Original Article

The Effects of Additional Intraoperative Epidural Morphine Bolus Followed by Postoperative Thoracic Epidural Analgesia in Patients Underwent Liver Resection: A Retrospective Study

Worapot Apinyachon MD[1], Napat Phanichaya MD[1], Wanlee Srichot MD[1], Phisut Lavanrattanakul MD[1], Ornpicha Chaiyakiatkamjorn MD[1], Inthuon Sangasilpa MD[1]

[1] Department of Anesthesiology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Background: Liver resection is a major surgery that usually causes immense postoperative pain. Thoracic epidural analgesia is one of the effective methods for postoperative pain control. However, inadequate epidural analgesia in liver resection is still high.

Objective: To compare the effectiveness of adding a bolus dose of morphine to epidural analgesia with the epidural analgesia alone in patients that underwent liver resection.

Materials and Methods: A retrospective study collected the data from medical records of patients aged 18 to 80 who underwent liver resection between October 2018 and March 2021. Patients were divided into two groups, the conventional group and the epidural morphine bolus group that received additional epidural morphine bolus intraoperatively followed by continuous epidural analgesia. The numeric pain rating scale and the requirement for breakthrough pain were collected either at the post-anesthetic care unit (PACU) or on the first postoperative day (POD1) at the ward. The epidural morphine-related side effects were reviewed.

Results: One hundred sixty-two patients that underwent liver resection and received thoracic epidural analgesia were reviewed. The eighty-four patients (51.8%) were in the epidural morphine bolus group. The median pain scores at PACU and POD1 in the epidural morphine bolus group and the conventional group were 2.5 (0 to 7) and 6 (1 to 8) (p=0.025), and 1 (1 to 6) and 6 (6 to 7) (p<0.001), respectively. Moreover, the requirement for rescue treatment of the epidural morphine bolus group at both PACU and POD1 was significantly lower than that of the conventional group. However, the incidence of pruritus in the epidural morphine bolus group was significantly higher.

Conclusion: Additional epidural morphine bolus into epidural analgesia provided better postoperative pain control and decreased the need for rescue treatment of breakthrough pain compared with the conventional technique. At the same time, the incidence of pruritus was significantly higher in the epidural morphine bolus group.

Keywords: Epidural analgesia; Epidural morphine; Hepatectomy; Morphine side effects; Postoperative pain

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Postoperative open liver resection commonly causes severe somatic and visceral pain. Inadequate postoperative pain management leads to increased postoperative morbidity and delayed recovery[1,2]. There are choices of postoperative analgesia for major abdominal surgery, including patient-controlled analgesia, intrathecal analgesia, subcostal transversus abdominis plane block, or epidural analgesia[3,4]. Currently, epidural analgesia provides high-quality pain control and reduces postoperative complications such as atelectasis, inadequate rehabilitation, and prolonged hospital stay[5,6].

In the authors' institute, the incidence of inadequate or failed epidural analgesia for postoperative liver resection was still high. From the acute pain service report, fifty-three percent of the post-liver resection patients who received postoperative epidural analgesia had moderate to

Correspondence to:

Sangasilpa I.

Department of Anesthesiology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, 270 Rama VI Road, Phayathai, Ratchathewi, Bangkok 10400, Thailand.

Phone: +66-2-2011513

Email: Inthuon.san@mahidol.ac.th

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severe pain on the first postoperative day (POD1). Nowadays, epidural analgesia can be administered via continuous infusion with local anesthetics alone or combined with opioids. Some patients received an additional bolus of epidural morphine intraoperatively to the conventional technique to provide better pain control. There are insufficient data about the effectiveness of an additional bolus of epidural morphine at the end of the surgery, including optimal dose, safety, and efficacy.

The present study was a retrospective study aimed to compare the effectiveness of additional epidural analgesia bolus with the conventional epidural analgesia technique in liver resection patients.

Materials and Methods

The present study was approved by the Institutional Ethics Committee of Mahidol University (MURA 2020/1156, approval date: July 13, 2020) and was registered on the Thai Clinical Trials Registry (identifier: TCTR20220127007). Then the medical records of patients that underwent open liver resection between October 2018 and March 2021 at Ramathibodi Hospital were reviewed retrospectively. In the present study, the patients between 18 and 80 years who underwent open elective liver resection and received epidural analgesia for at least 24 hours were included. The patient who had no records or incomplete records of pain scores, retained endotracheal tube within 24 hours, and added postoperative epidural morphine bolus were excluded. Then the patients were divided into two groups. The epidural morphine bolus group received intraoperative epidural morphine bolus at the end of surgery followed by a continuous epidural infusion. The conventional group received postoperatively continuous epidural infusion only.

The patients' medical records were reviewed. The patient characteristics, type of operation, and operative times were collected. The intraoperative epidural management was reviewed, including the insertion site, depth of catheter, local anesthetic type, concentration, mode of administration, and type of combined opioid. The amount and time of bolus were collected in patients that received additional epidural morphine bolus. At the authors' hospital, epidural analgesia for postoperative liver resection was usually given 0.08% to 0.1% bupivacaine combined with fentanyl 1 to 2 mcg/mL or morphine 10 to 20 mcg/mL via epidural infusion system started at 5 to 8 mL/hour at the end of the operation. Data at the post-anesthetic care unit (PACU) including maximum pain scores before discharge and methods of rescue therapy were collected. Postoperative data were collected, including maximum and minimal pain score, incidence of vomiting, pruritus, and opioid-related respiratory depression.

The patients had assessed their pain scores at PACU, before discharge from PACU, and every four hours by nurse anesthetists at PACU or registered nurses at the ward or intensive care unit. The numerical rating scale (NRS) was used to assess the patient's pain intensity reporting 0 to 10 points where 0 is no pain and 10 is the worst pain imaginable. The present study standard protocol of rescue pain therapy was intravenous tramadol, and its dose and number of administrations were reviewed. The moderate to severe pain was defined as a NRS of more than 3 points. The patients determined the incidence of vomiting and were given antiemetics. The incidence of pruritus was defined by the patient that needed intravenous chlorpheniramine. The incidence of opioid-related respiratory depression was characterized by the patients requiring naloxone to treat their symptoms.

The sample size was calculated by a pilot observation from the previous records of Ramathibodi Hospital that in every 15 patients that received the bolus dose of epidural morphine, one patient experienced moderate to severe pain. The odds ratio was calculated to be 0.31. This odds ratio was calculated the sample size via logistic regression, in which type I error was equal to 0.05, and type II error was 0.95. The result indicated that 158 patients were required.

Statistical analysis

Continuous data included age, body weight, height, duration of operation, and the pain scores were computed as median with interquartile range or mean with standard deviation. Categorical data included gender, the American Society of Anesthesiologists (ASA) physical status, underlying diseases, and opioid-related adverse were computed as numbers and percentages. The continuous variables were analyzed using Student t-test or Mann-Whitney U test. The categorical variables were analyzed using Pearson chi-square or Fisher's exact test. Univariable and multivariable logistic regression were performed for the incidence of moderate to severe postoperative pain on the first POD1. The variables with potential significance ($p<0.10$) during univariate analyses were included in a multivariate forward and backward-

Table 1. Demographic characteristics

	Epidural morphine bolus (n=84)	Conventional (n=78)	p-value
Age (year); mean±SD	59.5±12.7	59.9±11.6	0.816
Bodyweight (kg); mean±SD	62.8±10.9	61.3±12.7	0.384
Height (cm); mean±SD	162.4±7.6	160.1±7.7	0.265
Female; n (%)	43 (51.1)	38 (48.7)	0.212
Hypertension; n (%)	43 (51.6)	38 (48.7)	0.753
Diabetes mellitus; n (%)	17 (20.2)	18 (23.1)	0.661
Cirrhosis; n (%)	20 (23.8)	10 (12.8)	0.072
Hepatitis B; n (%)	16 (19.0)	10 (12.8)	0.281
ASA physical status; n (%)			0.391
1	5 (6.0)	6 (7.7)	
2	29 (34.5)	30 (38.5)	
3	50 (59.5)	40 (51.3)	
4	0 (0.0)	2 (2.6)	
Diagnosis; n (%)			0.083
Hepatocellular carcinoma	38 (45.2)	26 (33.3)	
Liver metastatic cancer	25 (29.8)	23 (29.5)	
Cholangiocarcinoma	11 (13.1)	19 (24.4)	
Liver donor	6 (7.1)	3 (3.8)	
Benign liver tumor	3 (3.6)	4 (5.2)	
Liver cyst	1 (1.2)	1 (1.3)	
Operation; n (%)			0.227
Left hepatectomy	10 (11.9)	15 (19.2)	
Right hepatectomy	29 (34.5)	24 (30.8)	
Segmentectomy	29 (34.5)	31 (39.7)	
Wedge hepatectomy	16 (19.0)	8 (10.3)	
Operative time; mean±SD	358.8±12.7	378.7±109.2	0.369

ASA=American Society of Anesthesiologists; SD=standard deviation

Continuous variables are presented as mean±SD, Categorical variables are presented as n (%)

stepwise logistic regression modeling. The odds ratio and 95% confidence interval with associated p-values for each variable were reported in the logistic models. A p-value less than 0.05 was considered statistically significant. IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses.

Results

The demographic characteristics were recorded, including age, body weight, height, ASA physical status, underlying diseases, and operation time. There was no significant difference between the two groups (Table 1). Hepatocellular carcinoma and right hepatectomy were the most diagnoses and operations, respectively.

The intraoperative epidural management is shown in Table 2. There were no significant differences between the two groups for the length of epidural catheter in epidural space, the level of epidural insertion, and the epidural management during anesthesia. The median (minimal to maximal) dose of the epidural morphine bolus was 2 with a range of 1 to 2 mg.

As shown in Table 3, at PACU, the median maximal pain score was significantly lower in the epidural morphine bolus group at 2.5 versus 6 (p=0.025). The number of patients needing rescue treatment was also significantly lower. There was no statistical difference in NRS before discharge between the two groups. On the first POD1, the median maximum and minimum pain scores in the epidural morphine bolus group were significantly lower than those in the conventional group. Subsequently, the requirement for rescue treatment for breakthrough pain was also lower in the epidural morphine bolus group.

There was no significant difference in post-operative vomiting. However, the incidence of pruritus in the epidural morphine bolus group was

Table 2. Intra- and postoperative epidural management

	Epidural morphine bolus (n=84)	Conventional (n=78)	p-value
Intraoperative epidural management			
Epidural level			0.243
• Thoracic level 6	3 (3.6)	3 (3.8)	
• Thoracic level 7	29 (34.5)	14 (17.9)	
• Thoracic level 8	35 (41.7)	38 (48.7)	
• Thoracic level 9	10 (11.9)	13 (16.7)	
• Thoracic level 10	2 (2.4)	5 (6.4)	
• Thoracic level 11	5 (6.0)	5 (6.4)	
Skin to epidural space distance (cm)	4.9±0.9	5.0±1.2	0.154
Epidural catheter in space (cm)	5.2±0.9	4.9±1.2	0.110
Mode of intraoperative administration			
Intermittent bolus	26 (31.0)	34 (43.6)	0.135
Continuous infusion	58 (69.0)	42 (53.9)	
No using epidural	0 (0.0)	2 (2.5)	
Intravenous NSAIDs	67 (79.7)	56 (71.7)	0.127
Postoperative epidural management			
Preparation of postoperative analgesic solution			
• Concentration of bupivacaine			0.610
0.08%	27 (32.5)	28 (36.4)	
0.1%	56 (67.5)	49 (63.6)	
• Type of opioid			0.001
Fentanyl	23 (27.7)	62 (86.1)	
Morphine	60 (72.3)	10 (13.9)	
• Infusion rate	6.9±1.2	6.9±1.9	0.978

NSAIDs=non-steroid anti-inflammatory drugs; SD=standard deviation

Continuous variables are presented as mean±SD, Categorical variables are presented as n (%)

Table 3. Postoperative outcomes

	Epidural morphine bolus (n=84)	Conventional (n=78)	p-value
PACU; n (%)			
Need rescue therapy	37 (46.8)	54 (71.1)	0.002
Rescue with IV analgesia	16 (19.0)	24 (30.8)	0.017
Rescue with epidural bolus	33 (39.2)	47 (60.2)	0.032
Maximum pain; median (IQR)	2.5 (0 to 7)	6 (1 to 8)	0.025
Pain before discharge from PACU; median (IQR)	0 (0 to 2)	0 (0 to 2)	0.113
Postoperative day 1; n (%)			
Maximum pain; median (IQR)	1 (1 to 6)	6 (6 to 7)	<0.001
Minimum pain; median (IQR)	0 (0 to 1)	2 (2 to 3)	0.001
Patient with moderate to severe pain score	38 (45.8)	55 (70.5)	
Need rescue tramadol	25 (30.1)	42 (43.8)	0.002
Vomiting	31 (36.9)	30 (38.4)	0.552
Pruritus	32 (38.6)	13 (16.7)	0.002

PACU=post-anesthetic care unit; IQR=interquartile range

Continuous variables are presented as median (IQR), Categorical variables are presented as n (%)

significantly higher than in the conventional group. There was no incidence of motor weakness and respiratory depression during the first postoperative period.

Table 4. Univariate- and multivariate analysis of patients with postoperative moderate to severe pain on the first postoperative day

	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age >60 years	0.41 (0.20 to 0.84)	0.016	0.47 (0.21 to 0.76)	0.013
BMI >35 kg/m^2	1.22 (1.12 to 1.35)	0.081	1.44 (0.98 to 1.67)	0.128
Operative time >360 minutes	1.31 (0.91 to 147)	0.271		
Skin to epidural space distance	1.06 (0.75 to 1.48)	0.231		
Epidural morphine bolus	0.46 (0.18 to 0.92)	0.045	0.33 (0.16 to 0.61)	0.002
Concentration of LA (reference: 0.1% bupivacaine)	0.62 (0.42 to 0.91)	0.016	0.43 (0.21 to 0.85)	0.012
Combined opioid (reference: morphine)	0.59 (0.28 to 1.39)	0.284		
Rate of infusion	0.91(0.71 to 1.15)	0.393		

OR=odds ratio; CI=confident interval; BMI=body mass index; LA=local anesthetics

Table 4 shows the independent factors associated with moderate to severe postoperative pain on the first POD1. The multivariable analysis results demonstrated that aged 60 years or more, epidural morphine bolus, and 0.1% bupivacaine for postoperative analgesia were independent risk factors.

Discussion

The present study showed that additional epidural morphine bolus into continuous epidural analgesia provides better postoperative pain control and decreases the need for rescue treatment of breakthrough pain compared with the conventional technique either immediately after an operation or on the first POD1.

Failed or inadequate epidural analgesia has been reported in postoperative upper abdominal surgeries. According to a previous study, 20% to 38% of all thoracic epidural analgesia failed[7,8]. The common causes could be a primary failure, incorrect catheter placement, secondary catheter-related problems, or suboptimal dosing of analgesic medications[8]. Consequently, immediately postoperative pain is associated with those problems. In the present study, the factors arising from primary failure could not be distinguished but other factors, including epidural location, depth of epidural catheter, and intraoperative epidural analgesia management, were not significantly different between the two groups.

The optimal dose of bupivacaine for thoracic epidural analgesia for abdominal surgery was 8 to 13 mg/hour administered along with 25 to 30 mcg/hour of fentanyl or 250 to 500 mcg/hour of morphine[9-11]. Combined low doses of opioids with epidural local anesthetics have increased analgesic quality for postoperative abdominal surgery[12]. In the present study, the amount of local anesthetics and opioid use in epidural analgesia regimen were lower compared to other studies. As a result, the incidence of moderate to severe pain after liver resection was high. Adding morphine to the epidural analgesia regimen helps to increase analgesia quality by mediated via spinal and supraspinal mechanisms[13]. The dose of additional morphine bolus in the present study was 1 to 2 mg, which was determined by the attending anesthesiologist.

There are studies regarding the optimal dose of morphine bolus in major abdominal surgery. Taura et al[14] studied epidural analgesia in liver resection. Their study reported the mean pain score was less than 3 twelve hours after surgery in patients receiving epidural morphine of 3.5 to 5 mg. Moreover, 40% of patients required the supplement pain medications fifteen hours after surgery. The previous study showed a bolus dose of 1 mg morphine followed by continuous epidural infusion of morphine 0.1 mg/hour with bupivacaine in lower abdominal and gynecologic surgery had a low mean pain score of 2.2, and only 16% of patients required the supplement analgesia[15]. The present study showed the supplement dose of morphine 1 to 2 mg to conventional epidural infusion provided a better quality of pain control.

Common side effects of epidural morphine are nausea, vomiting, pruritus, and respiratory depression. Those effects are dose-dependent. Previous studies found increased pruritus with incremental morphine doses[16]. The present study showed that the patients who received additional epidural morphine bolus experienced more pruritus and required more intravenous chlorpheniramine treatment than the conventional group. The opioid-related respiratory depression needed a higher dose of epidural morphine. The previous studies showed the safeness of epidural morphine from 1 to 5 mg in terms of respiratory depression. There was no incidence of respiratory depression over 24 hours postoperatively and no

patient needed naloxone to treat the respiratory depression[17]. However, obese patients are more prone to postoperative respiratory depression than the general population. Zotou et al[18] studied the effect of using 1 to 2 mg of epidural morphine in bariatric surgery and found only mild morphine-related side effects. In addition, no respiratory depression was observed in super-obese patients with a high prevalence of obstructive sleep apnea. The present study showed no morphine-related severe adverse effect observed as well.

The previous studies showed the elder patients increased sensitivity to epidural analgesia more than the younger patients[19,20]. In the present study, more than 65 years of age was the protective factor for moderate to severe pain on the first POD1. According to the literature, the postoperative epidural analgesia quality depends upon patient characteristics and anesthesia-related factors, including the amount or method of epidural administration and the type of local anesthetics and opioids[10,21,22]. In the present study, the authors found that the epidural administration of a higher concentration of local anesthesia at 0.1% versus 0.08% bupivacaine, was a protective factor for moderate to severe pain on the first POD1. The final independent protective factor was the additional dose of epidural morphine.

There are limitations in this study. Firstly, it was a retrospective study and data may have not been recorded. There were also limitations in data collection due to the differences in definition. As a result, the incidence of side effects like vomiting and respiratory depression may differ from other studies. Secondly, the present study intraoperative epidural management was not based on protocol-guided management. The type, concentration, and mode of administration of local anesthetics were varied. These differences may affect the quality of analgia and the level of pain at PACU. Lastly, the present study included only patients that underwent liver resection, one of the surgeries causing severe postoperative pain. The outcomes may differ in a different type of surgery.

Conclusion

Additional epidural morphine bolus into epidural analgesia provided better postoperative pain control. It decreased the need for rescue treatment of breakthrough pain compared with the conventional technique at PACU and on the first postoperative operative day. At the same time, the incidence of pruritus was significantly higher in the epidural morphine bolus group.

What is already known on this topic?

Liver resection surgery or major upper abdominal surgery causes profound postoperative pain. Thoracic epidural analgesia is the most effective analgesia technique. However, there has been a high incidence of insufficient postoperative analgesia.

What this study adds?

The conventional thoracic epidural analgesia for liver surgery showed a higher incidence of inadequate analgesia that required rescue treatment for breakthrough pain. This study found that intraoperatively administered 1 to 2 mg of additional epidural morphine bolus, provided higher quality of analgesia immediately after surgery or on the first postoperative day. However, this management increased the epidural morphine-related side effect. This study demonstrated the protective factors of moderate to severe pain on the first postoperative day, including patients aged more than 60 years, using epidural 0.1% bupivacaine or morphine bolus.

Authors' contributions

WA processed data clearance, data analysis, data interpretation, and drafted the manuscript, OC, PL, and WS participated in coordinating the study and data collection, NP contributed to data collection, prepared figures, and tables, and drafted the manuscript, and IS contributed to the study design and revised the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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