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ORIGINAL ARTICLE

Prospective Study

Effect of local wound infiltration with ropivacaine on postoperative pain relief and stress response reduction after open hepatectomy

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Abstract

AIM

To prospectively evaluate the effect of local wound infiltration with ropivacaine on postoperative pain relief and stress response reduction after open hepatectomy.

METHODS

A total of 56 patients undergoing open hepatectomy

were randomly divided into two groups: a ropivacaine group (wound infiltration with ropivacaine solution) and a control group (infiltration with isotonic saline solution). A visual analog scale (VAS) at rest and on movement was used to measure postoperative pain for the first 48 h after surgery. Mean arterial pressure (MAP), heart rate (HR), time to bowel recovery, length of hospitalization after surgery, cumulative sufentanil consumption, and incidence of nausea and vomiting were compared between the two groups. Surgical stress hormones (epinephrine, norepinephrine, and cortisol) were detected using enzyme-linked immunosorbent assay, and the results were compared.

RESULTS

VAS scores both at rest and on movement at 24 h and 48 h were similar between the two groups. Significantly lower VAS scores were detected at 0, 6, and 12 h in the ropivacaine group compared with the control group ($P < 0.05$ for all). MAP was significantly lower at 6, 12, and 24 h ($P < 0.05$ for all); HR was significantly lower at 0, 6, 12, and 24 h ($P < 0.05$ for all); time to bowel recovery and length of hospitalization after surgery ($P < 0.05$ for both) were significantly shortened; and cumulative sufentanil consumption was significantly lower at 6, 12, 24, and 36 h ($P < 0.05$ for all) in the ropivacaine group than in the control group, although the incidence of nausea and vomiting showed no significant difference between the two groups. The levels of epinephrine, norepinephrine, and cortisol were significantly lower in the ropivacaine group than in the control group at 24 and 48 h ($P < 0.01$ for all).

CONCLUSION

Local wound infiltration with ropivacaine after open hepatectomy can improve postoperative pain relief, reduce surgical stress response, and accelerate postoperative recovery.

Key words: Local wound infiltration; Ropivacaine; Open hepatectomy; Postoperative pain; Surgical stress

Core tip: This study prospectively evaluated the effect of local wound infiltration with ropivacaine on postoperative pain relief and stress response reduction after open hepatectomy. Wound infiltration with ropivacaine could provide more effective analgesia both at rest and on movement in the first 48 h after surgery, with lower mean arterial pressure, heart rate and sufentanil consumption, accelerated postoperative recovery, and reduced stress response. These results suggest that local wound infiltration with ropivacaine is a simple, convenient and effective analgesic method that can provide postoperative analgesia and short-term benefits after open hepatectomy.

Sun JX, Bai KY, Liu YF, Du G, Fu ZH, Zhang H, Yang JH, Wang B, Wang XY, Jin B. Effect of local wound infiltration with ropivacaine on postoperative pain relief and stress response reduction after open hepatectomy. *World J Gastroenterol* 2017; 23(36): 6733-6740 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i36/6733.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i36.6733

INTRODUCTION

Postoperative pain is an important issue for surgeons, anesthetists, patients, and other related personnel. The intensive pain caused by upper abdominal laparotomy may influence postoperative recovery, prolong hospitalization, and cause stress response and complications, including respiratory and cardiovascular depression and gastrointestinal and neuroendocrine dysfunction[1,2]. Currently, intravenous analgesia or epidural analgesia (EA) with a patient-controlled analgesia pump is the most common analgesic approach for controlling postoperative pain after laparotomy[3]. Although favored after major laparotomy, patient-controlled intravenous analgesia (PCIA) can delay postoperative recovery because of nausea and vomiting, excessive sedation, and dizziness; moreover, this analgesic mode involves the risk of addiction with large opioid dosages over long periods[4,5]. As to EA, which provides better analgesia than PCIA, it is restricted by contraindications, epidural puncture failure, and side effects[6,7]. Therefore, finding other analgesic strategies with fewer potentially serious adverse effects will be beneficial for patients suffering from postoperative pain.

Postoperative analgesia is a crucial section of perioperative management, and local anesthetic methods are more effective than systemic analgesia regardless of the operation type[8]. Currently, wound infiltration with local anesthetics, which is a simple, effective, and inexpensive method, is performed in various surgical procedures and provides satisfactory analgesia without major side effects[9]. Ropivacaine and bupivacaine, as long-acting local anesthetics, are commonly used for local anesthesia and pain management in China[10]. Ropivacaine has the same analgesic effects as bupivacaine and levobupivacaine, but it is associated with a low incidence of motor block[11]. Thus, ropivacaine appears to be an important component for local anesthesia and postoperative analgesia. Meanwhile, surgical pain frequently increases the systemic stress response during the perioperative period, which can induce the excessive release of catecholamines (epinephrine and norepinephrine) and cortisol. Optimistically, local anesthesia provides considerable advantages over general anesthesia by suppressing catecholamines and cortisol levels[12].

In this study, we aimed to assess the effect of local wound infiltration with ropivacaine on postoperative pain control, mean arterial pressure (MAP), heart rate

(HR), cumulative sufentanil consumption, incidence of nausea and vomiting, time to bowel recovery, and length of hospitalization after open hepatectomy. The changes of three stress hormones, namely, epinephrine, norepinephrine, and cortisol, were evaluated in patients undergoing wound infiltration with and without ropivacaine.

MATERIALS AND METHODS

A total of 56 patients undergoing open hepatectomy, which was performed by the same experienced surgical team at the Department of Hepatobiliary Surgery of Qilu Hospital of Shandong University from January 2016 to March 2017, participated in this study. The study was approved by the Medical Ethics Committee of Qilu Hospital of Shandong University (No. 2017052), and written informed consent was obtained from all patients. The inclusion criteria included adult patients (aged 18-75 years) who would undergo open hepatectomy and were classified as grades Ⅰ-Ⅲ according to the American Society of Anesthesiologists (ASA) Physical Status Classification System. Patients with a history of known allergy to local anesthetics, chronic preoperative opioid consumption, or any other analgesic treatment for chronic pain before surgery, psychiatric or neurological diseases, or acquired or genetic hemostatic abnormality were excluded from the study.

On the day of surgery, the patients were randomly divided into two groups with a table of random numbers. Surgeons and patients were kept blinded to the assigned treatment groups throughout the study. Wound infiltration was performed with a 7.5 mg/mL ropivacaine solution in the ropivacaine group and with an isotonic saline solution in the control group. Solutions were prepared and provided by the anesthetist, and surgeons were blinded to patient allocation. When closing the abdomen at the end of the surgical procedure, 20 mL of the prearranged solution was used to infiltrate the subcutaneous tissues, deep muscular fascia, and parietal peritoneum. Moreover, one or two drainage tubes were routinely placed near the cutting surface of the liver and then pulled out and fixed on the abdominal skin. In the presence of tube incision or pulling of the tube during movement or when turning over, the surrounding tissues of the tube were also infiltrated with the solution. Infiltration was performed under direct vision by the surgeon. All patients were given unrestricted access to sufentanil through a 100 mL disposable patient-controlled analgesic (PCA) device containing 1 μg/mL sufentanil that was delivered at a rate of 2 μg/h and a bolus of 0.5 μg with a 15 min lockout time. When the skin was closed, the PCA pump was connected to the venous catheter and routinely removed 36 h after the operation.

The intensity of postoperative pain at rest was measured on a visual analogue scale (VAS) graded from 0 (no pain) to 10 (very severe pain) for the first 48 h after surgery. Movement pain was scored using VAS when coughing or turning over. Pain scores were recorded both by nurses and surgeons blinded to patient allocation. Pain measurements were performed at 0, 6, 12, 24, and 48 h after the surgery. Other variables were recorded, including time to bowel recovery, length of hospitalization after surgery, hemodynamic data represented by MAP and HR, cumulative sufentanil consumption, and postoperative nausea and vomiting (PONV). The three surgical stress hormones, namely, epinephrine, norepinephrine, and cortisol, were detected using commercial enzyme-linked immunosorbent assay kits (Cusabio Biotech Co., Ltd., Wuhan, China). Time to bowel recovery was defined as the time to first anal exhaust. PONV was recorded with a three-point rating scale: 1, no nausea and vomiting; 2, nausea without vomiting; 3, nausea with vomiting.

Statistical analyses were performed with SPSS 19.0 (SPSS Inc., Chicago, IL, United States). All data were checked for normal distribution and the results are expressed as mean ± SD for continuous variables. The *t* test, χ^2 test, Fisher's exact test, or analysis of variance was carried out where appropriate. $P < 0.05$ was considered statistically significant.

RESULTS

All patients successfully received the surgical procedure, including the wound infiltration with a prearranged solution. However, three patients (two in the ropivacaine group and one in the control group) were dropped from the study for postoperative bleeding and bile leakage; finally, 26 patients were enrolled in the ropivacaine group and 27 enrolled in the control group. The demographic characteristics of the patients assigned to the two groups were comparable in terms of age, gender, weight, ASA grade, incision length, and postoperative pathology, except for operation type, which showed a statistical difference but had no clinical significance (Table 1).

The VAS scores both at rest and on movement were similar between the two groups at 24 h and 48 h after open hepatectomy (Figure 1A and B). Significant differences in VAS scores at rest were detected at 0 h ($P = 0.0106$), 6 h ($P = 0.0032$), and 12 h ($P = 0.0002$). Moreover, significant differences in VAS scores on movement were observed at 0 h ($P = 0.0208$), 6 h ($P = 0.0043$), and 12 h ($P = 0.0089$). The details are shown in Table 2.

Hemodynamic data are presented in Figure 1C and D and Table 2. MAP was significantly lower in the ropivacaine group than in the control group at 6 h ($P = 0.0241$), 12 h ($P = 0.0001$), and 24 h ($P = 0.002$). In the ropivacaine group, HR was significantly lower at 0 h ($P = 0.0103$), 6 h ($P = 0.0087$), 12 h ($P < 0.0001$), and

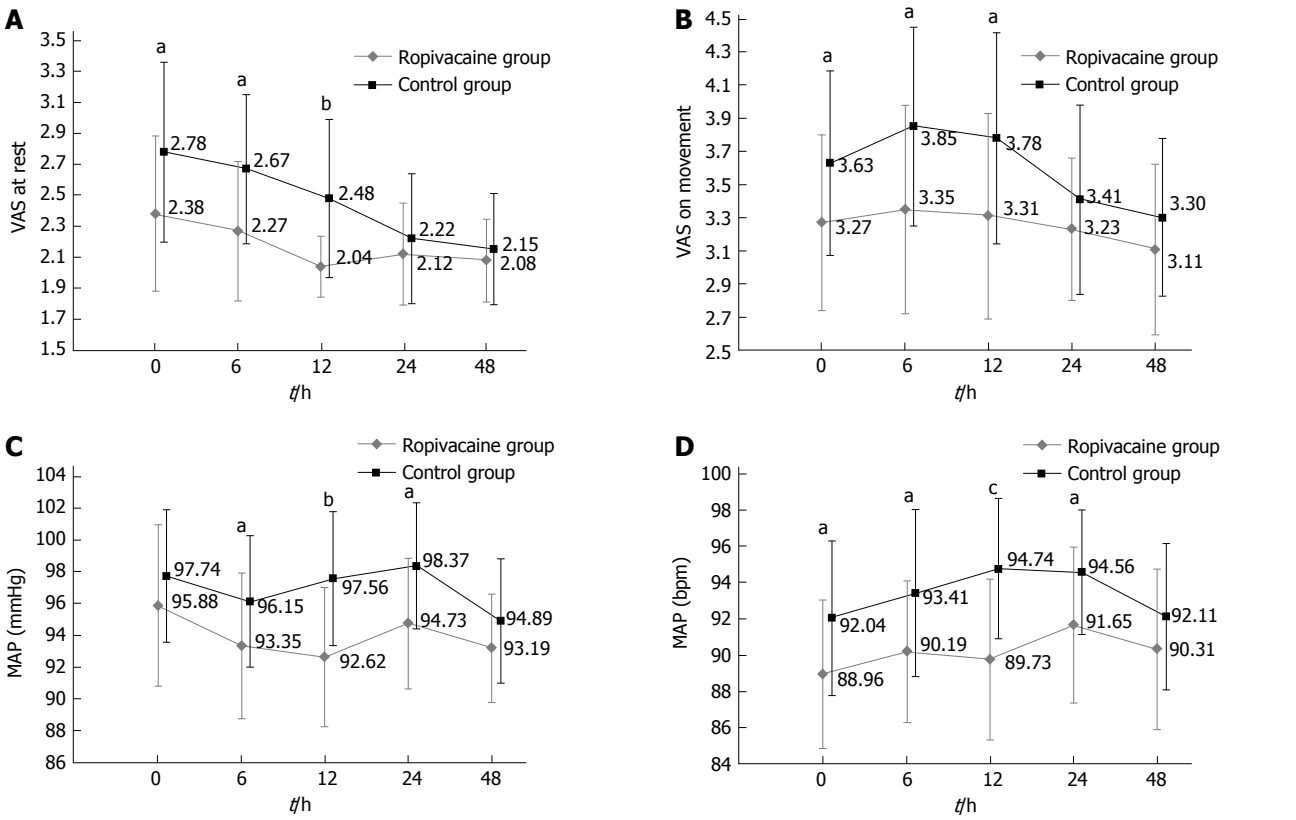

Figure 1 Visual analogue scale scores at rest and on movement, mean arterial pressure, and heart rate during the first 48 h after surgery. A: VAS scores at rest; B: VAS scores on movement; C: MAP; D: HR. [a]$P < 0.05$; [b]$P < 0.001$; [c]$P < 0.0001$. VAS: Visual analogue scale; MAP: Mean arterial pressure; HR: Heart rate.

Table 1 Demographic characteristics of the patients studied (mean ± SD)

Characteristic	Ropivacaine group	Control group	t/χ^2	*P* value
Age (yr)	48.38 ± 11.74	49.59 ± 12.42	-0.36	0.7176
Gender				
Male/female	18/8	18/9	0.04	0.8415
Weight (kg)	63.04 ± 9.21	66.04 ± 9.86	-1.14	0.2583
ASA grade				
I/II/III	4/17/5	7/15/5	0.92	0.6298
Incision length (cm)	24.65 ± 1.83	24.22 ± 2.76	0.67	0.5075
Operation type				
Left hepatectomy	8	5		0.0086
Right hepatectomy	13	8		
Mesohepatectomy	1	0		
Caudate lobectomy	2	1		
Irregular hepatectomy	2	13		
Postoperative pathology				
Hepatocellular carcinoma	22	18		0.3292
Intra-and extrahepatic cholangiolithiasis	3	7		
Hepatic focal nodular hyperplasia	1	1		
Hepatocellular adenoma	0	1		

ASA: American Society of Anesthesiologists.

24 h ($P = 0.0089$).

No statistically significant difference was observed in baseline levels (0 h) of epinephrine, norepinephrine, or cortisol between the two groups. The levels of epinephrine at 24 and 48 h were significantly lower in the ropivacaine group than in the control group ($P = 0.0064$, $P = 0.0078$). Similarly, the values of norepinephrine and cortisol at 24 and 48 h were significantly reduced in the ropivacaine group ($P < 0.0001$ for all), as shown in Figure 2A-C and Table 3.

Cumulative sufentanil consumption at 36 h after surgery is presented in Figure 2D and Table 2. The consumption was significantly lower in the ropivacaine group than in the control group at 6 h ($P = 0.022$),

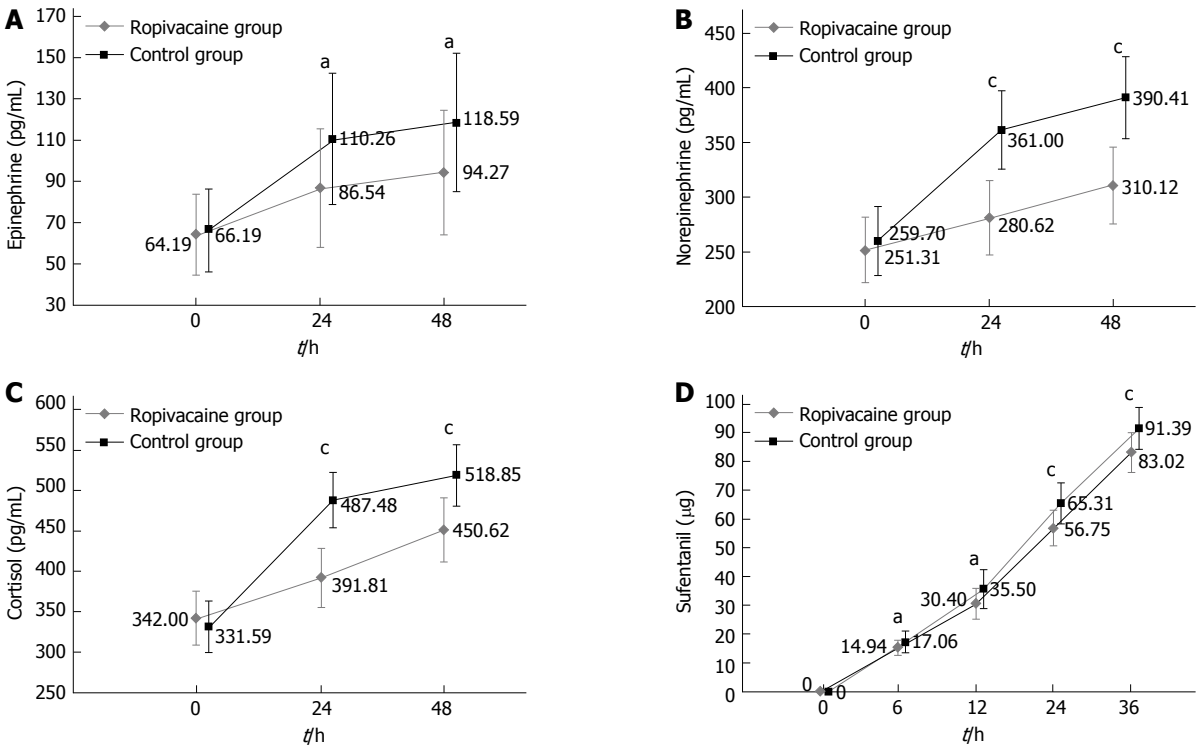

Figure 2 Plasma levels of epinephrine, norepinephrine and cortisol and cumulative sufentanil consumption during the first 48 h after surgery. A: Epinephrine; B: Norepinephrine; C: Cortisol; and D: Cumulative sufentanil consumption. $^{a}P < 0.05$; $^{c}P < 0.0001$.

Table 2 Visual analog scale scores at rest and on movement, mean arterial pressure, heart rate, and cumulative sufentanil consumption

Characteristic	0 h	6 h	12 h	24 h	48 h[1]
VAS at rest					
Ropivacaine group	2.38 ± 0.50	2.27 ± 0.45	2.04 ± 0.20	2.12 ± 0.33	2.08 ± 0.27
Control group	2.78 ± 0.58	2.67 ± 0.48	2.48 ± 0.51	2.22 ± 0.42	2.15 ± 0.36
t	-2.65	-3.17	-4.21	-1.03	-0.81
P value	0.0106	0.0032	0.0002	0.3096	0.4230
VAS on movement					
Ropivacaine group	3.27 ± 0.53	3.35 ± 0.63	3.31 ± 0.62	3.23 ± 0.43	3.11 ± 0.52
Control group	3.63 ± 0.56	3.85 ± 0.60	3.78 ± 0.64	3.41 ± 0.57	3.30 ± 0.47
t	-2.39	-2.99	-2.72	-1.27	-1.34
P value	0.0208	0.0043	0.0089	0.2110	0.1857
MAP (mmHg)					
Ropivacaine group	95.88 ± 5.08	93.35 ± 4.63	92.62 ± 4.43	94.73 ± 4.16	93.19 ± 3.41
Control group	97.74 ± 4.17	96.15 ± 4.14	97.56 ± 4.23	98.37 ± 3.99	94.89 ± 3.90
t	-1.46	-2.32	-4.16	-3.25	-1.69
P value	0.1515	0.0241	0.0001	0.0020	0.0981
HR (bpm)					
Ropivacaine group	88.96 ± 4.12	90.19 ± 3.92	89.73 ± 4.45	91.65 ± 4.30	90.31 ± 4.45
Control group	92.04 ± 4.27	93.41 ± 4.62	94.74 ± 3.88	94.56 ± 3.43	92.11 ± 4.05
t	-2.66	-2.73	-4.37	-2.72	-1.54
P value	0.0103	0.0087	< 0.0001	0.0089	0.1289
Cumulative sufentanil consumption (μg)					
Ropivacaine group	0	14.94 ± 2.56	30.40 ± 5.39	56.75 ± 6.20	83.02 ± 7.05
Control group	0	17.06 ± 3.81	35.50 ± 6.91	65.31 ± 7.09	91.39 ± 7.34
t		-2.36	-2.99	-4.67	-4.23
P value		0.0220	0.0043	< 0.0001	< 0.0001

[1]As to cumulative sufentanil consumption, the time point was set at 36 h. VAS: Visual analog scale; MAP: Mean arterial pressure; HR: Heart rate.

12 h ($P = 0.0043$), 24 h ($P < 0.0001$), and 36 h ($P < 0.0001$). Even so, the incidence of nausea and vomiting, the side effects of sufentanil, between the two groups had no significant difference (Table 4). Moreover, in the ropivacaine group, time to bowel recovery ($P = 0.0133$) and hospitalization after surgery

Table 3 Plasma concentrations of epinephrine, norepinephrine and cortisol (pg/mL)

Stress hormone	0 h	24 h	48 h
Epinephrine			
Ropivacaine group	64.19 ± 19.62	86.54 ± 28.64	94.27 ± 30.10
Control group	66.19 ± 20.30	110.26 ± 31.88	118.59 ± 33.65
t	-0.36	-2.85	-2.77
P value	0.7180	0.0064	0.0078
Norepinephrine			
Ropivacaine group	251.31 ± 30.19	280.62 ± 34.22	310.12 ± 35.15
Control group	259.70 ± 31.72	361.00 ± 36.06	390.41 ± 37.73
t	-0.99	-8.32	-8.01
P value	0.3286	< 0.0001	< 0.0001
Cortisol			
Ropivacaine group	342.00 ± 33.72	391.81 ± 36.53	450.62 ± 39.39
Control group	331.59 ± 31.92	487.48 ± 34.36	518.85 ± 38.21
t	1.15	-9.82	-6.40
P value	0.2537	< 0.0001	< 0.0001

Table 4 Time to bowel recovery, postoperative nausea and vomiting, and hospitalization length in the two groups

Characteristic	Ropivacaine group	Control group	t/χ^2	*P* value
Time to bowel recovery (d)	3.15 ± 1.01	3.93 ± 1.17	-2.56	0.0133
PONA				
No PONA	7	3		0.2729
Nausea without vomiting	16	18		
Nausea with vomiting	3	6		
Hospitalization (d)	8.65 ± 2.43	10.52 ± 3.49	-2.25	0.0289

PONA: Postoperative nausea and vomiting.

(*P* = 0.0289) were significantly shortened (Table 4).

DISCUSSION

Laparoscopic hepatectomy is commonly adopted in clinical settings because of its many advantages, including little trauma, low pain, fast recovery, and short hospitalization; however, open hepatectomy remains irreplaceable, especially in the presence of lesions close to or invading the root of the hepatic veins or the inferior vena cava, history of previous hepatectomy or any previous surgery potentially causing severe adhesion around the liver, and concomitant cardiopulmonary disease[13]. A right subcostal incision or reversed L-shaped incision (> 20 cm) is often made for open hepatectomy, and either of these two incision types is the most important source of postoperative pain. Thus, finding an effective way to reduce postoperative pain is urgent and necessary.

Local anesthetic wound infiltration is a useful and important component of a multimodality approach to postoperative pain control, and it can be applied in many types of surgery, including lumbar spine surgery, breast surgery, and inguinal hernia repair[9,14,15]. Local anesthetics used in the wound can block parietal afferents, reduce the sensitization of spinal dorsal horn neurons, and provide analgesia by inhibiting the transmission of noxious impulses from the incision[16]. Moreover, local anesthetics can suppress local inflammatory responses to incision injury that could sensitize nociceptive receptors and contribute to hyperalgesia[17]. Ropivacaine, a pure levorotatory stereoisomer and long-acting amide local anesthetic agent, has been widely used for local anesthesia and postoperative analgesia, and its reduced lipophilicity is associated with decreased incidence of central nervous system toxicity and cardiotoxicity[18]. Postoperative pain comes from superficial structures and deep muscular-peritoneal components; therefore, ropivacaine infiltrated not only the subcutaneous tissues but also the parietal peritoneum and deep muscular fasciae in our study. Our results showed that in the first 12 h after surgery, the local anesthetic ropivacaine significantly relieved the pain intensity at rest and on movement, demonstrating the potential of local wound infiltration with ropivacaine as a reliable analgesic strategy after open hepatectomy.

Surgical stress could cause a spectrum of changes in the body, involving the neuroendocrine, metabolic, immunological, and hematological systems[12]. The body's surgical stress response is mainly determined by the surgical wound severity, including the length of the incision in the abdominal wall from the skin to the parietal peritoneum[19]. The incision of open hepatectomy often exceeds 20 cm, and the surgical stress is thought to be high. Therefore, using local anesthetics to block surgical stress is feasible. Surgical stress response to injury causes a series of hormone changes; moreover, catecholamines (epinephrine and norepinephrine) and cortisol, as the main and most reliable peripheral hormones, correlate well with the extent of surgical stress. In this study, surgical stress was significantly reduced in the first 48 h after surgery as revealed by the levels of epinephrine, norepinephrine, and cortisol. Changes in MAP and HR were recorded, and the results demonstrated that the indexes of the ropivacaine group were obviously decreased. These results indicate that local wound infiltration with ropivacaine could also reduce surgical stress responses.

Opioids are commonly used for postoperative analgesia *via* venous access. However, they are associated with a potential risk of addiction, especially in large doses over long periods. Moreover, opioids possess potentially serious side effects, such as nausea, vomiting, constipation, respiratory depression, excessive sedation, and liver function impairment; hence, sparing opioids may reduce the incidence of the above side effects[20]. Reducing the dosage and duration of opioid usage is regarded suitable for avoiding

potentially serious adverse effects. Wound infiltration, as part of an opioid-sparing, multimodal analgesic regime, should therefore be recommended. Our current study showed that cumulative sufentanil consumption was significantly reduced in the ropivacaine group. Moreover, the time to bowel recovery was shorter in the ropivacaine group than in the control group. This may be caused by a combination of several reasons. First, sufentanil inhibits gut motility and propulsive activity by combining the μ-2 and κ receptors in the digestive tract[21]. Second, a previous animal study demonstrated that catecholamines reduce gut motility[22] and that the level of catecholamines in the ropivacaine group was reduced. Finally, ropivacaine could accelerate postoperative intestinal motility by reducing the inflammatory response.

The current study may have some limitations. The sample size was relatively small, and thus, more patients are needed in future studies to confirm our results. Compared with a previous study using catheters as a continuous wound infiltration method to deliver ropivacaine into the wound[23], we used single-shot ropivacaine infiltration into the superficial and deep muscular-peritoneal layers to achieve an analgesic effect. In our study, the drainage tube was routinely placed beside the liver resection surface and fixed outside. Movement and turning over could drag the tube and cause intensive pain, and thus, infiltration around the tube was highly effective. Moreover, the catheter under the wound could bring potential risks, such as infection and delayed wound healing, and the delivery rates and volumes of local anesthetics remain unidentified. Thus, single-shot infiltration with ropivacaine is a simple, convenient, and effective analgesic method that can bring short-term benefits for patients who underwent open hepatectomy. A previous study suggested that local anesthesia and stress response reduction could decrease cancer formation and that local anesthesia and analgesia may improve overall patient survival after oncologic surgery[24]. Thus, future research about local anesthesia, tumor recurrence, and patient survival after open hepatectomy is required.

In conclusion, local wound infiltration with ropivacaine after open hepatectomy can decrease acute postoperative pain and surgical stress response. This simple, convenient, and effective analgesic method provides postoperative analgesia and short-term benefits after open hepatectomy.

COMMENTS

Background

The postoperative pain caused by laparotomy delays patients' recovery and incurs stress response. Although commonly used to control pain, intravenous analgesia and epidural analgesia still have their contraindications and side effects. Local wound infiltration is a simple and effective method that can provide satisfactory analgesia without major side effects. The current study was designed to evaluate the effect of local wound infiltration with ropivacaine on postoperative pain and stress response after open hepatectomy.

Research frontiers

Postoperative analgesia is an indispensable component of fast track surgery for surgical patients, especially those who undergo laparotomy. Local anesthetics can effectively provide analgesia by inhibiting the transmission of noxious impulses from the wound and suppress local inflammatory responses to wound injury.

Innovations and breakthroughs

Wound infiltration with ropivacaine could provide effective analgesia in the first 48 h after open hepatectomy, with lower mean arterial pressure, heart rate and sufentanil consumption, accelerated postoperative recovery, and reduced stress response. These results suggest that this method is a simple, convenient and effective analgesic method that can provide postoperative analgesia and short-term benefits after open hepatectomy.

Applications

This study provides additional evidence supporting that local wound infiltration with ropivacaine after open hepatectomy can improve postoperative pain relief, reduce surgical stress response, and accelerate postoperative recovery.

Terminology

The intensity of postoperative pain at rest was measured on a visual analogue scale graded from 0 (no pain) to 10 (very severe pain) after surgery. Postoperative nausea and vomiting was recorded with a three-point rating scale: 1, no nausea and vomiting; 2, nausea without vomiting; 3, nausea with vomiting.

Peer-review

The study was well written and its findings are informative. Local wound infiltration with ropivacaine has good effects for pain relief and stress response reduction after open hepatectomy.

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