Clinical benefits of preemptive thoracic epidural analgesia with hydromorphone and bupivacaine in open thoracotomy lung surgery

Department of Anesthesiology and Pain Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, *Department of Anesthesiology and Pain Medicine, Veteran Health Service Medical Center, Seoul, Korea

Sang Hyun Lee, Woo-Seok Sim, Mikyung Yang, Jie Ae Kim, Hyun-joo Ahn, Byung-Seop Shin, Hyun-young Lim, Do-yeon Kim, and Jin Sun Yoon*

Background: Preemptive analgesia is known to decrease the sensitization of the central nervous system and reduce subsequent amplification of nociceptive stimuli. We investigated whether preemptive thoracic epidural analgesia (TEA) demonstrated intraoperative and postoperative short and long term clinical advantages.
Methods: Thirty patients scheduled for open thoracotomy were randomly allocated to one of two groups to receive continuous TEA (0.15% bupivacaine and 8 μg/ml hydromorphone) either before surgical incision (preemptive group) or at the end of the operation (nonpreemptive group). Incidence of hypotension during surgery was recorded. Numerical rating scales (NRS) and the incidence of side effects such as nausea, pruritus, sedation, hypotension, and respiratory depression were recorded at 2, 6, 24, and 48 hours postoperatively. Pulmonary function test (PFT) was performed before, 24 and 48 hours after the operation. Persistence of pain control was investigated at 6 months postoperatively.
Results: The NRS score, side effects, and PFT changes were comparable between the two groups. TEA and intravenous rescue morphine consumed at 2, 6, 24, and 48 hours postoperatively were not different between the two groups. During surgery, the incidence of hypotension was significantly higher in the preemptive group (P = 0.027). At 6-month follow up, two patients in the nonpreemptive group complained of persistent pain at wound and none in the preemptive group.
Conclusions: Preemptive TEA with hydromorphone and bupivacaine

during surgery may cause unnecessary intraoperative hypotension without a prominent advantage in reducing acute or chronic pain or enhancing pulmonary function after thoracotomy. The advantageous concept of preemptive TEA may be dubious and may not provide perioperative clinical benefits. **(Anesth Pain Med 2015; 10: 82-88)**

INTRODUCTION

Preemptive analgesia, which refers to an analgesic intervention facilitated before the onset of noxious stimuli to obliterate the sensitization of the central nervous system, is not a novel concept in postoperative pain management. It was allegedly known to exert more effective analgesia in acute pain and to decrease the incidence of hyperalgesia, allodynia, or chronic persistent pain [1]. However, the efficacy of preemptive analgesia still remains controversial [2,3].

Post-thoracotomy pain can be an excruciatingly painful experience which needs to be well controlled to reduce both acute pain and long term convergence to chronic pain [4]. Thoracic epidural analgesia (TEA) has been the gold standard for achieving pain relief after thoracotomy in lung resection [5,6]. Preemptive application of TEA, which means initiation of TEA before surgical incision, has been introduced and investigated extensively in clinical practice in addition to the conventional TEA regimen [4,7-13]. Many clinical investigations have been conducted to assess the efficacy of preemptive TEA in acute and chronic post-thoracotomy pain and a few studies on postoperative pulmonary functional recovery have been performed [7,8]. However, with respect to perioperative patient management, clinical usefulness and advantages of preemptive

TEA over conventional TEA including intraoperative hemodynamics and vasopressor requirement, and postoperative analgesia and pulmonary functional recovery have not been studied.

In this study, we aimed to assess whether there are intraoperative and short and long term postoperative clinical benefits of preemptive initiation of TEA compared to nonpreemptive TEA in patients undergoing thoracotomy for lung resection.

MATERIALS AND METHODS

After receiving approval from the Institutional Review Board of our hospital, 36 patients who were scheduled for an open thoracotomy were enrolled. Informed consent was obtained from all patients. For safety and correct placement, the thoracic epidural catheters were inserted such that their tips would be placed at thoracic levels T5-6 or T6-7 under fluoroscopic guidance at pain center, one day prior to the surgery. Patients were randomly allocated to either preemptive TEA initiation before surgery (preemptive group) or TEA initiation at the end of surgery (nonpreemptive group). An investigator conducted the randomized allocation process according to the group block number, generated by a computer based randomization program (www.randomizer.org) and a concealed envelope technique was used. This randomized study conformed to the CONSORT guidelines and Consort checklist and flow diagram were applied (http://www.consort-statement.org). This study was registered retrospectively in the Australian New Zealand Clinical Trials Registry (ANZCTR) with a registration number. Exclusion criteria were patients with renal, hepatic, or cardiac dysfunction, neurologic disorder, hematologic or coagulation disorder, infection at the epidural catheter insertion site, history of opioids, corticosteroids, or nonsteroidal anti-inflammatory drugs within one week of surgery, previous history of anticoagulation therapy, allergy to local anesthetics or opioids, or inability to use patient-controlled epidural analgesia device or to perform portable pulmonary function test (PFT). Demographic data were comparable between the two groups (Table 1).

Patients were not premedicated. General anesthesia was induced with thiopental sodium 5 mg/kg and 5 vol% sevoflurane. Trachea was intubated after injection of rocuronium 0.8 mg/kg. Intravenous fentanyl 1–2 µg/kg was given during induction of anesthesia and thereafter at the discretion of the anesthesiologist. Maintenance of anesthesia was carried out with either 1 minimum alveolar concentration of sevoflurane or isoflurane to target systolic blood pressure (SBP) within 30%

Table 1. Demographic Characteristics and Intraoperative Data

	Preemptive group (N = 15)	Nonpreemptive group (N = 15)	P value
Age (yr)	64.4 ± 9.5	60.4 ± 8.4	0.158
Sex (M/F)	14/1	13/2	1.000
Weight (kg)	65.1 ± 11.4	64.4 ± 7.2	0.934
Height (cm)	166.2 ± 5.8	165.0 ± 5.2	0.486
Type of operation			
Lobectomy	13	11	
Pneumonectomy	2	3	0.651
Lung decortication	0	1	
Operative time (min)	218.3 ± 64.3	201.3 ± 46.3	0.405
Anesthesia time (min)	272.5 ± 59.3	256.9 ± 48.2	0.418
Intraoperative fentanyl (ug)	90.0 ± 60.4	110.0 ± 38.7	0.251
Incidence of intraoperative hypotension (number)* requiring inotropes or vasopressor support	11/15*	4/15	0.027
Intraoperative crystalloid (ml)	1,636.7 ± 542.0	1,550.0 ± 446.4	0.739
Intraoperative colloid (ml)	710.0 ± 239.2	526.7 ± 279.0	0.106
Estimated blood loss (ml)	403.3 ± 215.9	378.0 ± 239.4	0.586
Urine output (ml)	716.0 ± 499.2	432.3 ± 212.1	0.125

Values are presented as mean ± SD. TEA: thoracic epidural analgesia. *The incidence of intraoperative hypotension refers to a persistent decrease of systolic blood pressure < 30% of baseline or mean blood pressure < 60 mmHg, which is not due to bleeding episode, and which requires a continuous infusion of inotropes or vasopressors despite intravenous bolus injections of ephedrine or phenylephrine. *P < 0.05 is significantly different compared to the nonpreemptive TEA group.

of baseline or mean blood pressure (MBP) > 60 mmHg. The choice of anesthetics was at the discretion of the anesthesiologist.

After induction of anesthesia, patients in the preemptive group received a bolus of 10 ml 0.1% bupivacaine with 100 μg hydromorphone via an indwelling epidural catheter followed by a continuous infusion with an infusion pump (Aim[®] Plus, Abbott Laboratories, Chicago, IL, USA) at least 30 minutes before surgical incision, while they were being sterilized and draped. Patients in the nonpreemptive group received the same 10 ml epidural drug administration and a continuous TEA regimen at the end of surgery. In both groups, the continuous TEA regimen was comprised of 0.15% bupivacaine with 8 μg/ml hydromorphone at a basal rate of 5 ml/hr and a 3 ml bolus with a 15 minutes lockout interval.

The incidence of persistent hypotension during surgery was recorded. Hypotension was defined as a persistent decrease of SBP < 30% of baseline or MBP < 60 mmHg, which was not due to a bleeding episode, and which required a continuous infusion of inotropes or vasopressors despite three or more consecutive intravenous (IV) bolus injections of 5–10 mg ephedrine or 1 μg/kg phenylephrine.

The amount of TEA and IV fentanyl administered during surgery was recorded.

Blindness was not achieved during surgery because of the different timing of TEA application. However, patient assessment after surgery was conducted in a blinded manner by an anesthesiologist unaware of patient allocation. Postoperative analgesia was maintained with TEA and rescue IV morphine or oral tramadol and acetaminophen combination (Ultracet[®], Janssen Korea Ltd., Seoul, Korea). Consumption of TEA after surgery was recorded. Numerical rating scales (NRS, a scale of 0–10 in which 0 is no pain and 10 is worst pain) for pain at rest and on coughing were used to assess the pain severity. The incidence of intraoperative hypotension, and side effects including nausea, pruritus, sedation, hypotension, and respiratory depression were recorded at 2, 6, 24, and 48 hours postoperatively. Functional vital capacity (FVC) and forced expiratory volume in 1 second (FEV$_1$) were measured by a portable spirometer (Micro[TM], Micro Medical Limited, Rochester, UK) before surgery and at 24 and 48 hours postoperatively.

Persistence of pain and pain characteristics at the surgical wound were also investigated at 6 months postoperatively.

Sample size with a power of 90% and a type I error of 5% was determined, and it was calculated to be 10 patients per group to detect a NRS difference of 3 with a standard deviation (SD) of 2 at 48 hours postoperatively. At least fifteen patients per group were planned to be enrolled in this study considering a dropout rate of 50% during the postoperative follow up.

Statistical analysis was carried out using SPSS 18.0 (SPSS, Chicago, IL, USA). The patient characteristics, intraoperative data, amount of TEA, and rescue IV fentanyl or morphine consumption, the NRS and PFT parameters were analyzed using the Mann-Whitney test with Bonferroni correction. The incidence of side effects was compared using the chi-square or

Table 2. Consumption of Thoracic Epidural Analgesia and Rescue Analgesics during the First 48 Hours after the Operation

		Preemptive group (N = 15)	Nonpreemptive group (N = 15)	P value
Intraoperative administration of TEA (ml)*		15.6 ± 4.9[†]	3.1 ± 0.8	< 0.001
Cumulative amount of postoperative administration of TEA (ml)[†]	0–2 h	11.8 ± 5.1	11.2 ± 4.3	1.000
	2–6 h	30.4 ± 10.8	28.7 ± 7.9	1.000
	6–24 h	92.0 ± 40.9	93.6 ± 33.8	1.000
	24–48 h	159.7 ± 75.0	170.4 ± 71.4	1.000
Rescue morphine sulfate (mg)	0–2 h	3.4 ± 4.1	2.2 ± 3.0	1.000
	2–6 h	0.6 ± 2.2	0.3 ± 1.3	1.000
	6–24 h	6.9 ± 6.7	5.8 ± 5.6	1.000
	24–48 h	6.9 ± 5.2	9.7 ± 5.5	0.868
Rescue oral analgesics (Ultracet[®]) (number of patients)	0–2 h	0	0	NA
	2–6 h	0	0	NA
	6–24 h	5/15	3/15	1.000
	24–48 h	5/15	5/15	1.000

Values are presented as mean ± SD or number of patients. TEA: thoracic epidural analgesia. *Intraoperative administration of TEA: the amount of TEA administered during surgery. [†]Cumulative amount of postoperative administration of TEA (ml): the amount of TEA administered after surgery. [†]P < 0.05 is considered significantly different compared to the nonpreemptive TEA group.

Fisher's exact test. The data are presented as mean ± SD or median (interquartile ranges) or numbers wherever appropriate.

RESULTS

Of the 36 enrolled patients, 30 patients completed the study (15 in the preemptive group and 15 in the nonpreemptive group). Six patients (three in each preemptive group and nonpreemptive group) were withdrawn from the study because TEA was discontinued before 48 hours after surgery due to nausea (3 patients), pruritus (2 patients), and respiratory depression (1 patient).

The incidence of hypotension, which was not related to bleeding and required intervention during surgery, was significantly higher in the preemptive group (11 patients in the preemptive group and 4 patients in the nonpreemptive group; P = 0.027). Intravenous fentanyl administration was similar between the two groups (Table 1). For postoperative analgesia, TEA, IV rescue morphine or rescue oral analgesics were administered. The requirement of TEA, IV rescue morphine or rescue oral analgesics were similar in both groups (Table 2).

The NRS scores for pain at rest and on coughing during the first 48 postoperative hours, and FEV1 and FVC changes from baseline at 24 and 48 hours postoperatively were similar between the two groups (Figs. 1 and 2).

The incidence of nausea, pruritus, sedation, hypotension, and respiratory depression was similar between the two groups throughout the study period (Table 3).

At the 6-month follow up, two patients in the nonpreemptive group complained of persistent pain at the surgical wound
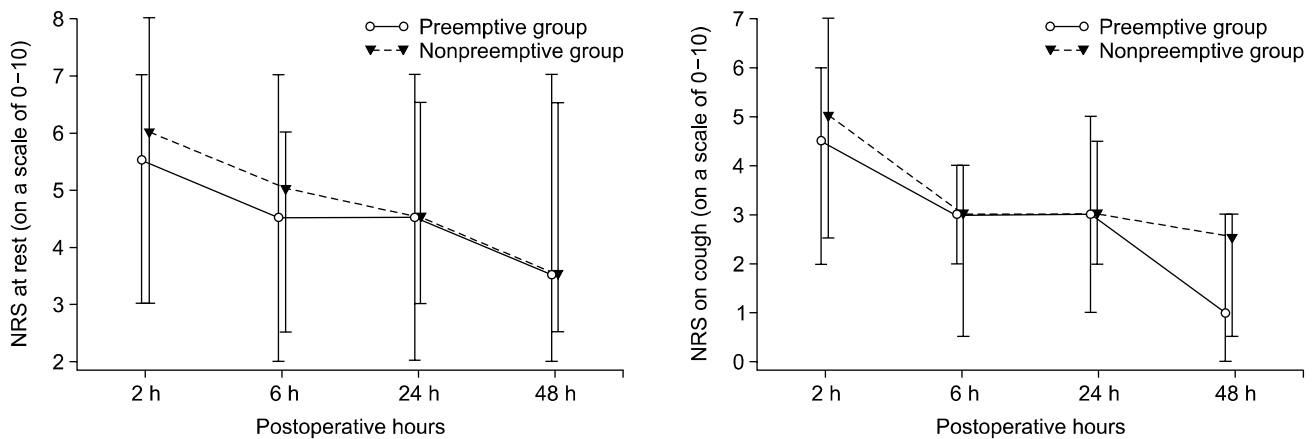
Fig. 1. Pain scores during the first 48 hours after surgery. Median pain levels at rest and on coughing according to the numerical rating scale (NRS) during the first 48 hours after surgery. Error bars indicate interquartile ranges.
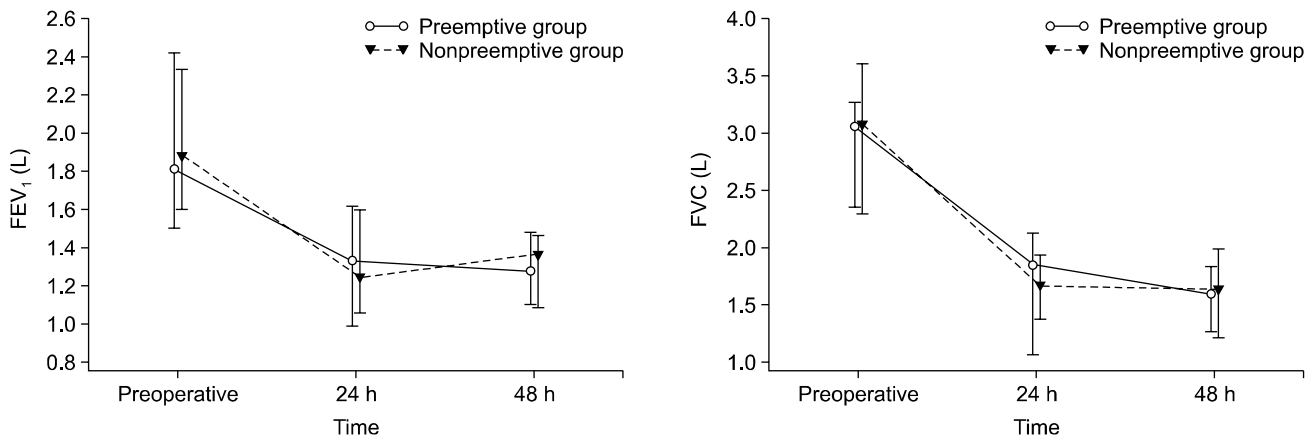
Fig. 2. Pulmonary function test. Median percentage changes in forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) compared to preoperative values during the first 48 hours after surgery. Error bars indicate interquartile ranges.

Table 3. Incidence of Postoperative Side Effects during the First 48 Hours after the Operation

	Postoperative hours	Preemptive group (N = 15)	Nonpreemptive group (N = 15)	P value
Nausea	0–2 h	1	2	1.000
	2–6 h	1	5	0.676
	6–24 h	3	3	1.000
	24–48 h	1	2	1.000
Pruritus	0–2 h	1	0	1.000
	2–6 h	3	2	1.000
	6–24 h	6	8	1.000
	24–48 h	5	4	1.000
Sedation	0–2 h	4	8	1.000
	2–6 h	6	8	1.000
	6–24 h	5	9	1.000
	24–48 h	5	9	1.000
Hypotension	0–2 h	0	2	1.000
	2–6 h	0	2	1.000
	6–24 h	0	0	NA
	24–48 h	0	0	NA
Respiratory depression	0–2 h	0	0	NA
	2–6 h	0	0	NA
	6–24 h	0	0	NA
	24–48 h	0	0	NA

Values are presented as the number of patients. NA: not applicable.

area. The pain characteristics in these two patients were acute penetrating pain with tingling sensation and allodynia.

DISCUSSION

Perioperative clinical benefits of preemptive TEA in patients undergoing thoracotomy were evaluated in this study. In this study, preemptive TEA did not show significant benefits in terms of acute pain control, opioid requirement, or pulmonary function changes after surgery. With respect to persistent pain after 6 months, none of the patients in the preemptive TEA group developed chronic pain, but two patients in the nonpreemptive TEA group complained of persistent pain despite oral analgesics.

Although several clinical and animal studies have investigated the effects of preemptive epidural analgesia on post-thoracotomy pain, acute and chronic analgesia with TEA remains controversial [2,14], and the overall quality of intraoperative anesthetic care in preemptive TEA and intraoperative use of TEA has not been widely studied. Our study focused on the quality of intraoperative anesthetic care in preemptive TEA, and a higher incidence of hypotension and

a greater requirement of inotropes or vasopressors were noted. An epidural bolus injection and continuous TEA in the preemptive TEA group caused frequent episodes of hypotension within 30 minutes after its initiation. In a recent study by Grider et al. [15], TEA with bupivacaine and hydromorphone provided enhanced analgesia compared to TEA with bupivacaine alone. TEA with bupivacaine alone increased the incidence of hypotension because an increased amount of basal bupivacaine was required to achieve analgesia. In our study, even at a low concentration of bupivacaine (10 ml 0.1% bupivacaine with 100 μg hydromorphone followed by a continuous infusion of 0.15% bupivacaine with 8 μg/ml hydromorphone at a basal rate of 5 ml/hr and a 3 ml bolus with a 15 minute interval), hypotension was significantly more frequent in the preemptive TEA group (11 patients in the preemptive group and 4 patients in the nonpreemptive group; P = 0.027). This finding may be attributed to anesthetic drugs and sympatholytic effect of epidural analgesia. Postoperative hypotension was observed in 2 patients of the nonpreemptive group; however, it was related to volume status of the patients, and patients were resuscitated with fluid administration. Therefore, risks and benefits of intraoperative use of more inotropes or vasopressors, and potential postoperative acute and chronic pain control should be weighed. Postoperative use of adrenergic drugs was a precipitating factor for cardiac arrhythmia after cardiac surgery [16]. Although a recent study did not identify inotropes or vasopressors as risk factors for atrial fibrillation after lung resection [17], postoperative supraventricular arrhythmia is not uncommon after lung surgery [18], and the possible risk should be considered. In our study, 14 out of the 15 patients in the preemptive group developed sustained hypotension requiring dopamine (13 patients) and/or phenylephrine (2 patients) continuous infusion (13 patients received dopamine only, 1 patient received phenylephrine only, and 1 patient received both dopamine and phenylephrine) and 2 out of these 14 patients developed intraoperative arrhythmia (atrial premature contraction [APC] and ventricular premature contraction [VPC] in 1 patient, and paroxysmal ventricular tachycardia in 1 patient). During postoperative care, among out of the 14 patients needing intraoperative dopamine infusion, 1 patient developed atrial fibrillation and another patient developed VPC. In the nonpreemptive group, 4 patients developed hypotension needing dopamine infusion, out of which 2 patients developed APC. We can not draw any conclusion from our findings regarding arrhythmias and intraoperative dopamine use; however, it should be cautioned that intraoperative TEA may cause

hypotension that may lead to unnecessary dopamine infusion during surgery.

Preemptive TEA was expected to provide benefits in acute and chronic pain control. However, a meta-analysis on the effects of preemptive TEA on post-thoracotomy pain showed that the efficacy of preemptive TEA was distinctive in only one of the six prospective, randomized controlled trials and this difference was attributed to the use of local anesthetics only without opioids in epidural drug regimen [8]. The authors postulated that opioids used with local anesthetics in TEA could have produced an effective analgesia that mimicked the potential benefits of preemptive epidural analgesia [8]. Also, the use of opioids as a premedication or during induction of anesthesia could have prevented the development of central sensitization [8]. This study used hydromorphone with bupivacaine in epidural regimen, and we also used IV opioid during induction as an adjuvant agent; therefore, potential benefits of preemptive TEA may have been masked and this resulted in similar results between the two groups in terms of acute and chronic analgesia. If systemic use of opioids prior to surgical incision or epidural use of opioids would have similar effects to those of preemptive TEA, and acute pain control can be achieved, then there may be no need to use TEA for preemptive purposes. However, although statistically insignificant, median acute pain levels were lower in the preemptive TEA group compared to the nonpreemptive TEA group, and there was no development of chronic persistent pain after 6 months in patients of the preemptive TEA group compared to two episodes of chronic sustained pain in the nonpreemptive TEA group in this study. According to studies by Senturk et al. [4] and Katz et al. [19,20], acute pain after thoracotomy could be a predictor of development of prolonged persistent pain; therefore, prevention or attenuation of chronic pain could be achieved with effective acute pain management. Association of acute pain with chronic pain development may need to be investigated further.

In our study, the incidence of side effects during the postoperative period was similar between the two groups. Pulmonary function test results were also not different between the two groups.

Limitations of this study are as follows: First, the number of patients in this study was small for generalization of issues such as relationship between acute and chronic persistent postoperative pain. The incidence of chronic pain may be low because of the small number of patients. Second, we used IV opioid for induction of anesthesia and hydromorphone in

epidural analgesia, which could have made it difficult to determine the pure preemptive effect of TEA. However, a multimodal approach to perioperative analgesia for thoracotomy pain is the treatment of choice and the use of IV opioid is a common practice in anesthesia; therefore, we considered that the use of low dose IV or epidural opioid was justified in this clinical study. Third, pulmonary function recovery was evaluated only during the first 48 hours. In previous studies, pulmonary function recovery was assessed over a longer period of time to determine the recovery of FEV1 and FVC close to the baseline. In this study, we were not able to evaluate whether the time required for recovery of pulmonary function to the baseline after preemptive TEA was shorter than that required after nonpreemptive TEA.

In conclusion, when TEA is applied with local anesthetics and opioids, preemptive TEA may not be necessarily advantageous over conventional TEA in acute and chronic perioperative patient management. However, with respect to long term pain control, further investigation may be necessary.

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