifteen (75%) of the liver resections were major hepatectomy. Surgical approach was laparoscopy in 10 (50%) cases. The median number of resected segments was 3 (2–4). A hepatic vascular clamping occurred in six (30%) cases (median duration of hepatic vascular clamping was 43 [10–108] min), and an associated surgical procedure such as cholecystectomy or adrenalectomy was performed in six (30%) patients. Average duration of surgery was 298 (210–320) min.

Table 2 shows the doses of lidocaine used. Median plasmatic lidocaine concentrations at T0, T1, T2, and T3 were 1.6 (1.3–2.1), 2.5 (1.7–2.8), 1.7 (1.3–2.0), and 1.2 (0.8–1.4) μg ml^{-1}, respectively [Figure 3]. No adverse event related to lidocaine infusion was reported.

Plasma concentrations of lidocaine at the end of surgery did not differ between surgeries with vascular clamping and without (1.2 [0.7–1.4] vs. 1.2 [0.8–1.4] μg ml^{-1}, $P = 0.898$).

Seven (35%) patients had a preexisting liver disease (three hemochromatosis, three patients with alcoholic liver disease Child-Pugh stage A, one nonalcoholic fatty liver disease). Characteristics of patients regarding the presence of a liver disease or not are presented in Table 3. There was no difference in the plasmatic concentrations of lidocaine between patients based on the history of liver disease ($P = 0.749$) [Figure 4].

Table 1: Baseline characteristics

General characteristics	Patients (*n*=20)
Gender (male)	8 (40)
Age (years)	67 (±9)
Height (cm)	166 (±8)
Weight (kg)	76 (±18)
BMI (kg m^{-2})	26 (±6)
Surgical indication	
Colorectal cancer liver metastasis	11 (55)
Hepatocellular carcinoma	6 (30)
Cholangiocarcinoma	2 (10)
Comorbidities	
Arterial hypertension	10 (50)
Liver disease	7 (35)
Chronic kidney disease	4 (20)
Asthma	2 (10)
Biological parameters	
AST (IU l^{-1})	34 (21–58)
ALT (IU l^{-1})	27 (21–52)
Bilirubin (μmol l^{-1})	12 (8–17)
PR (%)	100 (88–100)
Serum creatinine (μmol l^{-1})	75 (59–87)

ALT=alanine aminotransferase, AST=aspartate aminotransferase, BMI=body mass index, PR=prothrombin ratio, SD=standard deviation. Values are expressed as mean (±SD), number (proportion), or median (25th–75th percentile)

Discussion

The use of intravenous lidocaine in liver surgery was safe in our study population, with no plasma dosage over 5 μg ml^{-1}, which is the lowest toxicity threshold (maximum plasma value recorded was 3.8 μg ml^{-1}). Moreover, the lidocaine dosage used in our protocol permitted an effective concentration until surgical closure. These pharmacologic results are consistent

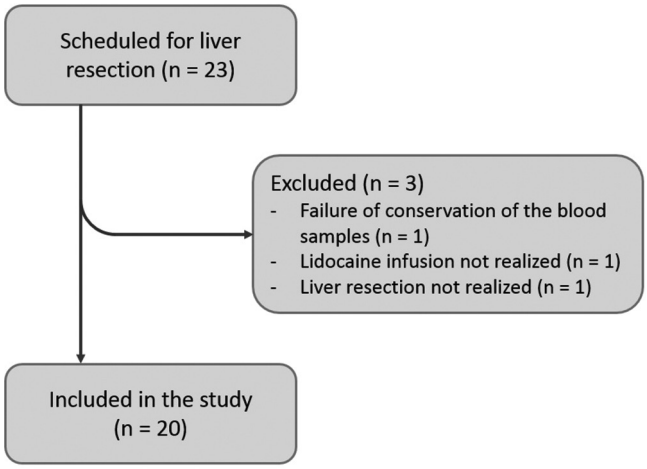

Figure 2: Flowchart of the study

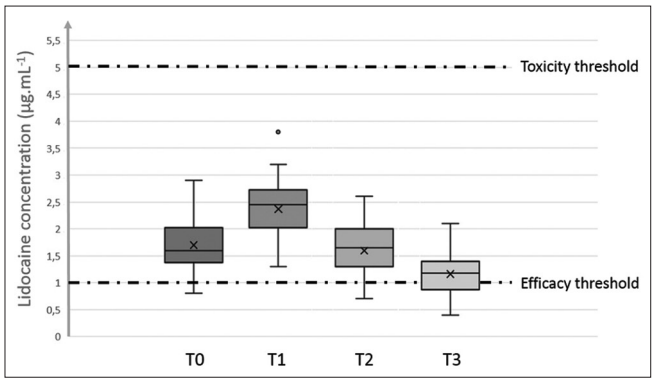

Figure 3: Plasmatic lidocaine concentrations at different operative time periods. Boxplots represent the median values and 25th and 75th percentiles. Dotted lines represent toxicity and efficacy thresholds. (T0 = 1 h after the initial bolus, T1 = start of hepatic resection and end of lidocaine infusion, T2 = 1 h after the start of hepatic resection, T3 = end of surgery)

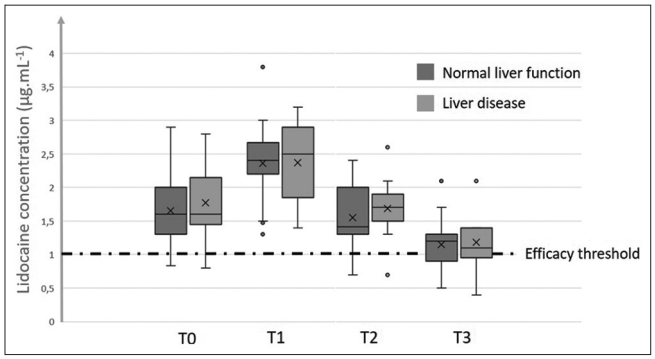

Figure 4: Dosages of plasmatic lidocaine regarding liver function. Boxplots represent the median values and 25th and 75th percentiles. Dotted line represents the efficacy threshold. (T0 = 1 h after the initial bolus, T1 = start of hepatic resection and end of lidocaine infusion, T2 = 1 h after the start of hepatic resection, T3 = end of surgery)

with the study of Koppert *et al.*,[13] using lidocaine dosages of 1.5 mg kg^{-1} and then 1.5 mg kg^{-1} h^{-1} in major abdominal surgery, and with the study of Plass *et al.*,[17] which showed a plasmatic concentration of lidocaine of 2.44 (±0.7) µg ml^{-1} at the end of bariatric surgeries with a similar protocol. In the

Table 2: Doses of lidocaine used in the intraoperative period

Bolus dose (mg)	100 (93–120)
Bolus dose (mg kg^{-1})	1.4 (1.2–1.5)
Continuous infusion dose (mg h^{-1})	140 (120–158)
Continuous infusion dose (mg $kg^{-1}.h^{-1}$)	1.9 (1.8–2)
Duration of intravenous infusion (min)	194 (133–218)
Total dose of lidocaine (mg)	499 (351–638)

Values are expressed as median (25th–75th percentile)

Table 3: Characteristics of the population regarding the presence of a liver disease

	No preexisting liver disease (*n*=13)	Liver disease (*n*=7)	*P*
General characteristics			
Gender (male)	5 (39)	3 (43)	1
Age (years)	66 (±11)	69 (±5)	0.691
Height (cm)	166 (±9)	166 (±8)	0.968
Weight (kg)	70 (±14)	86 (±22)	0.204
BMI (kg m^{-2})	26 (±4)	31 (±8)	0.081
ASA classification	2 (2–3)	3 (3–3)	0.054
Biological characteristics			
AST (IU l^{-1})	28 (19–39)	72 (55–83)	0.003*
ALT (IU l^{-1})	24 (17–34)	66 (42–93)	0.008*
Bilirubin (µmol l^{-1})	9 (5–12)	17 (10–21)	0.067
PR (%)	100 (98–100)	86 (76–100)	0.028*
Creatinine (µg l^{-1})	70 (60–86)	82 (58–93)	0.692
Surgical characteristics			
Major hepatectomy	9 (69)	6 (86)	0.613
Hepatic vascular clamping	5 (39)	1 (14)	0.070
Plasmatic lidocaine			
T0 (µg ml^{-1})	1.6 (1.2–2.1)	1.6 (1.4–2.5)	0.697
T1 (µg ml^{-1})	2.4 (1.9–2.7)	2.5 (1.4–3.1)	0.984
T2 (µg ml^{-1})	1.4 (1.2–2.0)	1.7 (1.3–2.1)	0.575
T3 (µg ml^{-1})	1.2 (0.8–1.4)	1.1 (0.8–1.4)	0.873

*ALT=alanine aminotransferase, ASA=American Society of Anesthesiologists, AST=aspartate aminotransferase, BMI=body mass index, IQR=interquartile range, PR=prothrombin ratio, SD=standard deviation. T0: 1 h after the initial bolus, T1: beginning of hepatic transection, T2: 1 h after the end of lidocaine infusion, T3: end of surgery (defined as the skin closure). Values are expressed as mean (SD), number (proportion), or median (IQR range). *P<0.05*

specific setting of liver surgery, the recent study of Jin *et al.*[18] evaluated the pharmacokinetics of intravenous lidocaine with regular blood samples. It was an observational study on 31 subjects under laparoscopic liver surgery, evaluating a protocol slightly different than ours with an infusion of 1 mg kg^{-1} h^{-1} intraoperatively. In this series of patients, the mean peak of lidocaine was 2097 µg ml^{-1} and the plasmatic concentrations did not exceed the therapeutic ranges, as in our study. These are the only two studies evaluating the pharmacokinetics of lidocaine during liver surgery, which is an uncommon practice probably because of a fear of overdosing a liver-metabolized molecule in a liver surgery. On the other hand, the study of the pharmacokinetics of lidocaine and its 80% metabolization

to MEGX can also be used to evaluate liver function.[19] In a population of patients with hepatocellular carcinoma, Ercolani *et al.*[20] showed that a lidocaine test with a low concentration of MEGX (therefore an altered hepatic metabolism of lidocaine) was associated with a high risk of liver insufficiency after hepatic resection.

We acknowledge the limitations of our study. First, intravenous lidocaine infusion ended at the beginning of hepatic transection in contrast to the protocols used in major abdominal surgery.[6,13,17] This early termination of intravenous infusion did not permit us to study the pharmacokinetics of lidocaine during liver parenchyma transection and during clamping of the hepatic blood vessels, while it seems that a correlation exists between the duration of vascular haptic clamping and the half-life of intravenous lidocaine and its metabolite, MEGX.[18] However, this protocol helped in preventing the risk of overdosage and local anesthetics' toxicity. In our study population, we did not find any significant difference of concentration in the subgroup analysis depending on the presence of intraoperative hepatic vascular clamping, but these data are from secondary analyses with small groups of patients. The second limitation is the sample size of the study. Given the pilot nature of the study, no sample size calculation was effectuated and only 20 patients were included and analyzed. However, all the 80 dosages were below the toxicity threshold, which seems sufficient for a safety study.

The assessed safety of intravenous lidocaine in our study and in the study of Jin *et al.*[18] permit to assess further the efficacy of intravenous lidocaine during liver surgery. Randomized trials comparing intravenous lidocaine to placebo in hepatic surgery are ongoing (ClinicalTrials.gov Identifier: NCT04295330).

Conclusions

This single-center, prospective study demonstrated the safety of intravenous lidocaine in the field of liver surgery. The subgroup analysis, depending on the presence of intraoperative hepatic vascular clamping or a preexisting liver disease, did not show any difference in the levels of plasma lidocaine, probably due to the small sample size. Further studies are necessary to assess its safety and efficacy on postoperative pain.

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Glossary
ALT: alanine aminotransferase
ASA: American Society of Anesthesiologists
AST: aspartate aminotransferase
BMI: body mass index
CHU: Centre Hospitalier Universitaire
CKD: chronic kidney disease
CLERS: Comité Local d'Ethique et de Recherche en Santé
CNIL: Commission Nationale de l'Informatique et des Libertés
ERAS: enhanced recovery after surgery
IQR: interquartile range
MEGX: monoethylglycinexylidide
PR: prothrombin ratio
SFAR: French Society of Anesthesia and Intensive Care Medicine (Société Française d'Anesthésie-Réanimation).

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Nil.

Conflicts of interest
There are no conflicts of interest.

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