

# Efficacy of Postoperative Continuous Wound Infiltration With Local Anesthesia After Open Hepatectomy

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**Objectives:** Local anesthetic wound infiltration is widely used as an effective adjunct during multimodal postoperative pain management. The aim of this study was to evaluate the effectiveness of continuous wound infusion of ropivacaine in postoperative pain relief, opioid sparing, incidence of nausea and vomiting, and bowel and liver function improvement in patients undergoing open hepatectomy.

**Methods:** Forty patients undergoing open hepatectomy were enrolled in this prospective, randomized, double-blinded, placebo-controlled trial. Patients were divided into 2 groups: the 0.9% saline continuous infusion group (the control group;  $n = 20$ ) and the ropivacaine continuous infusion group (the Ropi group;  $n = 20$ ). Outcomes measured postoperatively were pain score at rest and on movement, sufentanil consumption, incidence of nausea and vomiting, and sedation score across 48 postoperative hours. Time to bowel recovery, liver function change, mean length of hospitalization, patient satisfaction, and other data after 48 postoperative hours were collected until hospital discharge.

**Results:** Pain scores at rest were lower for the ropivacaine group and reached significance after 8 and 16 hours ( $P < 0.01$ ). Sufentanil consumption ( $41.50 \pm 21.80$  vs.  $89.70 \pm 35.22 \mu\text{g}$ ;  $P < 0.01$ ) after 48 hours, time to bowel recovery ( $1.80 \pm 0.70$  vs.  $3.15 \pm 1.04$  d;  $P < 0.01$ ), incidence of nausea and vomiting ( $1.75 \pm 0.72$  vs.  $2.40 \pm 0.68$ ;  $P < 0.05$ ), and mean length of hospitalization ( $5.6 \pm 2.44$  vs.  $7.35 \pm 2.85$  d;  $P < 0.01$ ) were significantly reduced, and the sedation score and liver function change were also comparable between the 2 groups. There was no difference with respect to pain scores on movement, nor with respect to patient satisfaction.

**Conclusions:** Surgical wound infusion with ropivacaine after hepatectomy can improve pain relief at rest and accelerate recovery and discharge.

**Key Words:** local anesthesia, ropivacaine, continuous wound infiltration, hepatectomy

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Control of postoperative pain is of interest to surgeons, anesthetists, hospital administrators, and patients. As a major form of upper abdominal surgery, hepatectomy is always accompanied by significant pain, and patients with

severe pain are less likely to cough or move after surgery, which interferes with the return of gastrointestinal and respiratory functions. The most often used analgesic methods for pain alleviation are epidural analgesia and intravenous opioid analgesics through patient-controlled delivery systems.<sup>1</sup> Unfortunately, epidural puncture is a relatively complicated process with potential complications. Patient-controlled pain management has the risk of addiction, as large doses of opioids are used for a long period of time. Furthermore, opioids have potentially serious side effects such as nausea, excessive sedation, respiratory depression, slowing down of bowel function, and impairment of liver function.<sup>2</sup> Thus, to avoid these potentially serious adverse effects, postoperative pain is often undertreated.<sup>3</sup>

Although wound infiltration for abdominal analgesia had been used as early as 1986,<sup>4</sup> lack of knowledge on the part of the surgeon and material limitation for localized persistent infiltration deterred it from being used to its full potential until the early 1990s. With the recognition of the important role played by parietal nociceptive afferents in the origin of overall pain, local anesthetic wound infiltration is widely recognized as a useful adjunct in multimodality approaches to postoperative pain management.<sup>5,6</sup> It has been demonstrated that the pain pump is safe and effective in a variety of procedures, but the efficacy of this technique has been poorly described in hepatectomy patients. After hepatectomy, patients are most likely to develop primary liver cancer or hepatolith, accompanied by liver dysfunction, and the procedure itself may worsen liver dysfunction and even lead to acute liver failure. Ropivacaine, as a widely used amide-type local anesthetic, has comparable efficacy to bupivacaine but lower systemic toxicity and shorter half-life to reduce the risk of plasma accumulation. Therefore, we speculate that wound instillation with 0.3% ropivacaine is an effective and well-tolerated method for postoperative analgesia after hepatectomy. We conducted a prospective, double-blinded, randomized, controlled design study to support our hypothesis.

## METHODS

Forty patients undergoing open hepatectomy requiring a subcostal incision  $> 20$  cm that was performed by the same experienced surgeon were enrolled into our study. The patients were hospitalized between May 2011 and July 2012. All patients signed a written informed consent form to participate in this study before the operation. Group allocation was done using computer-generated code allocation. Ropivacaine and saline were added to the elastomeric pump by an anesthesiologist not involved in the study. The patients, surgeons and investigator were kept blinded to the assigned treatment groups throughout the study period. Patients were randomized to receive a continuous surgical wound infusion of either 0.3% ropivacaine

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or 0.9% saline delivered through an elastomeric pump (TJPS120-2-250-5; 200 mL) by means of 2 soaker catheters. All patients were given unrestricted access to sufentanil (Graseby 9300; 200 mL) through a patient-controlled analgesic (PCA) device according to our hospital standard of care for breakthrough pain.

Patients with a history of adverse reactions to local anesthetics, obesity (BMI > 30 kg/m<sup>2</sup>), chronic pain, chronic preoperative opioid consumption, or psychiatric or neurological diseases, and those unable to use a PCA device, were excluded from the study.

When closing the abdomen, the surgeon inserted two 20-G multirope soaker catheters along the full length of the wound. One catheter was placed between the closed parietal peritoneum and the deep muscular fascia, and the other one was placed among the subcutaneous tissue.

Ten minutes before the end of the surgical procedure, 10 mL of 0.5% ropivacaine was injected through each catheter as an initial dose in both groups, and the catheters were connected to an elastomeric pump. After the patients' arrival in the recovery area, continuous instillation of 0.3% ropivacaine or 0.9% saline into the wound was commenced at an infusion rate of 2 mL/h per catheter. For recording data, the time immediately after the patient regained consciousness was considered as time 0. All patients had unrestricted access to sufentanil rescue use through an IV-PCA device (2 mg bolus dose, 5 min lockout time, 40 mg dose limit over 4 h). The patient-controlled analgesia and the wound catheter were removed at 48 hours.

The outcomes measured across 48 postoperative hours were: pain at rest and on movement, assessed using a numerical rating score (NRS) for pain (NRS, 0 to 10 scale); sedation, which was evaluated on the basis of Ramsay grades at various postoperative assessment times (1 = the patient is cooperative, oriented, and tranquil; 2 = the patient can be easily aroused through verbal stimuli; 3 = the patient is asleep, but shows brisk response to a light glabellar tap or loud auditory stimulus; 4 = the patient is asleep, and shows sluggish response to a light glabellar tap or loud auditory stimulus; 5 = the patient is asleep, and shows no response to an external stimulus); sufentanil consumption, which was measured on the PCA device; nausea and vomiting, which was recorded as absent or present (1 = no nausea or vomiting; 2 = nausea; 3 = vomiting); the success of treatment, which was judged by the patients on the day of discharge on a 4-point scale (1 = poor, 2 = fair, 3 = good, 4 = excellent); and changes in liver function (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], total bilirubin [TBIL], direct bilirubin [DBIL], albumin, prothrombin time [PT], and activated partial thromboplastin time [APTT]), which were recorded 3 days after surgery. The first postoperative bowel movement (first flatus as symbol), length of hospitalization, and other adverse events were also recorded until hospital discharge.

**STATISTICAL ANALYSIS**

On the basis of local data on total sufentanil consumption across 48 postoperative hours, a sample size of 20 in each group would have 88% power to detect a 30% reduction in the total dose. Statistical analyses were performed using SPSS software version 18.0. The data were presented as means ± SD for continuous variables. The  $\chi^2$  test, the *t* test, and repeated measures ANOVA were carried

out where appropriate. Statistical significance was set at *P* < 0.05.

**RESULTS**

Forty patients were initially enrolled in our study. However, 1 patient was lost because of postoperative bleeding, and thus, finally, 19 patients were included in the ropivacaine group and 20 in the control group. No significant differences in terms of age, height, weight, sex, incision length, and surgical procedures were observed between the 2 groups (Table 1).

Time to bowel recovery (1.80 ± 0.70 vs. 3.15 ± 1.04 d; *P* < 0.01), incidence of nausea/vomiting (1.75 ± 0.72 vs. 2.4 ± 0.68; *P* < 0.05), and mean length of hospitalization (5.6 ± 2.44 vs. 7.35 ± 2.85 d; *P* < 0.01) were significantly reduced. Liver function (AST, ALT, ALP, TBIL, and DBIL levels) recovery was better in the Ropi group than in the control group. There was no difference with respect to patient satisfaction (Table 2, 3).

The pain scores at rest are presented in Figure 1. Significant differences in pain scores at rest between the 2 groups were detected at 8 hours (NRS 1.5 ± 0.51 for the Ropi group and 2.45 ± 0.51 for the control group; *P* < 0.01) and at 16 hours (NRS 1.75 ± 0.44 for the Ropi group and 2.1 ± 0.31 for the control group; *P* < 0.01). However, there was no difference in pain score on movement between the 2 groups, as shown in Figure 2.

Sufentanil consumption calculated over 48 postoperative hours was significantly different between the 2 groups as shown in Figure 3. The mean total sufentanil consumption by the control group at 48 hours was double that of the Ropi group (89.70 ± 35.22 μg for the control group vs. 41.50 ± 21.80 μg for the Ropi group; *P* < 0.01).

The sedation scores are presented in Figure 4. It was higher in the control group than in the Ropi group at 0 and 8 hours; after 16 hours the scores became similar for the 2 groups.

**DISCUSSION**

Control of postoperative pain is of interest to patients. Optimal management of postoperative pain, a fast turnover, and a shorter length of hospital stay after a major surgery have been important concerns among surgeons, anesthetists and hospital administrators.

**TABLE 1.** Patient Characteristics, Incision Length, and Surgical Procedures

	Ropi Group (n = 19)	Control Group (n = 20)	<i>P</i>
Age	45.2 ± 9.8	50.3 ± 12.1	0.072
Height	160 ± 9.4	163 ± 7.8	0.561
Weight	65 ± 7.5	70 ± 8.2	0.820
Sex (male/female)	11/8	11/9	0.880
Incision length	23 ± 2.0	22 ± 3.0	0.942
Surgical procedures			
Right	12	14	
hepatectomy			
Left hepatectomy	2	3	
Posterior	4	3	
segmentectomy			
Caudate	1	0	
lobectomy			

Data are expressed as mean ± SD.

**TABLE 2.** Time to Bowel Recovery, Nausea/Vomiting, Hospital Stay, and Patient Satisfaction

	Ropi Group (n = 19)	Control Group (n = 20)	P
Time to bowel recovery (d)	1.80 ± 0.696	3.15 ± 1.040	0.000*
Nausea/vomiting	1.75 ± 0.716	2.4 ± 0.681	0.006*
Hospital stay (d)	5.6 ± 2.437	7.35 ± 2.852	0.044*
Patient satisfaction	3.35 ± 0.489	3.15 ± 0.366	0.152

Data are expressed as mean ± SD.  
\*P < 0.05

The most important source of postoperative pain is the surgical incision; for example, hepatectomy being a major abdominal surgery often has a subcostal incision > 20 cm. The traditional effective approaches are epidural analgesia, oral or injecting nonsteroid anti-inflammatory drugs, and opioids. As epidural puncture is always associated with side effects such as neuraxial hematoma and nerve damages, patients with spinal malformations, infectious puncture site, and anticoagulant therapy are normally precluded to use epidural analgesia. Opioid administration even at lower doses can induce oxidative stress in the liver, leading to hepatocyte

apoptosis and liver enzyme elevation.<sup>7</sup> Some studies have shown that repeated morphine administration, which is commonly used for pain relief, would interfere with liver antioxidant defense and hepatocyte vitality. Unexpected sensitivity to systemic opioid has been observed after hepatic resection. In addition, most hepatectomy patients experience liver dysfunction preoperatively, and surgery itself would aggravate liver dysfunction or even lead to liver failure. Thus, it would be dangerous for hepatectomy patients to consume continuous doses of opioids. The discovery of new analgesic techniques that work in different phases of analgesia can further improve the quality of medical care for hepatectomy patients.

Local anesthetic wound infiltration is now recognized as a useful adjunct in a multimodality approach to postoperative pain management. It has been reported that the method can be used in many types of surgery, such as cesarean delivery, inguinal hernia repair, total hip arthroplasty, and colorectal surgery.<sup>1,2,8</sup> However, to the best of our knowledge, the application of local anesthetic wound infiltration in hepatectomy patients has rarely been reported. Chan et al<sup>9</sup> first described the use of continuous ropivacaine infusion after open hepatic surgery. Different from theirs, we focus more on important functional measurements such as the return of bowel function, the recovery of liver function, and the duration of hospitalization.

**TABLE 3.** Liver Function Before Operation and 3 Days After Operation

Liver Function (IU)	Operation Time	Control Group (n = 19)	Ropi Group (n = 20)	95% CI	P
ALT (IU/L)	Pre	42.10 ± 13.40	43.15 ± 16.72		0.828
	Post	60.65 ± 13.86	51.80 ± 13.76		0.049*
	Pre-Post	-18.55 ± 4.89	-8.65 ± 10.96	-15.41 to -4.39	0.001*
AST (IU/L)	Pre	56.65 ± 18.23	61.85 ± 21.95		0.420
	Post	77.90 ± 19.82	57.85 ± 16.81		0.001*
	Pre-Post	-21.25 ± 13.20	4.00 ± 24.50	-37.97 to -12.53	0.000*
ALP (IU/L)	Pre	154.60 ± 27.29	161.35 ± 25.51		0.424
	Post	135.25 ± 20.89	111.70 ± 20.73		0.001*
	Pre-Post	19.35 ± 33.37	49.65 ± 29.77	-50.54 to -10.06	0.004*
ALB (g/L)	Pre	37.70 ± 1.63	37.20 ± 1.20		0.275
	Post	28.35 ± 2.06	28.00 ± 1.78		0.568
	Pre-Post	9.35 ± 2.64	9.20 ± 1.94	-1.33 to 1.63	0.839
TBIL (μmol/L)	Pre	41.74 ± 23.73	32.36 ± 20.14		0.186
	Post	28.28 ± 12.50	20.66 ± 8.40		0.029*
	Pre-Post	13.47 ± 13.27	11.70 ± 12.42	-6.47 to 9.99	0.433
DBIL (μmol/L)	Pre	28.58 ± 18.70	23.69 ± 15.60		0.375
	Post	17.52 ± 8.58	12.48 ± 4.78		0.027*
	Pre-Post	11.06 ± 12.20	11.21 ± 11.39	-7.71 to 7.40	0.967
PT (s)	Pre	13.10 ± 1.02	12.80 ± 0.82		0.321
	Post	12.81 ± 1.17	13.20 ± 1.40		0.344
	Pre-Post	0.29 ± 1.25	-0.40 ± 1.41	-0.17 to 1.53	0.113
APTT (s)	Pre	35.36 ± 2.30	36.19 ± 2.90		0.322
	Post	39.19 ± 1.29	38.84 ± 1.44		0.423
	Pre-Post	-3.84 ± 2.80	-2.66 ± 2.67	-2.93 to 0.57	0.181

Data are expressed as mean ± SD.  
\*P < 0.05.

ALB indicates albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; DBIL, direct bilirubin; TBIL, total bilirubin.

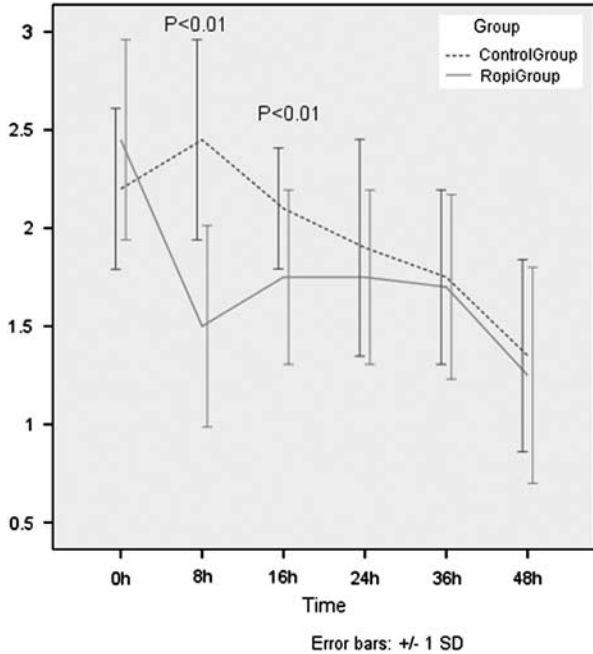


FIGURE 1. Mean numerical rating score at rest at each time interval.

We also measured liver enzyme changes instead of indocyanine green elimination rate, which reflect the liver reserve function, to assess liver cirrhosis or estimate surgical risk.

In our study, we confirmed a lower NRS score on rest and reduced sufentanil consumption after continuous infiltration of 0.3% ropivacaine into the wound among patients undergoing open hepatectomy. Local anesthetics can relieve pain intensity, shorten the duration of postoperative pain, and reduce analgesic requirements by

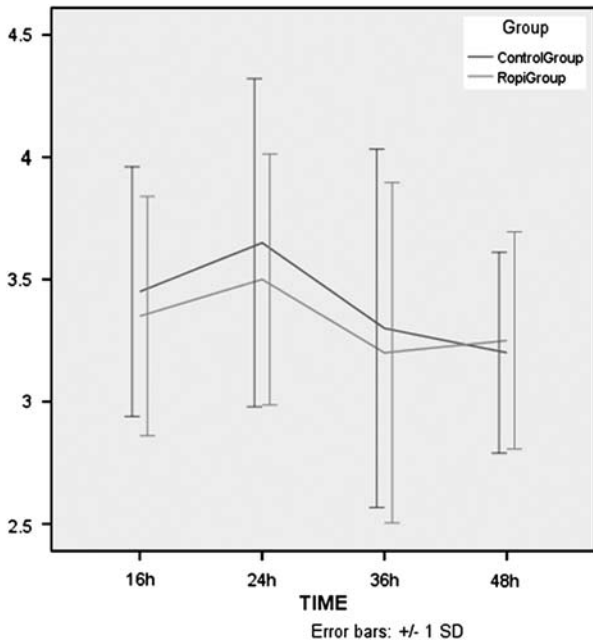


FIGURE 2. Mean numerical rating score on movement at each time interval.

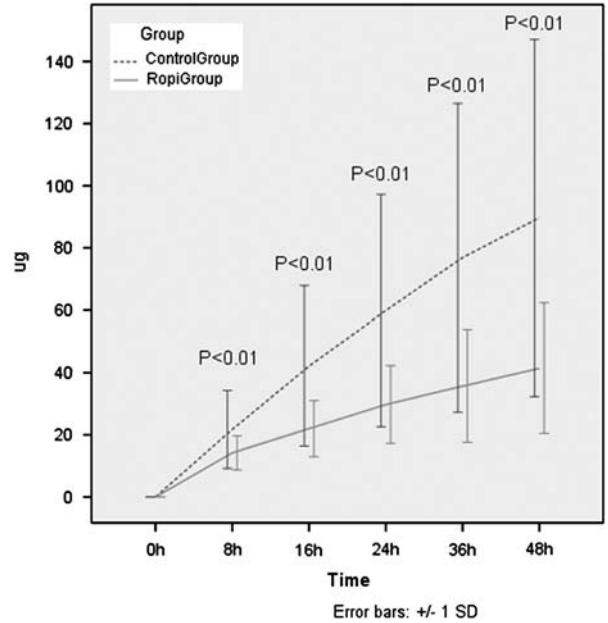


FIGURE 3. Cumulative sufentanil consumption (µg) at each time interval.

inhibiting the transmission of noxious impulses from the injured side.<sup>10</sup> Moreover, it can also inhibit the local inflammatory response to injury that could sensitize nociceptive receptors and contribute to hyperalgesia.<sup>11</sup> In contrast, a systemic effect of ropivacaine administered through a catheter cannot be ignored. Systemic local anesthetics can be analgesic and this effect has been clearly demonstrated. The potential mechanisms may involve an inhibition of central hyperalgesia and the axonal transportation of inflammatory mediators.<sup>11</sup> However, local anesthetic wound infiltration technically had no advantage in pain relief on movement in our study; maybe the infusion rate or

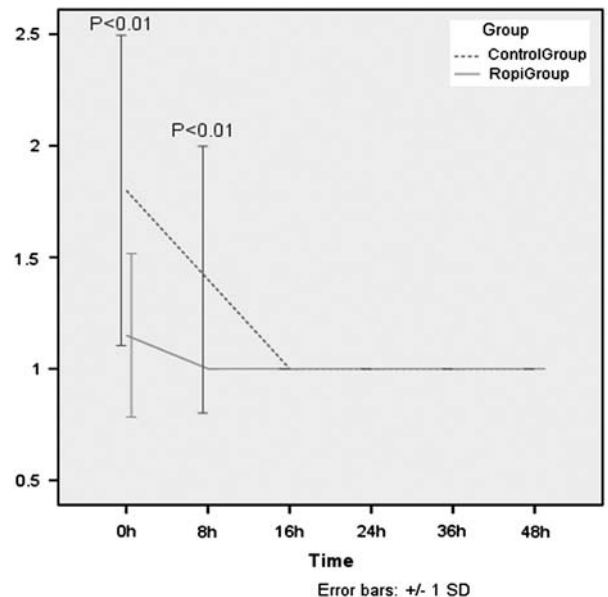


FIGURE 4. Sedation score at each time interval.

concentration of ropivacaine was not enough, and therefore further research is needed.

Reduced systemic sufentanil resulted in faster time to bowel recovery, as sufentanil inhibits gut motility and propulsive activity by combining the  $\mu$ -2 and  $\kappa$  receptors in the gastrointestinal tract, inducing bowel dysfunction.<sup>12</sup> In contrast, ropivacaine could accelerate postoperative intestinal motility by reducing the inflammatory response.

In our study, we chose to measure the liver serum biochemical index to compare the liver function between the 2 groups. Hepatocellular damage is the predominant pattern of hepatic damage. The Council for International Organizations of Medical Science proposed the evaluation of the levels of ALT or conjugated bilirubin, or a combined level of AST, ALP, and TBIL, when investigating drug-induced liver injury.<sup>13</sup> ALT is the most sensitive serum marker in drug-induced liver injury, as AST can reflect the severity of liver injury. Significant changes in liver enzymes (ALT, AST, and ALP) were observed in the Ropi group compared with the control group 3 days after surgery. TBIL and DBIL levels were also comparable after surgery. The bilirubin level decreased significantly in patients with biliary obstruction once the obstruction was relieved surgically. However, there were no differences in albumin, PT, and APTT levels; this may perhaps be because they mainly reflect the synthetic function of the liver and are not sensitive to drug-induced injury, or perhaps because protein and coagulation factors have a longer half-life and hence there were no changes 3 days later.

We found an interesting phenomenon in our study. Despite the increasing amount of sufentanil in the saline group, the sedation score was the same in both groups after 16 hours. Unlike other opioids, sufentanil is a highly selective  $\mu$  opioid receptor agonist, although it exerts a sedative effect by acting on  $\kappa$  receptors, which are located in the central nervous system. Studies have evaluated the dose of sufentanil (0.35  $\mu$ g/kg) that could have an effect on the central nervous system.<sup>14</sup> The consumption of sufentanil every 8 hours was much lower than 0.35  $\mu$ g/kg, and thus the sedation scores of the enrolled patients were all below 2, and after 16 hours all the patients in both groups became cooperative and oriented (sedation score = 1).

We choose ropivacaine, a pure levorotatory stereoisomer, as we can reduce its cardiotoxicity in the event of an overdose.<sup>15</sup> We did not measure the plasma ropivacaine concentrations in the present study, for it has been reported that the total plasma concentration of ropivacaine remains far below the known toxic threshold when larger amounts of ropivacaine are used.<sup>8</sup> Systemic toxicity has been defined by Labaille and colleagues as a serum level >4.0  $\mu$ g/mL, which was determined on the basis of healthy adult volunteers receiving intravenous infusions of ropivacaine.<sup>16</sup> However, the absorption, distribution, and elimination of drugs change in hepatic insufficiency. In Chan's study, the authors had measured plasma ropivacaine concentration (0.25%, 4 mL/h for 68 h) after open liver resection and only 2 patients were seen to have plasma ropivacaine concentrations >3.0  $\mu$ g/mL.<sup>8</sup> Different from the healthy individuals, there may be a reduced free fraction of local anesthetic after surgery owing to rising levels of  $\alpha$ -1-acid-glycoprotein, which has the potential advantage of buffering the unbound ropivacaine, providing a protective effect against toxic reactions.<sup>17</sup>

A significant proportion of postoperative pain comes from superficial structures, but peritoneal pain may also be

of importance. To affect the deep muscular-peritoneal component of abdominal pain, we placed 1 catheter between the parietal peritoneum and deep muscular fascia and the other catheter in the subcutaneous tissues. We finally obtained positive results in our trial compared with other studies conducted on only infiltrated skin or subcutaneous tissues. However, there were no differences in patient satisfaction. When we conducted the research, the investigators did not particularly disclose the study aspects of our research and only asked the patients to give a subjective evaluation of the entire hospital process. Maybe Chinese patients are more concerned about the success of the operation, the amount of bleeding, wound healing, postoperative complications, and postoperative care.

The wound infiltration technique is easy to administer and follow-up, with no extra training required and no motor nerve blockade. However, its success mostly depends on the effectiveness of the infiltration by the surgeons. Consequently, wound infiltration with local anesthetics not only provides pain control but also affects inflammatory responses and increases catecholamine, which has an added benefit of enhancing wound healing by increasing wound perfusion and oxygenation.<sup>18</sup> In our trial, there were no surgical wound infections, which was consistent with Luis's study in which use of an in-site preperitoneal catheter for postoperative anesthesia did not increase the risk for surgical site infection.<sup>19</sup> Hence, we again eliminate the anxiety of surgeons that continuous infusion of local anesthetic through a catheter will increase surgical wound infection.

The limitations of our study are the small number of patients included and the elastomeric pump running at a fixed rate of infusion (2 mL/h). A PCA pump may provide better analgesic effects. We did not measure the systemic concentration of ropivacaine in patients with liver dysfunction. We will conduct a study on the systemic concentration of free ropivacaine and  $\alpha$ -1-acid-glycoprotein while using a local wound instillation technique in liver or renal insufficiency patients. In our study, 1 patient underwent a reoperation because of bleeding. We found that the tissue planes were difficult to be identified and separated to appropriate position of the catheters. In conclusion, continuous surgical wound infusion with ropivacaine was effective and seemed to improve pain management and accelerate patient's recovery and discharge after open hepatectomy.

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