

Incidence of persistent postoperative pain after hepatectomies with 2 regimes of perioperative analgesia containing ketamine

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Abstract

Studies designed to assess persistent postoperative pain (PPP) incidence after hepatectomies are lacking. Our aim was to assess PPP incidence 6 months after hepatectomies with intravenous (IV) or epidural (EPI) analgesia containing ketamine.

Prospective observational comparative study between 2 cohorts of patients submitted to hepatectomy. Patients received 1 of 2 analgesic regimes containing ketamine: EPI group or IV group. Visual analog scale (VAS), Neuropathic Pain Symptom Inventory (NPSI), Pain Catastrophizing Scale (PCS), and quantitative sensorial testing (QST: to determine area of hyperalgesia/allodynia) were assessed preoperatively and postoperatively at 2 h, 24 h, 7 days, 1 month, and 6 months. VAS ≥ 1 at 1 and 6 months was considered indicative of PPP and VAS > 3 was considered as not controlled pain. Side effects and complications were registered.

Forty-four patients were included: 23 in EPI group and 21 in IV group. Patients in IV group were older and had more comorbidities. No patient presented VAS > 3 at 1 or 6 months. VAS ≥ 1 at 1 and 6 months was 36.4% and 22.7%, respectively. No differences in VAS, NPSI, or PCS were found between groups. Allodynia/hyperalgesia area did not differ between groups and was infrequent and slight. Pain pressure threshold in the wound vertical component was significantly higher in EPI group after 7 days. IV group showed more cognitive side effects.

Incidence of PPP at 6 months after open hepatectomies with EPI or IV analgesia containing ketamine was lower than previously reported for other abdominal surgeries.

Ketamine influence on low PPP incidence and hyperalgesia cannot be discarded.

Abbreviations: EFV = electronic Von Frey, EPI = epidural, IV = intravenous, NMDAr = N Metil D Aspartate receptors, NPSI = Neuropathic Pain Symptom Inventory, PCA = patient controlled analgesia, PCS = Pain Catastrophizing Scale, PONV = postoperative nausea/vomiting, PPP = persistent postoperative pain, QST = quantitative sensorial testing, VAS = visual analog scale, VFM = Von Frey monofilaments.

Keywords: hepatectomy, ketamine, neuropathic pain, persistent postoperative pain, quantitative sensorial testing

1. Introduction

Incidence of persistent postoperative pain (PPP) after abdominal surgery has been reported between 0% and 34%.^[1,2] Studies specifically designed to evaluate the incidence of PPP after open hepatectomies have not been published to date. In 2 studies on quality of life after hepatic surgery, the incidence of PPP was reported between 9% and 50%.^[3–5] The main component of PPP is neuropathic and the central sensitization after nervous injury

generates secondary hyperalgesia that could intervene not only in the intensity of the perception of immediate postsurgical pain but also in chronification of pain after healing of the wound.^[6–8] Nervous injury and intensity of acute postoperative pain are the most constant predisposing factors after abdominal surgery.^[9] Relation of PPP with uncontrolled postoperative pain makes postsurgical analgesia the most accessible way to prevent PPP.

Secondary hyperalgesia has been related to PPP.^[5] In conventional hepatic resection, the predominant surgical incision has a vertical supraumbilical medial component and a horizontal subcostal component. Thoracic epidural (EPI) analgesia has been considered the most effective analgesic technique for hepatic resection surgery in multiple series,^[10–13] although the frequent pre- and postsurgical coagulation alterations in these patients make its indication controversial.^[14,15] The doses of opioids^[16,17] and nonsteroidal anti-inflammatory drugs^[18] for intravenous (IV) analgesia are limited in patients with hepatic disease, reason for which low-dose ketamine is frequently associated.^[19]

N Metil D Aspartate receptors (NMDAr) have a key role in central sensitization causing PPP, which is manifested as secondary hyperalgesia. Ketamine is one of the few clinically available NMDAr antagonists and it is widely used in a complimentary way for postsurgical analgesia.^[19–23] There is clear evidence that ketamine decreases intensity of postsurgical acute pain,^[19,21,23] but results regarding its effect in PPP prevention are inconsistent, although it is proven to reduce the

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secondary hyperalgesia area.^[24–26] The possibility to reach higher concentrations closer to the NMDAr activation areas in the spinal cord by its EPI administration is being studied.^[24,27,28]

Great variability about PPP incidence and its response to treatments may be attributed to subjectivity in the evaluation of pain, lack of long-term follow-up, and heterogeneity in applied analgesic protocols. Our research group has designed a simplified protocol for PPP assessment that combines subjective scales with quantitative sensory tests (QST), to detect intensity, extension, and evolution of secondary hyperalgesia.^[24,29]

The aim of this study was to determine PPP incidence during the first 6 months after open hepatectomies and its relationship with the hyperalgesia area and with the analgesic techniques most frequently used in our institution.

2. Patients and method

2.1. Patients

The study was approved by the Research Ethics Board of our institution as an observational comparative study between 2 cohorts registered as HCB/2016/0690.

Patients over 18 years of age scheduled for conventional hepatic resection surgery according to Brisbane terminology^[30] in our institution during 18 months were considered for inclusion. Major resection was defined as the 1 developed on 3 or more adjacent segments. Inclusion was confirmed the day before surgery after obtaining written consent.

Exclusion criteria were patient refusal, previous chronic pain or chronic analgesic treatment, history of drug addiction or neurological/psychiatric disorder, cirrhosis, contraindication to any drug going to be used, emergency surgery, previous upper abdominal surgery, anticipation of nonresectable disease because of extension, and prevision of nonimmediate extubation after surgery.

The day before surgery, patients were instructed about how to refer pain using the visual analog scale (VAS 0–10) and the use of an electronic patient controlled analgesia (PCA) pump. Neuro-pathic Pain Symptoms Inventory (NPSI),^[24,31] Pain Catastrophizing Scale (PCS),^[24,32] and QST (Von Frey monofilaments [VFM], electronic Von Frey [EVF], and electric toothbrush) were explained and applied as baseline measurements. Patients were instructed to report a “painful” sensation with QST when a “change in perceived stimulation was disturbing enough to make him/her wish to stop it.”

Patients were classified into 2 groups according to the type of analgesia they received: EPI group or IV group. The decision on which type of analgesia each patient would receive was made by the responsible anesthesiologist (PT) based on general criteria of contraindications for both techniques.

According to the criteria previously used by our group,^[24,26] values of VAS ≥ 1 at 1 and 6 months were considered indicative of PPP and VAS > 3 was considered as not controlled pain. Any positive change in QST with respect to the preoperative baseline examination was considered as allodynia/hyperalgesia. Lack of sensitivity with all the QST was considered as anesthesia.

2.2. Anesthesia and surgical procedures

Sublingual diazepam 5 to 10 mg was administered the night before surgery and IV midazolam 0.025 mg kg^{-1} was given at the arrival to the operating room. In the EPI group, an EPI catheter was inserted at the vertebral interspace T7–8 before anesthesia induction. Monitoring included electrocardiogram, pulse oxymetry, capnography, invasive arterial pressure, central venous pressure, esophageal temperature, urine output, and bispectral index. Induction of anesthesia consisted of fentanyl ($2\text{--}3 \mu\text{g kg}^{-1}$), propofol (1 mg kg^{-1}), and cisatracurium (0.15 mg kg^{-1}). Anesthesia was maintained with desflurane 4% to 6% in O_2/air 60% (to keep BIS between 40 and 50) and cisatracurium $0.1 \text{ mg kg}^{-1} \text{ h}^{-1}$. After induction the analgesic technique was set up as foreseen, EPI group or IV group. Patients were extubated in the operating room when awake, following residual muscle block reversal with neostigmine. Patients remained monitored in the postanesthetic care unit for 24 h.

2.3. Analgesia

Analgesic regimen for both groups is described in detail in Table 1.

2.3.1. EPI group. Before surgical incision, an EPI bolus of lidocaine + morphine was administered. Twenty minutes before skin closure, patients received an IV bolus of morphine and the EPI PCA pump was started and kept for 5 days. PCA pump was programmed to administer 5 mL h^{-1} , with possibility of 2 boluses of 3 mL in 1 h and lockout interval of 20 min.

2.3.2. IV group. Before surgical incision, an IV bolus of ketamine was administered and an IV infusion of morphine was started. Twenty minutes before skin closure, patients received an IV bolus of morphine and the IV PCA pump was started and kept for

Table 1
Analgesic regimen administered in both groups.

	EPI group	IV group
Bolus before surgical incision	Epidural route: ketamine 0.5 mg kg^{-1} + morphine 4 mg + lidocaine 1% 6 mL	IV route: ketamine 0.5 mg kg^{-1}
Infusion during surgery	None	IV route: morphine $0.025 \text{ mg kg}^{-1} \text{ h}^{-1}$
Bolus 20 min before end of surgery	IV route: morphine 0.05 mg kg^{-1}	
Patient controlled analgesia started 20 min before the end of surgery until 5th postoperative day	Epidural route (5 mL h^{-1}): ketamine 1.5 mg mL^{-1} + morphine $15 \mu\text{g mL}^{-1}$ + ropivacaine 0.15%	IV route (1 mL h^{-1}): ketamine 7.5 mg mL^{-1} + morphine 1 mg mL^{-1} + ketorolac 1.5 mg mL^{-1}
Complementary analgesia since the end of surgery until 5th postoperative day	IV route: acetaminophen 1 g every 8 h and methadone 4 mg subcutaneous if VAS > 3	
Analgesic regimen from 5th postoperative day on	IV route: acetaminophen 1 g every 8 h and methadone 4 mg subcutaneous if VAS > 3	

EPI = epidural, IV = intravenous, VAS = visual analog scale.

5 days. PCA pump was programmed to administer 1 mL h^{-1} , with possibility of 3 boluses of 0.5 mL in 1 h and lockout interval of 5 min.

In addition, both groups received IV acetaminophen 1 g every 8 h and subcutaneous methadone 4 mg if VAS > 3. After PCA stop (either EPI or IV) on day 5 postsurgery, acetaminophen and methadone were continued.

2.4. Outcome assessment

2.4.1. Subjective scales. VAS was evaluated the day before surgery and postoperatively at 2 h, 24 h, 7 days, 1 month, and 6 months. Patients also completed NPSI,^[31] which allows identification and qualification of neuropathic symptoms reflecting spontaneous or paroxysmal pain and evoked pain, that was considered positive with scores higher than zero. PCS was also filled,^[32] which measures presence of distress reactions to nociceptive stimulation. These 2 last tests were evaluated the day before surgery and at 1 and 6 months after surgery. NPSI was also completed on day 7 after surgery.

2.4.2. Quantitative sensory testing. All tests were performed the day before surgery (baseline) and at 7 days, 1 month, and 6 months after surgery by the same expert investigator in this evaluation (BT). All mechanical measurements were carried out around the surgical incision (horizontal and vertical component) and at the middle third of the contralateral thigh as a control skin zone.

- Von Frey monofilaments (VFM): Area of allodynia/hyperalgesia for punctuate mechanical stimuli around the surgical incision was tested using nylon monofilaments (Bioseb, Vitrolles, France) of constant length and increasing diameter which exert escalating pressure proportional to their diameter. In accordance with the method described by Stubhaug,^[33,34] consecutive stimulation was applied with 3 monofilaments of 0.6, 2, and 10 g. The day before surgery, QST were applied in the area where the incision would be made and in the thigh. After the surgery, VFM were applied starting 10 cm away from the wound where no pain sensation was experienced, moving toward the incision in different radial axis until the patient reported a change in perception. In each axis, the first point where a “painful” or “sharper” sensation occurred was marked and the distance to the wound was measured. If no change in sensation occurred, the stimulation stopped at 0.5 cm from the incision. The area of allodynia/hyperalgesia was determined as a rectangle whose long axis was the wound length plus the distance of allodynia/hyperalgesia if present; and the short axis the distance of allodynia/hyperalgesia above and under the incision in the horizontal segment and at each side of it in the vertical component.^[2,24,35] VFM were applied at vertical and horizontal components of the wound and both areas were added without repeating the overlapping zone. Figure 1 shows the area explored.
- EVF: Pressure pain threshold was tested using an EVF device (Electronic Von Frey Anesthesiometer IITC, Woodland Hills, USA)^[29,36] with a constant slope of increasing pressure up to the detection of mechanical pain threshold. Threshold was defined as the lowest pressure that produced pain sensation. Measurements were performed at 6, 4, and 2 cm from the surgical incision, above and under the wound in the horizontal segment and at each side of it at the vertical component (Fig. 1). Each stimulus was applied 3 times and the average from the 6 measurements (3 at each side) for each segment was registered.

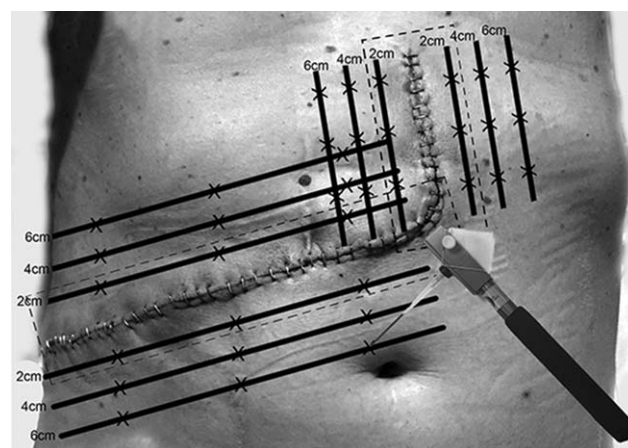


Figure 1. Von Frey monofilaments and electronic Von Frey measurements.

- Brush-evoked allodynia was explored using an electrical toothbrush applied to the skin area as described for VFM.
- Anesthesia area was calculated as described for VFM.

QST were applied in the anterior middle third of the left thigh at all times.

2.5. Side effects

Side effects were recorded during the 1st postsurgical week. Complications such as postoperative nausea/vomiting (PONV), hemodynamic side effects (new onset arrhythmia or 20% variation on median arterial pressure compared with the basal values), cognitive side effects (hallucinations, acute confusional syndrome, nightmares), visual side effects (diplopia), and sedation (Ramsay ≥ 2),^[37] hospital length of stay and need for vasoactive drugs or transfusion were registered. They were considered severe if they required treatment or withdrawal of analgesic regimen.

Postsurgical complications were registered according to Dindo-Clavien Classification.^[38] Analgesia requirement after discharge was also recorded.

2.6. Statistical analysis

This was an observational comparative study between 2 cohorts with the aim to describe several subjective pain scales and QST evolution in patients scheduled for major or minor conventional hepatic resection. Therefore, presence of PPP was not evaluated using just a single variable but a combination of several ones.

It was decided to recruit all patients who fulfilled inclusion criteria during 18 months. Forty-four patients were included and it was considered that this sample size would be representative of the population undergoing hepatic resection in a third-level hospital like ours. Comparisons between both groups for variables with a single measurement such as demographical data, preoperative and intraoperative variables, side effects, PONV incidence, hospital length of stay, and vasoactive or transfusion needs were analyzed by means Mann-Whitney *U* and data are reported as median [interquartile range: 25 and 75 percentiles] and absolute range if they were continuous variables. For qualitative variables Fisher exact test was applied and data are reported as absolute and relative frequencies. Inferential analyses in longitudinal results were conducted using general estimated equations; these were applied using an unstructured matrix to

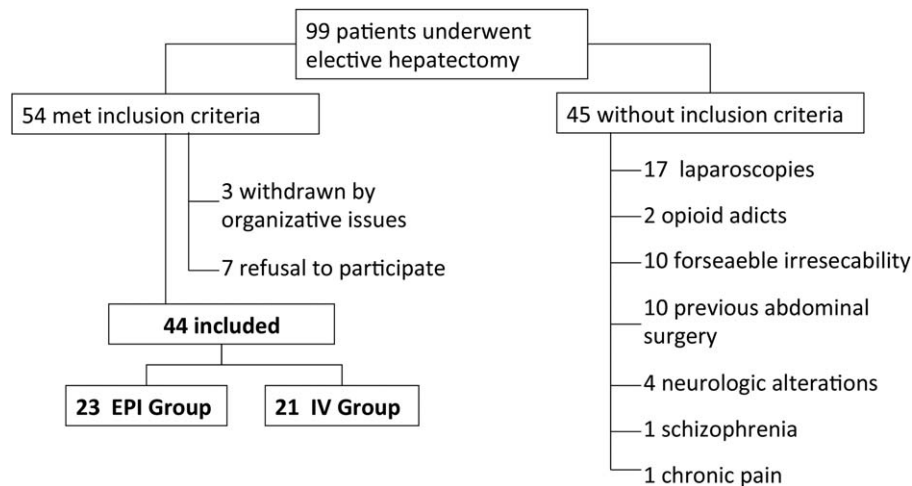


Figure 2. Patients flow chart.

account for within-subject correlations and an appropriated distribution for each dependent variable. These models were made to include groups, time, and their interaction, and the aim was to compare time-by-time VAS, analgesia requirement after discharge, NPSI, PCS, and QST evaluation between groups. Results of these variables are shown as mean (standard deviation) or absolute and relative frequencies for each time. Data were analyzed with statistical analysis software (SPSS version 20; IBM Corp., Armonk, NY) and the level of significance was set at the 2-sided 5% level.

3. Results

During the inclusion period, 99 patients underwent elective hepatic resection in our institution; 44 patients who met the inclusion criteria were analyzed: 23 in the EPI group and 21 in the IV group (Fig. 2). All patients completed follow-up (6 months).

In the demographic and prognostic characteristics, the only significant differences found were older age and more frequent American Society of Anesthesiologists Physical Status Classification System (ASA) III–IV class in the IV group (Table 2).

3.1. Subjective scales

Table 3 shows VAS values during the study in the whole sample and in each separate group. During the 1st postoperative week, mean VAS values remained below 3 and at 1 and 6 months below 1 without differences between groups. In the 1st week, the number of patients with VAS > 3 (not controlled pain) was low and similar between groups. No patient suffered VAS > 3 at 1 or 6 months. Patients with VAS ≥ 1 at 1 month were 36.4%, and at 6 months 22.7% without significant differences between groups.

Means of NPSI and PCS and frequencies of values >0 in the 2 groups and times are shown in Table 4. No significant differences were observed between groups. Total frequency of patients which still required analgesia at 1 month was 38.6%, and 13.6% at 6 months without significant differences between groups.

3.2. QST

At baseline exploration, no patients showed positive responses with VFM or toothbrush in the thigh or in the expected incision area. Pain threshold to pressure measured with EVF before surgery in the thigh or surgical area did not differ between groups

Table 2
Patients' characteristics.

Variables	EPI group	IV group	Total sample	P
Gender: male	14 (60.9%)	14 (66.70%)	28 (63.6%)	.761
Age, y	57 [45; 62]	67 [59; 74]	61 [53;69]	.001*
ASA III–IV	18 (78.3%)	21 (100%)	39 (88.6%)	.05*
Preoperative pain	1 (4.3%)	1 (4.8%)	2 (4.5%)	1
Preoperative analgesics intake	1 (4.3%)	1 (4.8%)	2 (4.5%)	1
Preoperative VAS	0 [0; 0]	0 [0; 0]	0	1
Preoperative NPSI	0 [0; 0]	0 [0; 0]	0 [0; 0]	1
Preoperative PCS	9 [4; 11]	4 [2; 7]	5 [3; 11]	.072
Total wound length, cm	28 [24; 34]	26 [25; 30]	28 [25; 31]	.875
Surgery duration, h	3.33 [2.83; 4]	3.17 [2.5; 3.75]	3.25 [2.5; 3.83]	.391
Major resection	12 (52.2%)	6 (28.6%)	18 (40.9%)	.136
Preoperative EVF in thigh	205 [175; 236]	197 [180; 220]	200 [178; 226]	.36
Preoperative EVF in surgical zone	188 [152; 215]	159 [146; 194]	175 [146; 211]	.155

Data are described as N (%) for qualitative variables and as median [25–75 percentiles] for quantitative variables. EVF data are expressed in grams.

ASA = American Society of Anesthesiologists Physical Status Classification System, EPI = epidural, EVF = electronic Von Frey, IV = intravenous, NPSI = Neuropathic Pain Symptom Inventory, PCS = Pain Catastrophizing Scale, VAS = visual analog scale.

* $P < .05$.

Table 3
VAS mean values and patients presenting VAS ≥ 1 and VAS > 3 throughout the study in both groups and in the whole sample.

Time	VAS mean ± 2 SD				VAS ≥ 1, N (%)				VAS > 3, N (%)			
	EPI group	IV group	Total	P	EPI group	IV group	Total	P	EPI group	IV group	Total	P
2 h	1.60 ± 1.3	1.95 ± 2.31	1.77 ± 1.84	.54	16 (69.6)	14 (66.7)	30 (68.2)	.84	1 (4.3)	2 (9.5)	3 (6.8)	.5
24 h	2.43 ± 1.87	2.04 ± 1.59	2.25 ± 1.74	.45	18 (78.3)	16 (76.2)	34 (77.3)	.87	6 (26.1)	4 (19)	10 (22.7)	.58
7 d	2.39 ± 1.33	2.79 ± 1.67	2.25 ± 1.5	.51	21 (91.3)	15 (71.4)	36 (81.8)	.08	6 (26.1)	5 (23.8)	11 (25)	.86
1 mo	0.82 ± 1.15	0.66 ± 1.06	0.75 ± 1.1	.63	9 (39.1)	7 (33.3)	16 (36.4)	.69	0 (0)	0 (0)	0 (0)	NA
6 mo	0.30 ± 0.70	0.33 ± 0.73	0.32 ± 0.71	.89	5 (21.7)	5 (23.8)	10 (22.7)	.87	0 (0)	0 (0)	0 (0)	NA

Data are described as mean ± 2 standard deviations for quantitative variables and as N (%) for qualitative variables. EPI = epidural, IV = intravenous, NA = not applicable, SD = standard deviation, VAS = visual analog scale.

Table 4
Mean values and frequencies of scores >0 of NPSI and PCS throughout the study in both groups.

	Mean ± 2 SD			N (%) of results >0		
	EPI group	IV group	P	EPI group	IV group	P
NPSI 7 d	7.0435 ± 3.95	8.24 ± 5.72	.41	22 (95.7)	20 (95.2)	.95
NPSI 1 mo	6.22 ± 6.98	4.5714 ± 4.49	.34	17 (73.9)	17 (81)	.58
NPSI 6 mo	3.09 ± 4.6	1.86 ± 2.83	.27	14 (60.9)	10 (47.6)	.37
NPSI 1 mo	8.57 ± 5.91	6.1 ± 7.4	.21	21 (91.3)	16 (76.2)	.17
PCS 6 mo	8.22 ± 6.82	5.71 ± 6.81	.21	20 (87)	17 (81)	.59

Data are described as mean ± 2 standard deviations for quantitative variables and as N (%) for qualitative variables. EPI = epidural, IV = intravenous, NPSI = Neuropathic Pain Symptom Inventory, PCS = Pain Catastrophizing Scale, SD = standard deviation.

Table 5
Means of areas and frequencies of results >0 of allodynia/mechanical hyperalgesia with VFM of 10g at 7 days and 1 month and of anesthesia areas at 7 days, 1 month, and 6 months.

	Mean ± 2 SD in cm ²			N (%) of results >0		
	EPI group	IV group	P	EPI group	IV group	P
10 g VFM area 7 d	8 ± 30	19 ± 38	.26	3 (13)	7 (33.3)	.10
10 g VFM area 1 mo	6 ± 17	15 ± 29	.2	3 (13)	5 (23.8)	.35
Anesthesia area 7 d	26 ± 45	8 ± 18	.08	8 (34.8)	4 (19)	.23
Anesthesia area 1 mo	27 ± 40	13 ± 20	.12	11 (47.8)	7 (33.3)	.32
Anesthesia area 6 mo	19 ± 30	7 ± 14	.09	10 (43.5)	5 (23.8)	.16

Data are described as mean ± 2 SDs for quantitative variables and as N (%) for qualitative variables. EPI = epidural, IV = intravenous, SD = standard deviations, VFM = Von Frey Monofilaments.

(Table 2). No patient showed changes in QST in the thigh at any time of the study.

Regarding postsurgical allodynia/mechanical hyperalgesia in the surgical incision area, no patient showed positive responses with 0.6 or 2 g VFM at any time of the study. With 10g VFM, small and infrequent areas of allodynia/mechanical hyperalgesia were found at 7 days and 1 month without statistical differences between groups. At 6 months, no patient showed positive responses with any of the VFM. Regarding anesthesia no statistical significant differences were found between groups (Table 5). Brushed evoked allodynia was not found in any patient during the study.

Pain thresholds measured with EVF are shown in Table 6. No significant changes were observed between baseline and postsurgical values at any time. There were no significant differences between groups in the evolution of the horizontal component of the incision. In the vertical segment of the wound, pain thresholds were higher in the EPI group compared with the IV group at all times with significant differences at 2 cm from the incision at day 7 and 6 months and at 6 cm from the wound in the 1st month.

3.3. Side effects and postsurgical complications

Table 7 shows incidence of postsurgical side effects, needs for analgesia rescue, and length of hospital stay in the whole general sample and in the 2 separate groups. Twenty-five percent of patients did not suffer postsurgical complications according to Dindo-Clavien criteria; 25% presented type I complications, 34.1% type II, 13.6% type III, and 2.3% type IV without significant differences between groups.

No hemodynamic alterations were detected. No significant differences were observed between groups regarding sedation or visual alterations. No patient in the EPI group showed cognitive alterations while in the IV group, 19% (4 patients) presented cognitive alterations ($P = .044$). Out of 4, 3 patients in the IV group who suffered cognitive side effects, presented them concomitantly with postsurgical complications type II or of Dindo-Clavien. None of the side effects was considered severe and withdrawal of analgesic treatment was not needed in any case.

PONV had a global incidence of 13.6% and need for analgesic rescue with methadone 15.9%, without differences between

Table 6
Pain thresholds with EVF at 6, 4, and 2 cm from the surgical wound.

	6 cm			4 cm			2 cm		
	EPI group	IV group	P	EPI group	IV group	P	EPI group	IV group	P
7 d									
Horizontal	176 ± 72	149 ± 54	.16	159 ± 79	153 ± 77	.78	145 ± 65	150 ± 89	.82
Vertical	181 ± 74	152 ± 43	.1	172 ± 69	143 ± 48	.1	167 ± 58	129 ± 45	.01*
1 mo									
Horizontal	144 ± 40	136 ± 63	.58	131 ± 38	140 ± 62	.57	134 ± 41	139 ± 77	.8
Vertical	158 ± 41	132 ± 39	.03*	144 ± 32	124 ± 38	.06	128 ± 32	124 ± 48	.72
6 mo									
Horizontal	176 ± 51	157 ± 36	.13	164 ± 54	150 ± 40	.31	158 ± 50	147 ± 40	.38
Vertical	179 ± 51	158 ± 42	.11	169 ± 48	151 ± 37	.14	164 ± 48	144 ± 33	.02*

Data are described as mean ± 2 SDs. EVF data are expressed in grams.

EPI = epidural, EVF = electronic Von Frey, IV = intravenous, SD = standard deviation.

* $P < .05$.

Table 7
Postsurgical complications, side effects incidence, needs for analgesia rescue, and length of hospital stay.

	EPI group	IV group	Total	P
Hemodynamic side effects	0	0	0	NA
Sedation	2 (8.7)	1 (4.8)	0.6	.1
Cognitive alterations	0	4 (19)	4 (9.1)	.04*
Visual alterations	1 (4.3)	2 (9.5)	3 (6.8)	.6
Postoperative nausea and vomiting	3 (13)	3 (14.3)	6 (13.6)	.1
Methadone analgesic rescue	4 (17.4)	3 (14.3)	7 (15.9)	.1
Length of hospital stay	10 [8; 16]	10 [8; 14]	10 [8; 15]	.89
No Dindo-Clavien complications	6 (26.1)	5 (23.8)	11 (25)	.34
Dindo-Clavien complications type I	8 (34.8)	3 (14.3)	11 (25)	
Dindo-Clavien complications type II	6 (26.1)	9 (42.9)	15 (34.1)	
Dindo-Clavien complications type III	2 (8.7)	4 (19)	6 (13.6)	
Dindo-Clavien complications type IV	1 (4.3)	0	1 (2.3)	
Vasoactive drugs need	12 (52.2)	6 (28.6)	18 (40.9)	.14
Transfusion needs	4 (17.4)	7 (33.3)	11 (25)	.30

Data are described as N (%) for qualitative variables and as median [25–75 percentiles] for quantitative variables. EVF data are expressed in grams.

EPI = epidural, EVF = electronic Von Frey, IV = intravenous, NA = not applicable.

* $P < .05$.

groups. Median hospital length of stay was 10 days in both groups. There were no significant differences regarding need for vasoactive drugs or transfusion.

4. Discussion

The aim of this study was to determine PPP incidence after 6 months of open hepatectomies, given the absence of prospective data in the reviewed literature. The study was designed in order to evaluate PPP incidence according to clinical manifestations and neurosensitive changes with 2 different postsurgical analgesic regimens commonly prescribed in our institution: EPI or IV analgesia, both containing ketamine.^[19] Results showed a global clinical PPP incidence of 22.7% (considering it as VAS ≥ 1) at 6 months with a median VAS < 0.33 and analgesic requirement at this time in 13.6% of cases. No patient showed not-controlled pain (considered as VAS > 3) at 6 months. There were no differences in PPP incidence assessed neither by VAS nor by NPSI or PCS between patients with EPI and IV analgesia. Allodynia/secondary hyperalgesia area assessed by QST was found in few patients and, when present, it was small sized. Despite the fact that the study has limitations that will be discussed later, it provides new information.

Pain after conventional hepatic resection is considered of high intensity and it is usually treated with potent analgesic techniques such as EPI. Nevertheless, PPP research after this specific type of surgery is limited. Available information about PPP after major abdominal surgery is in general controversial and PPP following hepatectomy has not been specifically addressed.

A retrospective control–case study performed on 101 patients who underwent different types of abdominal surgeries, which compared combination of epidural technique and general anesthesia with general anesthesia alone found a PPP incidence (measured thorough SF-36 questionnaire^[1,39]) at 6 months of 25.7%. In 85 patients who had rectal adenocarcinoma surgery performed with different analgesia regimens, all of them including ketamine, a prospective study with telephonic control of VAS after hospital discharge reported a PPP incidence between 0% and 48% after a year.^[2] On the other hand, in a prospective series on 20 patients intervened from gastrointestinal or urinary surgery, PPP (considered as VAS > 0 in movement or rest) incidence was 30%.^[15]

Available data on PPP after hepatic resection surgery are scarce. There is a retrospective study on 65 liver living donors in which almost all patients received IV ketamine in antihyperalgesic doses at the anesthesia induction. It showed a PPP

incidence of 9.23% assessed 3 months after surgery without specifying VAS level.^[5] There are also 2 studies designed to evaluate quality of life in which PPP is indirectly evaluated. One prospective study on 21 liver living donors that describes an incidence of “wound-related symptoms” of 24% using the SF-36 form^[40] and a questionnaire^[4] and another on 96 patients who underwent hepatic resection and who received and returned the SF-12 formulaire^[41] and a VAS by email 3 to 36 months after surgery. This last one reported a “50% of patients pain-free.”^[3] However, none of these studies specified VAS level.

Data from published studies make difficult to get clear information on this topic and to compare our results with others. Previous studies show disparities regarding analgesic regimes with or without ketamine, divergence and simplicity in PPP assessment (only by subjective scales: VAS, SF-36, and SF-12 formulaires and other questionnaires administered by email), little information about PPP definition, and lack of long-term prospective follow-up.

PPP is a chronic kind of pain with neuropathic characteristics and neurosensorial alterations that range between anesthesia and allodynia/hyperalgesia. These changes are expressed around the wound (secondary hyperalgesia area), are related with neuroplasticity, and could be related, according to some authors, with PPP.^[2] Assessment of neurosensorial changes before and after surgical operation should be part of a PPP evaluation together with subjective scales in order to get information about neuropathic changes generated after surgery. Nevertheless, the conventional complete neurosensitive assessment is not applicable to surgical patient or to repeated explorations. An assessment protocol previously applied by our investigation group^[24,29] has been used in this study. This protocol evaluates patients from the presurgical time until 6 months after surgery combining subjective scales with semiobjective assessment through QST. It includes VAS measuring (defining presence of clinical pain at 6 months as $VAS \geq 1$ and uncontrolled pain as $VAS > 3$), PCS, NPSI, analgesic requirement after discharge, and secondary hyperalgesia area exploration through QST in order to detect changes. Applying this standard PPP exploration procedure, assessed in a prospective and extensive way and with a longer follow-up period than other series, our study provides information on PPP incidence after hepatectomies not available in the existing literature. This protocol of PPP assessment is easy to apply repeatedly in postsurgical patients and permits comparison of data after surgery with that before it. This makes possible to follow-up pain characteristics from its beginning until its eventual chronification, allowing to correlate the intensity of acute pain with QST findings and PPP development.^[5]

Our results suggest that PPP incidence (considering it as $VAS \geq 1$ in context of other subjective scales and QST results) after 6 months of conventional hepatic resection with usual analgesic regimes containing ketamine is in the low range, 22.7% and that information was not reported before.

Available data about the influence of different postoperative analgesic techniques in abdominal surgery regarding PPP incidence are contradictory.^[1,2] The advantages of EPI analgesia after hepatectomy regarding quality of analgesia, hospital length of stay, and postsurgical complications are not clear and it is associated with an increase in transfusion and fluids requirements.^[10–12,42,43] In our study, no differences in analgesic efficacy, PPP, or other perioperative variables were found in patients receiving IV or EPI analgesia regimens, both containing ketamine. Therefore, the EPI route does not seem to offer advantages in these patients who also have frequent contra-

indications for EPI catheter insertion.^[1,10,14,44] The only difference between both analgesic techniques used was a higher incidence of cognitive alterations in the IV group. According to one previous study which used the same doses of ketamine and published by our group,^[31] plasmatic levels of ketamine were similar with IV or EPI administration, therefore we attribute cognitive alterations found in IV group to the older age and more frequent comorbidities of the patients. The fact that the election of EPI or IV analgesic technique relied upon the single treating anesthesiologist could have biased the distribution of patients. In older patients with more comorbidities, IV analgesia would have been considered safer than the EPI technique. This is a study limitation because it does not allow to compare PPP incidence between groups. However, this does not invalidate the low global incidence of PPP and secondary hyperalgesia after conventional hepatic resection surgery found in this study.

The importance of secondary hyperalgesia area in PPP prediction and its possible reduction with ketamine is a topic of great interest because it would allow an early detection of patients that could more probably develop PPP and to act upon it. Although the secondary hyperalgesia area that we have found in our study was small and in few patients, we cannot discard that ketamine could have had an influence in the low incidence of PPP. Up to now, it has not been reliably proved that ketamine reduces PPP incidence, despite the fact that it diminishes the opioid requirements in postoperative period^[20,23] and the size of secondary hyperalgesia area.^[2] In the literature, doses and routes of administration of ketamine as antihyperalgesic in the perioperative period are very variable and generally given during less time than in our study, in which all patients received it, either IV or EPI, during surgery and for the first 5 postsurgical days. The doses administered in the present study have demonstrated to achieve plasmatic levels within the recommended antihyperalgesic range.^[24]

The exploration of the secondary hyperalgesia area with QST has been made in different surgical incisions, but not after hepatectomies.^[2] Conventional hepatic resection wound is different to lineal incisions like those made for thoracotomies or other laparotomies^[2,31] because it has an “L” shape with a vertical and a horizontal components. The hyperalgesia area that has to be evaluated should include the 2 components, which coincide in the angle zone, and although we have not found references to this type of calculation, it is considered the best way to do it (Fig. 1).

Among the QST applied in our study, we considered that small size VFM would explore mechanical allodynia (A β fibers). The thicker VFM of 10g in this case could reach to explore A δ and C fibers that would correspond to mechanical hyperalgesia, although this threshold has not been clearly established. The only response suggestive of secondary hyperalgesia found, was with 10g VFM, but it was discrete and infrequent. We cannot discard that if we had applied thicker VFM or a “pin prick” test, more marked changes would have been detected. This simplified QST exploration protocol used could have been a study limitation and after discussing this point we have included in our protocol thicker VFM as well as temperature exploration which would give information about changes in A δ and C fibers and would not complicate the exploration too much.

Regarding pain threshold with EFV, changes found throughout the study have been also very discrete; however, an interesting finding was that the vertical component, but not the horizontal one showed differences between groups. In the EPI group, EFV threshold was higher compared with the IV one. In spite of this,

we have not found data in the literature about QST in complex wounds like that of hepatectomy. We speculate that perhaps because the vertical component of the incision injures more nerves with the corresponding increase in the neuropathic component,^[45,46] the EPI block containing ketamine could be more effective to prevent secondary hyperalgesia. These differences were not evident with any of the subjective scales.

The lack of correlation between QST and subjective pain expression is frequently found in the literature,^[24,33,34,47] which has made that some authors doubt about the relationship between the hyperalgesia area and PPP.^[39,45] When this study was designed, we expected both PPP and QST changes to be higher, but their low incidence did not allow us to assess their relationship. The small size of the sample is a limitation of this study. Nevertheless, even though our hospital is a reference center for hepatic and transplantation surgery, to recruit our sample took a long time.

In PPP development, the concept of “diffuse noxious inhibitory control” (DNIC) is gaining more importance.^[8] For this reason, we included in our protocol the assessment of a distant area from the wound as the thigh. Although we did not find any changes in this area, we believe that it is worth considering because it is a very simple exploration that allows discarding central influences.

In conclusion, PPP incidence after open hepatectomies with EPI or IV analgesia containing ketamine was 22% at 6 months after surgery. Secondary hyperalgesia responses were infrequent and small sized. Immediate clinical application of our results is that EPI analgesia does not offer advantages in front of IV analgesia in these particular patients with potential coagulation alterations. On the other hand, it seems advisable to include ketamine in the analgesic regimes, considering the low incidence of adverse effects and PPP found in this study. Regarding research in PPP, the various responses to the QST found in the vertical component of the incisions demonstrate the importance of establishing exploration protocols in different types of wounds.

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