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Pain management after open liver resection: Procedure-Specific Postoperative Pain Management (PROSPECT) recommendations

Audrey Dieu ¹, Philippe Huynen,² Patricia Lavand'homme,¹ Hélène Beloeil,³ Stephan M. Freys,⁴ Esther M Pogatzki-Zahn,⁵ Girish P. Joshi,⁶ Marc Van de Velde,^{2,7} On behalf of the PROSPECT Working Group of the European Society of Regional Anaesthesia and Pain Therapy (ESRA)

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For numbered affiliations see end of article.

Correspondence to

Dr Audrey Dieu, Department of Anesthesiology, Cliniques universitaires Saint-Luc, Bruxelles B-1200, Belgium; audrey.dieu@uclouvain.be

AD and PH contributed equally.

AD and PH are joint first authors.

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ABSTRACT

Background and objectives Effective pain control improves postoperative rehabilitation and enhances recovery. The aim of this review was to evaluate the available evidence and to develop recommendations for optimal pain management after open liver resection using Procedure-Specific Postoperative Pain Management (PROSPECT) methodology.

Strategy and selection criteria Randomized controlled trials (RCTs) published in the English language from January 2010 to October 2019 assessing pain after liver resection using analgesic, anesthetic or surgical interventions were identified from MEDLINE, Embase and Cochrane databases.

Results Of 121 eligible studies identified, 31 RCTs and 3 systematic reviews met the inclusion criteria. Preoperative and intraoperative interventions that improved postoperative pain relief were non-steroidal anti-inflammatory drugs, continuous thoracic epidural analgesia, and subcostal transversus abdominis plane (TAP) blocks. Limited procedure-specific evidence was found for intravenous dexmedetomidine, intravenous magnesium, intrathecal morphine, quadratus lumborum blocks, paravertebral nerve blocks, continuous local anesthetic wound infiltration and postoperative interpleural local anesthesia. No evidence was found for intravenous lidocaine, ketamine, dexamethasone and gabapentinoids.

Conclusions Based on the results of this review, we suggest an analgesic strategy for open liver resection, including acetaminophen and non-steroidal anti-inflammatory drugs, combined with thoracic epidural analgesia or bilateral oblique subcostal TAP blocks. Systemic opioids should be considered as rescue analgesics. Further high-quality RCTs are needed to confirm and clarify the efficacy of the recommended analgesic regimen in the context of an enhanced recovery program.

INTRODUCTION

Liver resection is increasingly performed on patients with benign tumors, liver metastases and hepatocellular carcinoma.¹ In addition, living liver donation constitutes an expanding field, given the well-known organ shortage.² Although variations exist, the most frequent approaches for open liver resection include the use of a right subcostal incision or a

reversed L-shaped incision.³ Therefore, liver resection irrespective of the approach can be associated with significant postoperative pain. Effective pain control can facilitate early mobilization and reduce postoperative complications.⁴ It has been emphasized that adequate pain management is a key to the success of an enhanced recovery after surgery (ERAS) program in liver resection.^{1,5}

However, the optimal pain management regimen for open liver resection remains controversial. Thoracic epidural analgesia (TEA) has traditionally been used for pain management after major open upper abdominal surgery; however, there are concerns of a coagulopathy after liver resection or intraoperative vascular clamping, preventing its intraoperative use.⁶ Moreover, the emphasis on early postoperative mobilization has reduced its use in recent years.^{1,5}

The Procedure-Specific Postoperative Pain Management (PROSPECT) Working Group is a collaboration of anesthesiologists and surgeons working to formulate procedure-specific recommendations for pain management after surgical procedures. These recommendations are based on procedure-specific literature review. The PROSPECT approach to develop guidelines is unique, such that the available evidence is critically assessed for current clinical relevance.⁷ In addition, the approach reports true clinical effectiveness by balancing the invasiveness of the analgesic interventions and the degree of pain after surgery, as well as balancing their efficacy and adverse effects.⁷

The aim of this review was to evaluate the available literature on the management of pain after open liver resection in adults regardless of the indication. Postoperative pain outcomes defined as pain scores and opioid requirements were the primary focus, but other recovery outcomes, including adverse effects, were also assessed, when reported, and the limitations of the data were reviewed. The ultimate aim was to develop recommendations for pain management after open liver resection.

METHODS

A review of randomized controlled trials (RCTs) and systematic reviews/meta-analyses published between January 2010 and October 2019 assessing analgesia after liver resection was performed



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using MEDLINE (PubMed), Embase and Cochrane databases. The search terms relating to pain interventions for open liver resections included (“hepatectomy” OR “hepatectomies” OR “liver resection” OR “liver resections” OR “hepatic resection” OR “hepatic resections” OR “hepatic lobectomy” OR “hepatic lobectomies” OR “living donor hepatectomy”) AND (“pain” OR “pains” OR “pain management” OR “postoperative pain” OR “VAS” OR “visual analog” OR “VRS” OR “verbal rating scale” OR “NRS” OR “numerical rating scale” OR “pain rating” OR “epidural” OR “neuraxial” OR “intrathecal” OR “paravertebral” OR “spinal” OR “infiltration” OR “nerve block” OR “neural block” OR “paravertebral block” OR “field block” OR “transversus abdominis plane block” OR “TAP block” OR “NSAID” OR “nonsteroidal anti-inflammatory” OR “non-steroidal anti-inflammatory” OR “COX-2” OR “paracetamol” OR “acetaminophen” OR “clonidine” OR “opioid” OR “ketamine” OR “corticosteroid” OR “gabapentin” OR “pregabalin”).

The RCTs that reported data pooled from patients undergoing simultaneous surgical procedures were excluded as were the RCTs evaluating combinations of different perioperative interventions such as studies comparing ERAS programs to conventional care, because the variability of definitions and protocols can make practical recommendations about a particular intervention impossible. Meta-analyses that reported data on mixed surgical procedures were only included when a subanalysis on liver resection was available.

Data extraction and data analysis adhered to the PROSPECT methodology (Online supplemental file 1).⁷ Pain intensity scores were used as the primary outcome measure. We regarded a change of more than 10 mm out of 100 mm on the Visual Analog Scale (VAS) or more than one out of 10 on a Numerical Rating Scale (NRS) as clinically relevant.⁸ Secondary outcomes included cumulative 24 hours of opioid requirements, other supplementary analgesic use, opioid-related adverse events and patient-related outcome measures.

Recommendations were made according to PROSPECT methodology.⁷ To be recommended, the intervention must be shown to be beneficial in at least two RCTs. Additionally, to ensure clinical relevance, the relevance to current perioperative practice was assessed. Likewise, we assessed if the analgesic intervention would improve postoperative pain relief and/or outcomes when added to the ‘basic analgesic regimen’ or would be beneficial if this regimen is not possible or is contraindicated. Furthermore, the balance between the invasiveness of the analgesic technique and the consequences of postoperative pain, as well as the balance between the analgesic efficacy and the adverse event profile of the analgesic technique, was considered. The opioid-sparing effects of acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) (termed as basic analgesic regimen) are well described for all surgical procedures.⁷ The PROSPECT group assessed if the addition of an analgesic intervention would further improve pain relief when combined with these simple, effective, non-opioid analgesics. Five questions about each recommendation were investigated: (1) Is the recommended intervention clinically relevant? (2) Does it add to the ‘basic analgesic technique’? (3) Does the balance between efficacy and adverse effects allow recommendation? (4) Does the balance between invasiveness of the analgesic intervention and degree of pain after surgery allow recommendation? (5) Are the reasons for not recommending an analgesic intervention appropriate?

The proposed recommendations were sent to the PROSPECT Working Group for review and comments, and a modified Delphi approach was used.⁷ The Delphi approach included rounds of individual comments followed by face-to-face discussions. Each

working group member responded to the questions posed to the subgroup leader, which were presented during the face-to-face meeting. This was followed by a discussion among members and a consensus was finally developed. The Delphi process resulted in complete agreement for recommendations we propose in the manuscript. Once a consensus was achieved, the lead authors drafted the final document, which was ultimately approved by the working group.

RESULTS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart demonstrating the search data is presented in [figure 1](#). A total of 125 studies assessing analgesic interventions were identified. Ultimately, 31 RCTs and 3 systematic reviews were included for the final qualitative analysis. The characteristics of the included studies are presented in [tables 1 and 2](#).

Preoperative interventions

Non-steroidal anti-inflammatory drugs

Two placebo-controlled RCTs investigated the effects of preoperative and postoperative administration of parecoxib with rescue analgesia provided by intravenous patient-controlled analgesia (PCA) opioid.^{9 10} Both studies reported significant pain relief and opioid sparing with parecoxib.^{9 10} Another RCT compared a combination of parecoxib with transversus abdominis plane (TAP) blocks with placebo and no TAP blocks reported significantly lower pain scores on postoperative days 1 and 2 in the study group.¹¹ Acetaminophen, as co-analgesic, was not used in any of these studies.

Intrathecal morphine

In one RCT, intrathecal morphine 400 µg reduced pain at rest for 30 hours and on coughing for 24 hours.¹² Pruritus was more frequent in the intrathecal morphine group.¹² Another RCT compared intrathecal morphine 400 µg with a continuous ropivacaine wound infusion.¹³ Pain scores at rest in the intrathecal morphine group were significantly reduced only for the first 12 hours. However, pain scores on coughing were similar between groups throughout the study period. No differences in side effects were reported.¹³ Basic analgesics like acetaminophen and NSAIDs were not administered in both RCTs.

Intraoperative interventions

Magnesium sulfate

A placebo-controlled study compared a loading dose of magnesium sulfate 30 mg/kg followed by a continuous infusion of 10 mg/kg/hour, showing significantly reduced pain scores and opioid requirements.¹⁴ Basic analgesics were not administered in the control group.

Alpha-2 adrenergic agonists

A placebo-controlled RCT reported that dexmedetomidine 0.5 µg/kg over 10 min before intubation followed by 0.3 µg/kg/hour reduced postoperative pain scores at rest for 8 hours, and on coughing for 48 hours.¹⁵

Interfascial plane blocks

Six RCTs focusing on the use of bilateral oblique subcostal TAP blocks with or without rectus sheath block were identified.¹⁶⁻²¹ Single-injection bilateral subcostal TAP block reduced pain at rest and with movement and reduced opioid use for 24 hours after surgery.¹⁶ Baseline analgesic consisted of acetaminophen every 6 hours.¹⁶ Another placebo-controlled RCT reported that

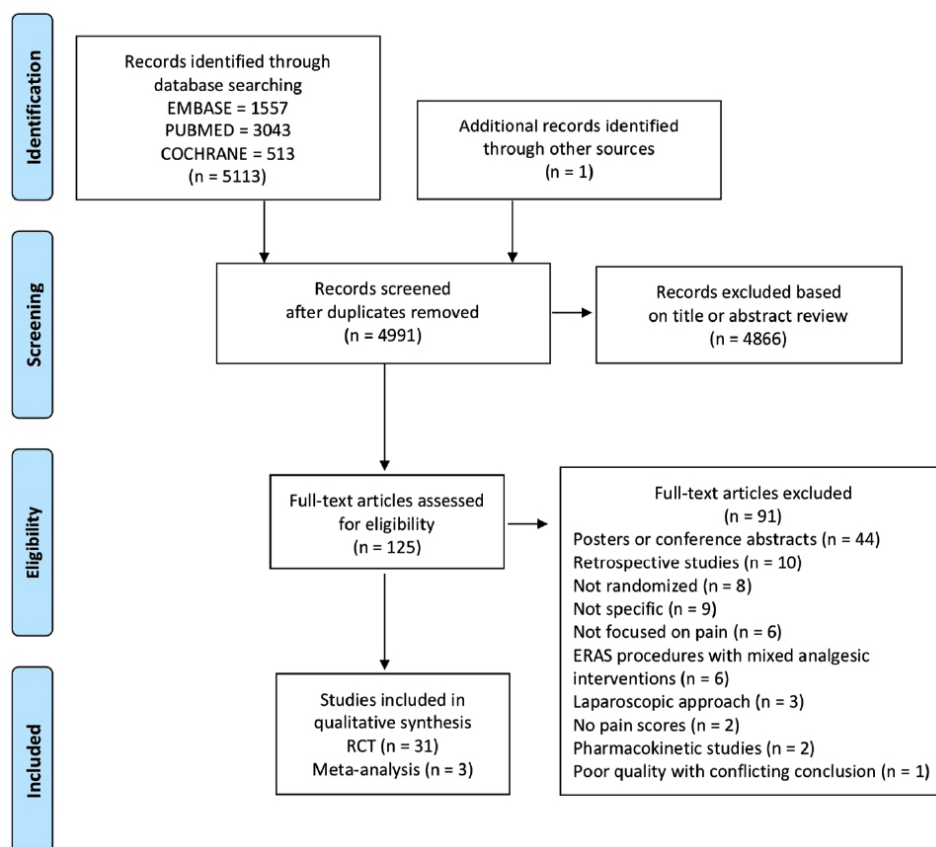


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. ERAS, enhanced recovery after surgery; RCT, randomized controlled trial.

single-injection bilateral oblique subcostal TAP blocks performed before the incision significantly reduced pain scores at rest at 2 and 4 hours.¹⁷ Baseline analgesia was provided with parecoxib and dexmedetomidine, with opioid as rescue analgesia.¹⁷

A placebo-controlled study reported that bilateral local anesthetic infusion via catheters placed in the medial TAP space and posterior rectus sheath both reduced pain scores at rest and with coughing and reduced opioid use for 3 days (ie, the duration of local anesthetic infusion).¹⁸ Baseline analgesic included celecoxib 200 mg two times per day.¹⁸ Bilateral TAP blocks with bupivacaine administered before surgery followed by postoperative boluses every 8 hours via catheters placed by the surgeon provided similar pain control at rest to the control group.¹⁹ However, pain on coughing was significantly lower in the TAP group during the first three postoperative days.¹⁹ Basic analgesics (ie, acetaminophen and/or NSAIDs) were not administered. Another placebo-controlled RCT evaluated the analgesic effects of bupivacaine administered 8 hours via catheters placed by the surgeon in the TAP space and rectus sheath space.²⁰ Pain scores and opioid use were reduced during the first two postoperative days in the intervention group. No basic analgesics were administered.

Local anesthetic infusion through catheters placed in the TAP space and the posterior rectus sheath was compared with TEA.²¹ The authors showed better pain control in the TEA group immediately after surgery and during the first postoperative day. After this period, differences in pain scores were less than 1/10 on a NRS. It should also be noted that the TEA group showed a relatively high rate of technical failure (20%) compared with the abdominal wall catheter group (7%). In one patient, a

deranged biochemical coagulation led to the delay of removal of the epidural catheter. Oral analgesics were mentioned but not specified.²¹

An RCT investigated the analgesic effects of the quadratus lumborum (QL) block with ropivacaine infusion and boluses, if needed. Intravenous NSAIDs were administered in both groups at the end of the surgery. Pain scores were lower in the QL block group at rest, but these results were only significant at 48 hours, and the significance was lower when assessed on movement for each time interval.²²

Paravertebral blocks

Compared with bilateral continuous paravertebral blocks (PVBs), TEA provided significantly lower pain scores at rest and on deep breathing up to the second postoperative day.²³ Of note, basic analgesics such as intravenous ketorolac or acetaminophen were only used based on the estimated need for supplemental analgesia rather than on a scheduled basis. A mild degree of coagulopathy developed in both groups with an increase in international normalized ratio (INR) and a decrease in platelet count, which was most pronounced on the second postoperative day. Although this did not result in a delay in catheter removal in the PVB group, in the TEA group, 3 out of 41 patients had a delay in catheter removal. None of the patients in both groups developed complications related to coagulopathy.²³ In a placebo-controlled study, continuous right thoracic PVB showed superior pain control at rest and with movement, as well as reduced opioid use on the first postoperative day.²⁴ No basic analgesics were used in this study.

Table 1 Summary of key results from studies evaluating analgesic interventions that are recommended in patients undergoing open liver resection

Study	Study design	Pain scores	Cumulative opioid dose	Basic and baseline analgesia
Preoperative interventions				
NSAIDs				
Wang <i>et al</i> ⁹	Procedure: open liver resection for hepatocellular carcinoma. Parecoxib intravenous 40 mg 30 min before induction followed by 40 mg every 12 hours for 48 hours after the operation (n=40) versus placebo (n=40).	VAS scores lower at rest at 2, 6, 12 and 24 hours in the parecoxib group; no difference at 48 hours. VAS scores during coughing significantly lower at 2, 6, 12, 24 hours in the parecoxib group, no difference at 48 hours. However, VAS difference at 12 and 24 hours is <1/10 (not clinically relevant).	Fentanyl intravenous-PCA consumption lower in the parecoxib group (reduction of about 8%).	No basic analgesia and no additional baseline analgesia.
Chen <i>et al</i> ¹⁰	Procedure: open liver resection for hemangioma. Parecoxib intravenous 40 mg before incision and two times per day for 3 days after surgery (n=28) versus placebo (n=28).	Parecoxib provided greater relief than placebo following liver resection with lower VAS scores at 30, 42 and 54 hours after surgery.	Sufentanil intravenous PCA consumption at 54 hours, as well as meperidine as pain supplement for insufficient analgesia, was lower in the parecoxib group than in the control group.	No basic analgesia and no additional baseline analgesia.
Qiao <i>et al</i> ¹¹	Procedure: open liver resection for hepatocellular carcinoma. Parecoxib intravenous 40 mg 30 min before induction (and every 12 hours for 72 hours)+TAP block (150 mg of 0.375% ropivacaine+5 mg dexamethasone) (n=51) versus placebo (n=49) before anesthesia induction without TAP block.	VAS pain scores in the parecoxib+TAP group were lower for POD 1-2-3 (not mentioned if resting/coughing). However, VAS difference between groups on POD 3 is not clinically relevant (<1/10).	Not mentioned.	No basic analgesia and no additional baseline analgesia.
Intraoperative interventions				
Interfascial plane blocks				
Kitlik <i>et al</i> ¹⁶	Procedure: open liver resection for living donation. US-guided bilateral subcostal TAP block (1.5 mg/kg bupivacaine diluted with saline to 40 mL volume) (n=25) versus no block (n=25).	VAS lower in the TAP group at 0, 2, 4, 6 and 24 hours both on rest and on movement. Difference in pain score always >1/10.	Morphine intravenous PCA consumption lower mean dose over 24 hours: 40 mg (TAP) vs 65 mg (non-TAP).	No basic analgesia and no additional baseline analgesia.
Guo <i>et al</i> ¹⁷	Procedure: open liver resection for hepatocellular carcinoma. US-guided bilateral subcostal TAP block (40 mL ropivacaine 0.375%) (n=35) versus placebo (n=35).	NRS at rest significantly lower at 2 hour (median NRS 2 (1-3) vs 2 (1-2)) and 4 hour (median NRS 2 (1-3) vs 1 (1-2)) postoperatively. NRS at coughing significantly lower at 2 hour, 4 hour, 12 hours and 24 hours but not 5 min after extubation.	Intraoperative and postoperative sufentanil dose significantly lower at extubation, 2 hour, 4 hour, 12 hours and 24 hours.	Basic analgesia: parecoxib 40 mg every 12 hours for 3 days. No additional baseline analgesia.
Karanicolas <i>et al</i> ¹⁸	Procedure: open liver resection for various indications. MOTAP: Surgical placed catheters (TAP and posterior rectus abdominis space); ropivacaine 0.2%, 2×20 mL at conclusion of surgery and 2×5 mL/hour for 72 hours (n=71) vs placebo (n=82).	NRS lower POD 0 until 3 (removal) at rest and movement (cough), higher proportion of patients with pain score of 'moderate' (defined as NRS score≥4/10) or higher at rest and when coughing. No difference in reported quality of pain control/satisfaction.	Reduced opioid requirements from 48 and at 72 hours.	Basic analgesia: celecoxib 200 mg every 12 hours. No additional baseline analgesia.
Serag <i>et al</i> ¹⁹	Procedure: open liver resection in patients with cirrhosis (child A). US-guided bilateral posterior TAP block (bupivacaine 0.375%, 15 mL on both sides, before skin incision)+bolus injections of bupivacaine 0.375% every 8 hours via surgical inserted TAP catheter (n=25) versus no TAP block (n=25).	Similar effective pain score at rest (VAS score<3). Lower pain score when coughing on POD 1-3.	Intraoperative fentanyl dose comparable in both groups, less fentanyl use in TAP+intravenous PCA group.	No basic analgesia and no additional baseline analgesia.

Continued

Table 1 Continued

Study	Study design	Pain scores	Cumulative opioid dose	Basic and baseline analgesia
Yassen <i>et al</i> ²⁰	Procedure: open liver resection in patients with cirrhosis (child A). Surgically placed catheters (TAP+RSP 0.2 mL/kg of bupivacaine 0.25% three times a day) (n=30) versus placebo (saline injection via catheter) (n=25).	On movement and early ambulation, VAS score for pain was reduced during the first two postoperative days in the TAP+RSP group. During rest, pain control was equally effective for both groups (VAS score≤3).	Fentanyl consumption was significantly lower on POD 1 and POD 2.	No basic analgesia and no additional baseline analgesia.
Bell <i>et al</i> ²¹	Procedure: open liver resection for various indications. Catheters in the TAP space and posterior rectus sheath, bolus 20 mL bupivacaine 0,5% followed by 4 mL/hour bupivacaine 0,25%+intravenous PCA (morphine/oxycodone based) for 60 hours postoperatively (n=42) vs EA (bupivacaine 0,15%+fentanyl 2 µg/mL 6–10 mL/hour) (n=41).	Median pain scores were worse in the CWI group than in the EA group on POD 0, afternoon of POD 1 and morning of POD 2 but not afterwards. However, the only clinical relevant difference in VAS score (>1/10) was noted on POD 0.	Not mentioned.	No basic analgesia and no additional baseline analgesia.
Epidural analgesia intraoperatively and postoperatively				
Fayed <i>et al</i> ²⁵	Procedure: open liver resection for hepatocellular carcinoma in patients with cirrhosis (child A). EA at T11–T12 (bupivacaine 0.125%+2 µg/mL fentanyl, 6 mL/hour, bolus 3 mL, lockout 15 min) (n=17) versus intravenous PCA (n=17) (fentanyl, bolus 15 µg, 10 min lockout, max 90 µg/hour).	Pain scores at rest similar for POD 0–3 Pain scores with coughing lower on POD 2 (difference<1/10) and POD 3 (difference>1/10) No difference in patient satisfaction.	More sedation on POD 1 in intravenous PCA and fewer PONV in EA (1/17 vs 3/17).	No basic analgesia and no additional baseline analgesia.
Qi <i>et al</i> ²⁶	Procedure: open liver resection. ERAS program with middle thoracic EA (local anesthetics and low-dose opioid, no more details) (n=80) versus conventional care without epidural (n=80)	Lower pain scores in the ERAS group Significantly higher satisfaction in the ERAS group.	Not mentioned.	Not mentioned.
Atalan <i>et al</i> ²⁷	Procedure: open liver resection for living donation. EA (L1–L2, confirmation with epiduroscopy, 10 mL bupivacaine 0.25%+50 µg fentanyl to achieve a sensorial block at T4, then starting an infusion of the same solution at 7 mL/hour before starting anesthesia and until end of operation)+TIVA (propofol only)+EA postoperatively (5 mL/hour) (n=33) versus TIVA (propofol–remifentanyl) and postoperative tramadol infusion (0.25 mg/kg bolus+0.15 mg/kg/hour) (n=33).	Lower VAS sore at the end of operation up to 24 hours. Pulmonary function tests were better protected with the use of EA, decreased anesthesia requirements (mean propofol dose) and reduced atelectasis score and better pain control (significantly lower VAS score). Total propofol dose, decrease in FEV1 and VAS at end of surgery were associated with atelectasis score, and atelectasis score was associated with LOS.	Not mentioned.	Not mentioned.
Hausken <i>et al</i> ²⁸	Procedure: open liver resection for colorectal metastasis. EA at T8–T9 (bupivacaine 1 mg/mL+fentanyl 2 µg/mL+epinephrine 2 µg/mL, at 5–15 mL/hour Bolus 5 mL, maximum of two per hour) (n=77) vs ketobemidone intravenous PCA (1 mg bolus, lockout 8 min, max 7 mg/hour)+ketorolac 30 mg every 8 hours+local wound infiltration (bupivacaine 0.5% 20 mL or 0.25% 40 mL) (n=66).	No difference in mean pain scores (NRS) for PODs 0–5 (1.7 (intravenous PCA) vs 1.6 (EA), non-inferiority). Lower pain scores (NRS) in EA versus intravenous PCA on POD 0 and POD 1, but higher or equal on PODs 2–5. Significantly less patients with severe pain (NRS score≥4) on POD 0 in EA, no significant difference afterwards.	Intravenous PCA group was associated with earlier discontinuation of pump and with lower consumption of MED. However, both groups received oral oxycodone and epidural fentanyl converted to MED as if intravenous fentanyl.	Basic analgesia: Acetaminophen 1 g every 6 hours. Baseline analgesia: oxycodone 10 mg every 12 hours from POD one to POD 2.

Continued

Table 1 Continued

Study	Study design	Pain scores	Cumulative opioid dose	Basic and baseline analgesia
Li <i>et al</i> ⁴⁰	Systematic review and meta-analysis. Intravenous PCA versus EA after open hepatic resection.	Pain scores at rest at 12 hours no difference, at 24 hours higher pain scores in intravenous PCA group (significant), at 48 hours no statistical significance. Pain scores at movement at 24 and 48 hours: no difference. At 2 and 12 hours: higher scores in the intravenous PCA group (but did not reach statistical significance).		NA

CWI, continuous wound infiltration; EA, epidural analgesia; ERAS, enhanced recovery after surgery; FEV₁, forced expiratory volume in 1 s; LOS, length of stay; MED, morphine equivalent dose; MOTAP, medial open transversus abdominis plane; NA, not applicable; NRS, Numerical Rating Scale; NSAID, non-steroidal anti-inflammatory drug; PCA, patient-controlled analgesia; POD, postoperative day; PONV, postoperative nausea and vomiting; RSP, rectus sheath plane; TAP, transversus abdominis plane; TIVA, total intravenous anesthesia; US, ultrasound; VAS, Visual Analogue Scale.

Continuous local anesthetic infusion in the surgical wound

Four RCTs compared the analgesic effect of continuous local anesthetics infusion via wound catheters (continuous wound infiltration (CWI)) versus saline infusion and one RCT compared CWI to intravenous analgesics. Of note, the catheters were placed at different anatomical planes. A double-blind placebo-controlled RCT found that local anesthetic infusion via a subfascial catheter reduced pain intensity after 6 hours until the second postoperative day; however, the differences were not clinically significant with both groups reporting low absolute pain scores (NRS score < 3/10).²⁵ There were no differences in opioid consumption either between the groups.²⁵ Baseline analgesia included intravenous NSAIDs and acetaminophen. Another similar study found that local anesthetic infusion through a subfascial catheter reduced opioid use but did not influence pain scores.²⁶ Basic analgesia consisted of acetaminophen and nefopam.²⁶ Yet another placebo-controlled RCT reported that local anesthetic infusion through two catheters placed—one in the subfascial plane and the other subcutaneously—resulted in significantly lower pain scores at rest at 8 and 16 hours but no difference on pain associated with movement.²⁷ The use of basic analgesics was not reported. CWI was associated with an accelerated recovery and discharge compared with placebo.²⁷ In another study, CWI via two multiorifice wound catheters buried in the musculofascial layer reduced pain at rest and during spirometry and reduced opioid use from 4 to 72 hours.²⁸

A three-arm study investigated local anesthetic infiltration of the skin and muscular layers followed by CWI, intravenous PCA fentanyl or intravenous tramadol. Compared with the intravenous tramadol group, wound infusion and intravenous PCA fentanyl groups had lower pain scores at 6, 12, 24 and 48 hours.²⁹ Compared with intravenous PCA fentanyl, wound infusion provided superior pain relief in the first 12 hours postoperatively. The use of basic analgesic was not mentioned.²⁹ Local anesthetic infiltration of the parietal peritoneum, fascia and subcutaneous planes improved pain control at rest and with movement for 12 hours postoperatively; however, the differences in pain scores were not clinically significant (ie, less than 1/10 on the NRS).³⁰ An opioid-sparing effect was also noted. Other analgesics were not used.³⁰

Two RCTs compared the analgesic effect of CWI to TEA provided for 48 hours after surgery. Pain scores were similar in both the groups at rest and with movement.³¹ Opioid use was higher in the CWI group until the first postoperative day but higher in the TEA group afterwards. Baseline analgesia was provided with intravenous acetaminophen. Time to functional recovery (ie, independent mobilization, eating and drinking and

need of intravenous fluids) was reduced in the CWI group.³¹ In another study, lower pain scores at rest and with movement were observed in the TEA group and opioid consumption was higher in the CWI group.³² All patients received intravenous acetaminophen if no concern for size or quality of the liver remnant existed.³²

Two meta-analyses evaluated the analgesic effects of TEA and CWI.^{33–34} A subgroup analysis of four RCTs (n=684 patients) for open liver surgery within a larger meta-analysis found lower pain scores in the TEA group at 2 hours at rest and at 12 hours with movement.³³ Another meta-analysis of three RCTs (n=240 patients) showed no significant difference in pain scores between the CWI and TEA groups on the first and third postoperative days.³⁴ However, the TEA analgesia group had lower pain scores on the second day after surgery. Opioid consumption was also reduced on the first postoperative day in the TEA group.³⁴ This meta-analysis incorrectly included a study²¹ comparing TEA analgesia with interfascial plane blocks (TAP and rectus sheath blocks) rather than CWI. Thus, the conclusions of this meta-analysis are questionable since it may overestimate the beneficial effect of CWI.

Thoracic epidural analgesia

Five RCTs^{35–39} and one meta-analysis⁴⁰ compared the analgesic effect of TEA with opioid intravenous PCA. The meta-analysis that included four RCTs (n=278 patients) demonstrated that, compared with opioid intravenous PCA, TEA provided superior pain relief at rest and with movement at 12 and 24 hours after surgery, with no significant difference in hospital length of stay (LOS).⁴⁰ Of the four RCTs included in the meta-analysis, two RCTs^{32–35} are also included in our review. Of note, the meta-analysis did not consider the use of basic analgesics in the included RCTs. The RCTs included in our review but not in the meta-analysis⁴⁰ also reported lower pain scores with TEA. One RCT compared TEA with ketobemidone (opioid) intravenous PCA combined with intravenous NSAIDs, while both groups received acetaminophen on a scheduled basis.³⁸ Another placebo-controlled RCT compared intraoperative TEA with sham epidural analgesia and intrathecal morphine (500 µg) and fentanyl (15 µg). Patients in the TEA group suffered less pain at rest and with movements, and demonstrated significantly lower opioid use.³⁹

Interpleural analgesia

Interpleural analgesia with levobupivacaine infusion reduced resting pain scores at 6 hours and movement-evoked pain for 24

Table 2 Summary of key results from studies evaluating analgesic interventions that are not recommended in patients undergoing open liver resection

Study	Study design	Pain scores	Cumulative opioid dose	Basic and baseline analgesia
Preoperative interventions				
Intrathecal morphine				
Ko <i>et al</i> ¹²	Procedure: open right liver resection for living donation. Intrathecal morphine 400 µg single preoperative injection (n=20) versus no intrathecal morphine (n=20).	Patients in the intrathecal morphine group had less pain at rest up to 30 hours and when coughing up to 24 hours.	Patients in intrathecal morphine group showed longer time to receive the first rescue meperidine (45.7±23 hours vs <1 hour). The amounts of supplementary meperidine (0 vs 175 mg) and fentanyl intravenous PCA (407.2 µg vs 594.8 µg) required were significantly less in the intrathecal morphine group. Cumulative consumption of meperidine and fentanyl until 72 hours was significantly less in the intrathecal morphine group.	No basic analgesia and no additional baseline analgesia.
Lee <i>et al</i> ¹³	Procedure: open right liver resection for living donation. CWI (bolus ropivacaine 0.75% 10 mL after catheter placement at the end of surgery followed by ropivacaine 0.5% 4 mL/hour for 72 hours) (n=19) versus intrathecal morphine (400 µg) preoperative+continuous intravenous fentanyl (15 µg/hour) postop (n=21)	During the first 12 hours, VAS score at rest was lower for the intrathecal morphine+intravenous fentanyl group. The VAS scores at rest thereafter were similar between the groups. The VAS scores with coughing were similar between the groups throughout the study time period.	Rescue intravenous fentanyl requirements were significantly higher in the CWI group during the first 24 hours after surgery, but they became similar to the requirements in the intrathecal morphine/intravenous fentanyl group 24–28 hours and 48–72 hours after surgery.	No basic analgesia and no additional baseline analgesia.
Intraoperative interventions				
MgSO₄				
Mahmoud <i>et al</i> ¹⁴	Procedure: open liver resection for living donation. Intraoperative MgSO ₄ infusion (30 mg/kg bolus followed by 10 mg/kg infusion until the end of surgery) in living liver donors (n=25) versus placebo (n=25)	Postoperative VAS lower in the MgSO ₄ group (1.2 vs 3.8).	Postoperative fentanyl intravenous PCA requirement lower (70 µg/hour vs 114 µg/hour).	No basic analgesia and no additional baseline analgesia.
Dexmedetomidine				
Zhang <i>et al</i> ¹⁵	Procedure: open liver resection. Dexmedetomidine (0.5 µg/kg loading dose, 0.3 µg/kg/hour during surgery) combined with postoperative oxycodone+dexmedetomidine intravenous PCA (n=26) versus placebo (n=26) during surgery, postoperative oxycodone intravenous PCA alone.	VAS scores lower in the dexmedetomidine group at rest at 1, 4 and 8 hours postoperatively. VAS scores lower in the dexmedetomidine group at coughing at 24 and 48 hours postoperatively.	Postoperative consumption of oxycodone intravenous PCA was lower in the dexmedetomidine group at 4, 8, 12, 24 and 48 hours. Also, rescue analgesics requirement (parecoxib and tramadol) in PACU higher in the control group (34.62% vs 11.54%).	No basic analgesia and no additional baseline analgesia.
QL blocks				
Zhu <i>et al</i> ²²	Procedure: open liver resection. US-guided continuous QL block (ropivacaine 0.4% 0.6 mL/kg, then a catheter is placed: ropivacaine 0.2%, continuous infusion at 5 mL/hour, bolus 5 mL, 15 min lockout, max 20 mL/hour max) (n=32) versus no continuous QL block (n=31).	Pain scores (NRS) at rest lower in the QL block group but only significant at 48 hours postoperatively. Pain scores (NRS) at movement lower in the QL block group at all times.	No significant difference in the postoperative self-administered analgesic dose.	Basic analgesia: flurbiprofen 100 mg at the end of surgery. No additional baseline analgesia.
Paravertebral nerve blocks				
Schreiber <i>et al</i> ²³	Procedure: open liver resection. EA (5–8 mL/hour ropivacaine 0.2%, bolus 3 mL/hour) (n=41) versus continuous bilateral PVB (n=39) (T7, 15 mL ropivacaine 0.5% bolus each side, followed by 7–12 mL/hour ropivacaine 0.2% each side, bolus 3 mL each side/hour) during 3 days for open liver resection. The infusions were started after resection, before emergence.	VRS lower at rest and during deep inspiration at 24 and 48 hours in the EA group at 48 hours (not clinically relevant at 24 hours, with VAS difference<1/10).	Hydromorphone intravenous PCA until at least POD 3; no difference in opioid administration, no difference in acetaminophen, ketorolac or ketamine-infusion in both groups.	Basic analgesia: acetaminophen and ketorolac. Baseline analgesia: ketamine infusions were used by intraoperative practitioners or added by the acute pain service, but according to those practitioners preference.

Continued

Table 2 Continued

Study	Study design	Pain scores	Cumulative opioid dose	Basic and baseline analgesia
Chen <i>et al</i> ²⁴	Procedure: open right liver resection. Continuous right thoracic PVB (T7, ropivacaine 0.2% 10 mL bolus, 6 mL/hour for 24 hours) (n=24) versus placebo (n=24) infusion; first bolus before emergence.	Pain scores (NRS) lower on rest and coughing in the PVB group for each time point but not clinically relevant (VAS difference>1/10) at rest at 24 hours.	Lower cumulative consumption of sufentanil (54.3 µg/24 hours vs 68.1 µg/24 hours).	No basic analgesia and no additional baseline analgesia.
Wound infiltration				
Dalmau <i>et al</i> ²⁵	Procedure: open liver resection. CWI (ropivacaine 0.23% 10 mL bolus, 5 mL/hour for 48 hours) (n=53) versus placebo (n=46) infusion.	Pain scores (NRS) were lower in the CWI group with significance after 6 hours until POD 2 but not clinically significant (VAS difference between groups<1/10).	No difference in morphine consumption.	Basic analgesia: dextropropofen and acetaminophen. No additional baseline analgesia.
Peres-Bachelot <i>et al</i> ²⁶	Procedure: open liver resection for liver metastasis. CWI with ropivacaine 0.375%, 40 mL bolus followed by 8 mL/hour for 96 hours (n=42) vs placebo (n=43) infusion.	Non-significantly lower pain score (VAS) in the CWI group.	Less morphine consumption (0.5 mg/kg less) on PODs 1 and 2, no significant difference on PODs 3 and 4. Total median requirements of acetaminophen was reduced but no difference in total median nefopam requirements.	Basic analgesia: acetaminophen 1 g at the end of surgery. No additional baseline analgesia.
Xin <i>et al</i> ²⁷	Procedure: open liver resection. CWI with ropivacaine 0.5%, 20 mL via two catheters 10 min before end of surgery in both groups. On arrival in PACU: ropivacaine 0.3% 2 mL/hour per catheter (=4 mL/hour) for 48 hours (n=20) vs control: saline 4 mL/hour for 48 hours (n=20)	Lower pain score at rest at 8 and 16 hours. No difference in pain score on movement.	Lower sufentanil consumption. Despite increased use of sufentanil in the saline group, no difference in sedation score after 16 hours.	No basic analgesia and no additional baseline analgesia.
Chan <i>et al</i> ²⁸	Procedure: open liver resection. CWI with ropivacaine 0.25% bolus 20 mL at the end of the surgery then 4 mL/hour via two multiorifice catheters placed within the musculofascial layer before skin closure for 68 hours (n=22) vs placebo (n=22).	Ropivacaine group had less pain at rest at 4–72 hours and after spirometry at 4–72 hours.	Ropivacaine group had reduced mean total morphine consumption (58 vs 86 mg).	No basic analgesia and no additional baseline analgesia.
Wu <i>et al</i> ²⁹	Procedure: open liver resection for hepatocellular carcinoma. CWI with ropivacaine 0.25%, 50 mL infiltration followed by ropivacaine 0.25%, 5 mL/hour (n=20) vs fentanyl+tropisetron intravenous PCA 24–30 µg/hour, bolus 6–7.5 µg, lockout 15 min, for 2 days (n=20) versus control with tramadol intravenously according to NRS (n=20).	NRS scores at 6, 12, 24 and 48 hours in both CWI and intravenous PCA groups were significantly lower than those in the control group. NRS scores at 6 and 12 hours lower in the CWI group than those in the intravenous PCA group.	Not mentioned. PONV lower in the CWI group than in the intravenous PCA, no difference between CWI and control.	No basic analgesia and no additional baseline analgesia.
Sun <i>et al</i> ³⁰	Procedure: open liver resection. Surgical wound infiltration (ropivacaine 0.75% 20 mL) (n=26) versus placebo (n=27).	Lower VAS scores at 0, 6 and 12 hours postoperative in the intervention group at rest and movement but not clinically relevant (difference in mean VAS score<1/10 at all time).	Sufentanil consumption lower at 6, 12, 24 and 36 hours.	No basic analgesia and no additional baseline analgesia.
Hughes <i>et al</i> ³¹	Procedure: open liver resection. Surgically placed catheters (TAP+posterior rectus abdominis space; 40 mL 0.125% L-bupivacaine on closure, elastomeric reservoir 0.375% L-bupivacaine 4 mL/hour for 48 hours) (n=49) versus EA (T8–T9, 10 mL L-bupivacaine+100 µg fentanyl epidural loading and infusion 0.1% L-bupivacaine+2 µg/mL fentanyl for 48 hours) (n=48).	Pain scores (NRS) were not significantly different at rest nor on movement. No difference in pain score (NRS), but advantage of CWI in recovery time over EA.	Intraoperative and postoperative opioids (converted to MED); opioid consumption was greater in the CWI group up to POD 1; thereafter, EA received a significantly greater amount of opioids.	Basic analgesia: acetaminophen 1 g every 6 hours on PODs 1 and 2. No additional baseline analgesia.
Revie <i>et al</i> ³²	Procedure: open liver resection. CWI+PCA (at the end of the surgical procedure, infiltration with 20 mL L-bupivacaine 0.25% then L-bupivacaine 0.375% 4 mL/hour over 48 hours) (n=33), vs EA at T7–T8 peroperatively bupivacaine 0.1% 7–10 mL/hour+fentanyl 2 µg/mL (n=32).	Pain scores lower in the EP group at rest. Pain scores lower in the EA group with movement. Median pain scores at rest in both groups equally mild.	Opioid use greater in the CWI group as opioid PCA was routine in this group.	Basic analgesia: standardized enhanced recovery protocol; acetaminophen every 6 hours (except if concern regarding remnant liver). POD 2: addition of ibuprofen 400 mg every 8 hours. No additional baseline analgesia.

Continued

Table 2 Continued

Study	Study design	Pain scores	Cumulative opioid dose	Basic and baseline analgesia
Li <i>et al</i> ³³	Meta-analysis on open abdominal surgeries (subanalysis for open liver resection): EA versus CWI.	Significantly lower pain scores in EA at 2 hours on rest and 12 hours on mobilization than those in the CWI group after liver surgery.	Not mentioned.	NA
Gavriilidis <i>et al</i> ³⁴	Meta-analysis on open liver resection: CWI versus EA.	No statistically significant difference in pain scores between groups on PODs 1 and 3, but on POD 2, patients with had lower pain scores.	On POD 1, patients with EA had significantly lower opioid consumption. On PODs 2 and 3, patients who had CWI had significantly lower opioid consumption.	NA
Epidural analgesia with local anesthetics alone, only used intraoperatively				
Mondor <i>et al</i> ³⁹	Procedure: open liver resection. Epidural T7–T8 or T8–T9 with local anesthetics without opioids (bupivacaine 0.5%: first bolus of 3 mL followed by an infusion of 3 mL/hour intraoperatively then a bolus of 3 mL at the end of the surgery, before the catheter was removed) (n=22) vs placebo sham epidural (n=21).	VAS score at rest lower in the epidural group. However, the difference was only clinically relevant at 6, 9, 24 and 36 hours (not at 12, 18 and 48 hours). VAS with movements lower in the epidural group and the difference was clinically relevant at each time interval.	The sham group used twice as much morphine as the epidural group.	No basic analgesia. Baseline analgesia: intrathecal morphine 500 µg+intrathecal fentanyl 15 µg before the surgery.
Interpleural analgesia				
Weinberg <i>et al</i> ⁴¹	Procedure: open liver resection. Interpleural analgesia with a 20 mL loading dose of L-bupivacaine 0.5% at the end of the surgery, followed by a continuous infusion of L-bupivacaine 0.125%+multimodal analgesia (n=25) vs multimodal analgesia with morphine intravenous PCA (n=25).	During the first 24 hours postoperatively, the only significant difference in resting pain scores between the groups was found at 6 hours. However, pain intensity using the VAS score was less on movement in the interpleural group compared with the intravenous PCA group for the first 24 postoperative hours. The greatest difference in VAS score on movement was also found at 6 hours postoperatively where the mean VAS score on movement was 42 mm in the interpleural group and 61 mm in the intravenous PCA group (difference 18 mm, 95% CI 4 to 32 mm, adjusted). At 24 hours postoperatively, mean (SD) VAS scores during movement remained lower in the interpleural group compared with the intravenous PCA group 44 (22) mm vs 51 (18) mm, respectively). However, after 48 hours, VAS score for pain at rest and during movement was similar in both groups.	At 24 hours postoperatively, the cumulative mean morphine consumption was similar in the groups.	Basic analgesia: acetaminophen 1 g every 6 hours for the first 24 hours.
Postoperative interventions				
NSAIDs started after completion of the surgery				
Yassen <i>et al</i> ⁴²	Procedure: open right liver resection for living donation. Ketorolac 15 mg over 30 min after surgery+48-hour infusion (60 mg ketorolac/240 mL saline=250 µg/mL, 50 µg/kg/hour) (n=28) vs placebo (saline) over 30 min after surgery+48 hour infusion (240 mL saline) (n=29).	VAS pain scores were lower in the ketorolac group compared with the placebo group starting from 6 to 36 hours.	Daily doses of fentanyl were lower in the ketorolac group at 24 and 48 hours.	No basic analgesia and no additional baseline analgesia.

CWI, continuous wound infiltration; EA, epidural analgesia; MED, morphine equivalent dose; MgSO₄, magnesium sulfate; NA, not applicable; NRS, Numerical Rating Scale; NSAID, non-steroidal anti-inflammatory drug; PACU, postoperative care unit; PCA, patient-controlled analgesia; POD, postoperative day; PONV, postoperative nausea and vomiting; PVB, paravertebral block; QL, quadratus lumborum; TAP, transversus abdominis plane; US, ultrasound; VAS, Visual Analog Scale; VRS, Verbal Rating Scale.

hours after surgery.⁴¹ Baseline analgesia included acetaminophen in both groups.⁴¹

Postoperative interventions

A placebo-controlled RCT evaluated the analgesic effects of intravenous ketorolac initiated postoperatively for 48 hours, and found lower pain scores and an opioid-sparing effect from 6 until 36 hours after surgery.⁴²

DISCUSSION

This review aimed to synthesize the available evidence on procedure-specific pain management after open liver resection. We found analgesic efficacy for NSAIDs as basic analgesics administered preoperatively or intraoperatively and then continued postoperatively on the 'round-the-clock' or scheduled basis. No study investigated the analgesic efficacy of acetaminophen in liver resection, although given its relative safe profile and the few side effects, it is considered as basic (ie, first-line) analgesic according to the PROSPECT methodology.⁷ There is a concern of potential toxicity of acetaminophen due to possible impaired hepatic metabolism after liver resection. Nevertheless, acetaminophen was used as basic analgesic in several RCTs included in this review. A prospective case-control study investigated the glutathione and urinary acetaminophen metabolite levels after liver resection when acetaminophen was administered in a dose of 1 g four times a day.⁴³ Residual liver volume was inversely correlated with postoperative urinary metabolite levels; however, no glutathione deficiency occurred.⁴³ The risk factors for hepatotoxicity that should be considered before using acetaminophen include liver disease, age, malnutrition and intraoperative liver ischemia. The altered pharmacokinetics in patients with liver disease or after major liver resections might influence the acetaminophen dose.^{44 45} Overall, there is a low risk of acetaminophen toxicity after liver resection, and therefore, it is recommended as basic analgesic. Of note, the use of non-opioid analgesics is important in patients undergoing liver resection because it may influence opioid pharmacokinetics and thus may lead to opioid overdose.⁴⁵

In addition to basic analgesics (ie, acetaminophen and NSAIDs), regional analgesic techniques such as TEA and subcostal TAP blocks were also found to be effective. Several studies confirmed the analgesic efficacy of TEA typically administered in the postoperative period, particularly during coughing and deep breathing. The limitations with TEA in patients undergoing liver resection include concerns of epidural hematoma and subsequent catastrophic neurological injuries or unplanned delays in postoperative removal of the epidural catheter due to coagulopathy and the avoidance of intraoperative use due to the potential hemodynamic effects of vascular clamping, as well as the concerns of delaying patient mobilization in the context of ERAS pathways. In fact, a large (n=68 028) retrospective analysis of an administrative database found that the use of TEA for major liver resection is very low (approximately 6%).⁴⁶ The propensity-matching technique showed that TEA did not seem to influence the incidence of postoperative complications, although it was associated with an increased use of blood transfusions and a longer hospital LOS in this particular population who had undergone major liver resection.⁴⁶

The risk of spinal hematoma after epidural analgesia remains a matter of debate.^{47 48} After liver resection, coagulation disorders may develop, leading to concerns regarding the safety of removing the epidural catheter.⁴⁹ The most important identified factors to predict hemostatic alterations are the preoperative

liver dysfunction, the Model for End-Stage Liver Disease score, and the extent and mass of resected liver tissue.⁶ Nevertheless, we note that one RCT investigating TEA³⁵ was carried out in child A cirrhotic patients who do not show an alteration in basic coagulation tests. Of note, in patients with liver disease, an elevated INR does not necessarily predict an increased risk of bleeding. Indeed, the complex interplay of fluctuating procoagulants and anticoagulants leads often and paradoxically to a prothrombotic state.⁵⁰ Nevertheless, caution should be exercised and the benefits versus harm must be carefully evaluated in this particular population. Yet, for a large number of hepatic resections and especially in the case of living donation or resection of metastases in healthy patients, TEA seems safe.⁵⁰

Another concern of TEA includes delayed ambulation due to orthostatic hypotension or cumbersome equipment. However, some evidence suggests that TEA can be integrated into ERAS pathways, and its effects on attenuating the stress response to surgery and reducing postoperative pain may outweigh the other limitations.⁵⁰ A recent study reported reduced risk of respiratory complications and shorter hospital LOS in patients receiving TEA.⁵¹ Furthermore, TEA allows opioid-sparing and improves gastrointestinal function.^{52 53} Also, TEA may reduce intraoperative blood loss,⁵⁴ given the associated sympathetic blockade and vasodilatation which may reduce central venous pressure.⁵⁰ Nevertheless, in order to attain enhanced recovery with TEA, it is imperative that the level of insertion of the epidural catheter (mid-thoracic) and the doses of local anesthetics must be carefully chosen so as to adequately cover the surgical incision site without causing motor blockade.⁵⁰ Thus, the benefits of TEA may be achieved when used intraoperatively as well as postoperatively, as practiced in five included RCTs.^{21 35-38}

Interfascial plane blocks (eg, subcostal TAP blocks, QL blocks and erector spinae blocks) administered as single shot injection or as continuous local anesthetic infusion have been shown to be efficacious in several RCTs. Most of the studies of interfascial plane blocks related to subcostal TAP blocks with or without rectus sheath block, while only one study investigated QL blocks. QL blocks are gaining more attention recently and have been validated in numerous abdominal surgeries.⁵⁵ A recent meta-analysis reported the superiority of QL blocks over TAP blocks,⁵⁶ but head-to-head comparison between these two techniques in liver resection is lacking. Newer ultrasound-guided interfascial plane blocks (eg, erector spinae plane blocks) that provide abdominal wall analgesia are increasingly being developed⁵⁷; however, more procedure-specific evidence is necessary before they can be recommended. Therefore, at least for now, only subcostal TAP blocks should be considered. To cover the entire surgical incision, these TAP blocks should be performed bilaterally and local anesthetics should be distributed in a subcostal and lateral approach. Since there are no studies comparing the continuous infusion of local anesthetics via catheters placed in the TAP space to a single-shot infiltration, we cannot give preference to one or the other technique.

With interfascial plane blocks, especially with continuous infusion technique, typically larger total volumes of local anesthetic are used. Given the fact that all of the currently used local anesthetics are metabolized by the liver and are highly protein bound, the possible effects of liver disease and liver surgery should be taken into account. In a double-blinded, randomized, placebo-controlled trial, the authors developed a pharmacokinetic model for ropivacaine after TAP blocks in patients undergoing hepatectomy.⁵⁸ Interestingly, although the free ropivacaine clearance decreased by 53% when three or more liver segments were resected, toxic concentration threshold was never exceeded.

Box 1 Analgesic interventions that are recommended for pain management in patients undergoing open liver resection

Preoperative/intraoperative

- ▶ Acetaminophen.
- ▶ Non-steroidal anti-inflammatory drugs (NSAIDs).
- ▶ Thoracic epidural analgesia.
- ▶ Subcostal transversus abdominis plane blocks (single shot and/or continuous local anesthetic infusion).

Postoperative

- ▶ Acetaminophen and NSAIDs.
- ▶ Catheter-based regional analgesia technique chosen in the preoperative/intraoperative period.

Given the low extraction ratio for ropivacaine, altered metabolic function and protein binding after liver surgery appears to be more important than reduction of liver blood flow. The authors showed a higher total concentration of ropivacaine on the second postoperative day; however, the unbound ropivacaine concentration remained in the same range or was lower on the second postoperative day when more or less than three segments were resected, respectively. Although direct measurements of α_1 -acid glycoprotein were not performed, the increase in binding site concentration can be explained by a postoperative increase in this specific protein, which is the most important binding protein for local anesthetics. Since toxicity correlates with the unbound rather than the total local anesthetic concentration, these findings suggest that classical dosing of local anesthetics, even after major liver surgery, seems safe. Of note, the authors used a weight-based dosing regime in which a dose ropivacaine of 3 mg/kg was administered as a bolus every 12 hours for 48 hours via a catheter in the TAP space. Although the absolute quantity of infused ropivacaine is in the same range of the doses of ropivacaine in the TAP blocks evaluated in the studies in our review, the dosing regime is fundamentally different (bolus vs continuous infusion), thus potentially limiting the generalizability of these results. Apart from ropivacaine, many authors in the studies in this review used levobupivacaine as a long-acting local anesthetic. Studies investigating the pharmacokinetic profile of this specific local anesthetic in liver surgery are currently lacking. Although the distribution and elimination profile of ropivacaine and levobupivacaine are comparable, further research is necessary to confirm adequate dosing of long-acting local anesthetics

Table 3 Analgesic interventions that are not recommended for pain management in patients undergoing open liver resection

Intervention	Reason for not recommending
Ketamine	Lack of procedure-specific evidence
Gabapentinoids	Lack of procedure-specific evidence
Intravenous lidocaine	Lack of procedure-specific evidence
Dexamethasone	Lack of procedure-specific evidence
Intraoperative use of dexmedetomidine	Limited procedure-specific evidence
Intraoperative use of magnesium sulfate	Limited procedure-specific evidence
Intrathecal morphine	Limited procedure-specific evidence
Quadratus lumborum block	Limited procedure-specific evidence
Continuous wound infiltration	Limited procedure-specific evidence
Continuous paravertebral nerve block	Limited procedure-specific evidence
Postoperative intrapleural local anesthetics	Limited procedure-specific evidence

in liver surgery. Of note, local anesthetic toxicity occurred in none of the RCTs.

Of course, the choice of TEA versus interfascial plane blocks would depend on the potential concerns with TEA as described previously and the anesthesiologists' familiarity with the techniques.

Compared with placebo, surgical wound infiltration only demonstrated analgesic effects in the absence of basic analgesia (ie, acetaminophen and NSAIDs). Furthermore, in an RCT lacking basic analgesia,²⁷ the analgesic effect of the continuous infusion of local anesthetics was only demonstrated during the first sixteen postoperative hours. Therefore, we do not recommend routine use of CWI; however, it may be considered as a second-line regional analgesic technique, when TEA and interfascial plane blocks (ie, subcostal TAP blocks) are not possible. Of note, it is critical to recognize that, depending on the mass of liver resected, the pharmacokinetic characteristics of local anesthetics may be impaired, which may increase the potential for systemic local anesthetic toxicity. Specific studies investigating the pharmacokinetics of CWI after liver surgery are currently lacking.

Two RCTs reported reduced pain with intrathecal morphine. One RCT compared intrathecal morphine with no treatment,¹² while the other RCT compared its use with continuous local anesthetic wound infusion.¹³ It should be noted that the dose of morphine used in both RCTs was high (ie, 400 μ g), which increases the risk of adverse events such as pruritus and respiratory depression. Also, the RCTs of intrathecal morphine did not use basic analgesics. Taken together, intrathecal morphine could not be recommended. There was insufficient procedure-specific evidence to support the use of magnesium and dexmedetomidine since only one included RCT investigated each intervention. Similarly, there was insufficient evidence for PVBs and interpleural analgesia. There was lack of evidence of gabapentinoids, intravenous lidocaine infusion, intravenous ketamine infusion and corticosteroids.

The limitations of this review are related to those of the included studies. There was considerable heterogeneity between studies, such as variable dosing regimens, variable methods of administration, a variable use of analgesics in the control groups, as well as variable time points of pain measurement. Many of the included studies suffered from small sample size and therefore it is hard to draw firm conclusions regarding the side-effect profile of the proposed interventions. In addition, most RCTs did not include basic analgesics (ie, acetaminophen and NSAIDs) in the control group, thus making it difficult to determine if the positive efficacy of the analgesic interventions studied would yield the same results when combined with basic analgesics. Furthermore, while the PROSPECT initiative promotes multimodal, non-opioid analgesic strategies and modern perioperative care, only few studies applied the multimodal analgesia or ERAS pathways.⁷ Future adequately powered studies should assess analgesic interventions in comparison with basic analgesics, as well as assess side effects of analgesic interventions, and it would be optimal if the role of analgesic interventions was assessed in the context of ERAS programs.

In recent years, minimally invasive approaches (eg, laparoscopic approach) are increasingly being used because they are associated with reduced pain and enhanced postoperative recovery. In carrying out this review, we also initially assessed the publications relating to minimally invasive approaches such as laparoscopic approach. Unfortunately, there were only a few (ie, three RCTs) publications investigating these surgical approaches and meeting the inclusion criteria, which are too few to draw

any relevant conclusions. Nevertheless, similar to other surgical procedures⁵⁹ performed through laparoscopic approaches, basic analgesics (eg, acetaminophen and NSAIDs) and infiltration of surgical incision or interfascial plane blocks may be adequate. In contrast, although TEA provides excellent pain relief after 'open' liver resection, its role in laparoscopic approach is questionable.

In summary, this review identified an analgesic regimen for optimal pain management after open liver resection, which is listed in **box 1**. We suggest perioperative pain management for liver resection to include, unless contraindicated, acetaminophen and an NSAID administered either preoperatively or intraoperatively and continued postoperatively. In the absence of contraindications, either TEA or bilateral subcostal TAP blocks are recommended. Systemic opioids should be reserved as rescue analgesics in the postoperative period. In addition, we also identified analgesic interventions that are not recommended for pain management in patients undergoing open liver resection, listed in **table 3**. Future high-quality studies are needed to clarify the efficacy of recommended approaches in the context of an enhanced recovery pathway.

Author affiliations

¹Department of Anesthesiology, Cliniques universitaires Saint-Luc, Bruxelles, Belgium

²Department of Cardiovascular Sciences, KULeuven, Leuven, Belgium

³Anesthesia and Intensive Care Department, University of Rennes, CHU Rennes, Inserm, INRA, CIC 1414 NuMeCan, Rennes, France

⁴Department of Surgery, DIAKO Ev. Diakonie-Krankenhaus, Bremen, Germany

⁵Department of Anesthesiology, Intensive Care Medicine and Pain Therapy, University Hospital Münster, Münster, Germany

⁶Department of Anesthesiology and Pain Management, University of Texas, Southwestern Medical Center, Dallas, Texas, USA

⁷Department of Anesthesiology, UZ Leuven, Leuven, Belgium

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ORCID iD

Audrey Dieu <http://orcid.org/0000-0002-6026-1734>

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APPENDIX :

PROSPECT working group

G.P. Joshi, E. Pogatzki-Zahn, M. Van de Velde, S. Schug, H. Kehlet, F. Bonnet, N. Rawal, A. Delbos, P. Lavand'homme, H. Beloeil, J. Raeder, A. Sauter, E. Albrecht, P. Lirk, S. Freys and D. Lobo.

PROSPECT METHODOLOGY

1. Once the Working Group identifies the surgical procedure (new or update) to be reviewed, a subgroup will be selected. The subgroup consists of at least two members of the Working Group and co-opted external members as required (e.g., surgeons and/or anesthesiologists) with specific expertise in the surgical procedure to be reviewed. In addition, specialists in literature searches and/or data analysis may also be included in the subgroup. The subgroup may also include research fellows assisting with the project.
2. For new procedures, a 10-year period is chosen because it more likely resembles relevant clinical practice given that rapid changes occur in peri-operative care including surgical techniques, although older studies may be included if considered currently clinically relevant. For updates, the literature search will be from the end date of the previous review.
3. The review process begins with a systematic search for literature specific to peri-operative pain management for the selected procedure in accordance with the preferred reporting items for systematic review and meta-analysis protocols (PRISMA) recommendations
4. Inclusion/exclusion criteria: RCTs and systematic reviews of analgesic, anesthetic, and surgical interventions, published in the English language, addressing pain management relating to the surgical procedure being reviewed. In addition, included RCT's should report pain scores (e.g, visual analogue scale, verbal or numerical rating scale). The RCTs that reported data pooled from patients undergoing simultaneous surgical procedures are excluded as are the RCTs evaluating combinations of different perioperative interventions such as studies comparing ERAS programs to conventional care, because the variability of definitions and protocols can make practical recommendations about a particular intervention impossible. Meta-analyses that reported data on mixed surgical procedures are only included when a sub-analysis on the surgical procedure studied is available.
5. A PRISMA flow chart is utilised to present the results of the search data, records screened, records excluded with reasons for exclusion and studies included in the qualitative analyses.
6. Once the studies for inclusion are finalized, the excluded studies will be tabulated with reasons for exclusion.
7. The included studies are stratified by the timing of the intervention (preoperative, intraoperative, and postoperative), and are then further categorised into the type of intervention: analgesic (systemic analgesics, analgesic adjuncts, and regional analgesia techniques) and anaesthetic, or non-

pharmacological interventions. The studies assessing the effects of surgical techniques on analgesic outcomes will be grouped separately.

8. The subgroup prepares a draft table of the recommendations of analgesic, anesthetic or surgical interventions based upon the following considerations.
 - To be recommended the intervention must be beneficial in at least two RCT's
 - Consider if the differences in pain scores between the groups are clinically relevant (i.e., differences should be 1/10 cm or 10/100 mm on the VAS or 1/10 point on NRS/VRS)
 - Determine if the analgesic intervention would further improve postoperative pain relief and/or outcome when added to the "basic" analgesic regimen (acetaminophen, NSAIDs, COX-2 inhibitors) Alternatively, previously recommended interventions may be considered as "basic" analgesia (e.g., acetaminophen + NSAIDs + trocar site local infiltration for laparoscopic cholecystectomy etc.)
 - Determine if the intervention would be beneficial if basic regimen was not possible or was contraindicated.
 - Consider the relevance of intervention in current clinical practice with respect to the anesthetic/analgesic technique.
 - Consider balance between the invasiveness of the analgesic technique and consequences of pain
 - Consider balance between the analgesic efficacy and adverse event profile of the intervention [adverse effects are identified through an extensive literature search, which may not be procedure-specific; however, the risks are adjusted for the procedure being evaluated. Case-control studies and cohort studies or observational studies can be used to determine adverse effects of analgesic interventions].
 - Confirm that the reasons for not recommending an analgesic intervention are appropriate.
 - Relevant patient characteristics (e.g. opioid tolerance and psychiatric comorbidities) may be included to ensure not only procedure-specific but also patient-specific aspects of pain management are taken into consideration.
9. A modified Delphi process which consists of several rounds of communication will be used.
 - First round: each Working Group member will email their comments to the subgroup leader but not to the whole Working Group.
 - Second round: will occur at the face-to-face/virtual meeting during which one of the members of the subgroup, as determined by the subgroup leader, will briefly present the evidence and reasons for recommendations and non-recommendations as well as the collated results from the first Delphi round.
 - The Working Group will discuss and recommendations may be modified, if necessary, and attempt to achieve a consensus. The members will then vote for the second time. This voting may be open or anonymous as determined by the Group.

- The Delphi process will run for up to 3 rounds. In the absence of consensus, the percentage of agreement will be included in the final manuscript.
10. The Working Group will also develop clinical questions that need to be answered in the future; these should be discussed in the manuscript.
 11. The final document with the consensus agreements will be circulated (*via* email) to the Working Group for a review and approval.