p-ISSN 1859 - 3461
e-ISSN 3030 - 4008

THE ANALGESIC EFFICACY OF LEVOBUPIVACAINE - FENTANYL VIA PATIENT-CONTROLLED EPIDURAL ANALGESIA AFTER RENAL TRANSPLANTATION

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ABSTRACT

Objective: *Evaluating the analgesic effect of patient-controlled epidural analgesia (PCEA) using a mixture of Levobupivacaine 0.1% and Fentanyl 2 µg/ml after renal transplantation.*

Methodology: *A prospective, descriptive, longitudinal study was conducted on 50 patients (n = 50) over 18 years old (ASA II - IV) who underwent renal transplantation (RT) surgery at 103 Military Hospital from August 2023 to October 2023. The PCEA solution comprised 0.1% Levobupivacaine combined with 2 µg/ml Fentanyl. Analgesic efficacy was assessed using the Visual Analog Scale (VAS) score both at rest and during movement (coughing) across time points up to 72 hours post-surgery.*

Results: *The PCEA method provided effective pain control. Mean VAS scores significantly decreased from baseline (H_0: 7.1 ± 1.08) to H_{72} (0.26 ± 0.29 at rest; 0.65 ± 0.49 during movement) ($p < 0.001$). The average percentage of successful demand requests (A/D ratio) was 85.53 ± 5.48%. Hemodynamic parameters (HR, SBP, MAP) showed statistically significant reductions ($p < 0.001$) compared to H_0 but remained stable within safe clinical limits throughout the monitoring period. The average respiratory rate decreased from 23.90 ± 2.49 breaths/min (H_0) to 14.64 ± 1.60 breaths/min (H_{72}). No respiratory depression or motor blockade (100% Bromage M0) was observed. Common adverse drug reactions (ADRs) included nausea/vomiting (16.0%) and itching (12.0%). Patient satisfaction was high, with 88% very satisfied and 12% satisfied.*

Conclusion: *PCEA utilizing a mixture of Levobupivacaine 0.1% and Fentanyl 2 µg/ml is a highly effective and satfety method for managing acute postoperative pain after renal transplantation surgery, achieving stable, low VAS scores below the clinically accepted threshold throughout the 72-hour observation period.*

Keywords: *Levobupivacaine, Fentanyl, Patient-Controlled Epidural Analgesia, Renal Transplantation, Postoperative Pain.*

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Ngày gửi bài: 28/10/2025; Ngày nhận xét: 21/11/2025; Ngày duyệt bài: 26/11/2025
https://doi.org/10.54804

p-ISSN 1859 - 3461
e-ISSN 3030 - 4008

1. INTRODUCTION

Postoperative pain management is a fundamental component of patient care and recovery. In complex surgical cases, such as renal transplantation (RT), effective pain control is critical, as severe pain can induce physiological stress responses, potentially leading to factors like increased blood pressure and impaired kidney function, which may negatively impact the transplanted graft [1]. Given that the use of non-steroidal anti-inflammatory drugs (NSAIDs) is often restricted due to the risk of nephropathy and acute kidney injury, alternative, non-systemic methods are essential [2].

Patient-controlled epidural analgesia (PCEA) is an advanced regional technique proven to provide superior pain management, characterized by patient self-administration and control, which reduces anxiety and discomfort associated with waiting for nurse-administered medication. PCEA optimizes analgesic efficacy while minimizing the amount of drug used and reducing systemic side effects [3].

The combination used in this study involves levobupivacaine, an S-isomer local anesthetic known for its efficacy comparable to bupivacaine but with less cardiotoxicity and central nervous system toxicity, combined with a small dose of fentanyl, a highly lipophilic opioid [4]. This combination provides a multimodal approach with synergistic effects, leading to high efficacy and allowing for the use of a lower concentration of local anesthetic [5].

While PCEA efficacy using Levobupivacaine - Fentanyl has been established in various major abdominal surgeries [5], [6], its specific application in renal transplantation requires careful evaluation. This study aims to evaluate the analgesic effect of the combination of Levobupivacaine and Fentanyl using patient-controlled epidural analgesia after renal transplant surgery.

2. METHODOLOGY

2.1. Subjects

This prospective, descriptive, longitudinal study was conducted on 50 patients (n = 50) scheduled for renal transplantation at 103 Military Hospital, Vietnam, between August and October 2023.

Inclusion Criteria: The study enrolled 50 patients (n = 50) who were over 18 years old and classified as ASA II-IV. Patients must have undergone general anesthesia with endotracheal intubation (ETI) and extubation in the operating room, and possess the capability to understand and press the PCA button.

Exclusion criteria: Included severe cardiovascular conditions (severe aortic or mitral stenosis), known allergies to Levobupivacaine or Fentanyl, local infection at the puncture site, coagulopathy, spinal deformities, or refusal to participate.

2.2. Drugs and research equipments

2.2.1. Drugs used in the study

- Levobupivacaine 0.5% 50 mg/10ml from CPC1 Pharmaceutical Joint Stock Company, Hanoi (Vietnam).

- Fentanyl 0,5 mg/10ml from B. Braun (Germany).

- Lidocain 2% 2 ml (Central Pharmaceutical Enterprise of Vietnam).

- Anesthetic drugs: Propofol 200 mg/20ml, Sevoflurane 250ml bottle, Rocuronium 50 mg/5ml.

p-ISSN 1859 - 3461
e-ISSN 3030 - 4008

- Drugs used in kidney transplant surgery: antibiotics (cefazolin), hemostatic agents (transamine), immunosuppressive drugs (solumedrol), diuretics (furosemide, mannitol),...

- Respiratory resuscitation drugs, circulatory drugs, and various types of infusions.

2.2.2. Research equipments

- The Perifix epidural pain management kit by B. Braun(Germany) includes: G.18 Touhy needle, epidural catheter, bacterial filter, catheter connector, 01 5ml syringe, 01 10ml syringe without graduation, 01 20ml syringe.

- PCA Perfusor Space pump (B.Braun) from Germany.

- The pain assessment scale (VAS) ranges from 0 to 10.

- Multi-parameter monitor: heart rate, non-invasive blood pressure, respiratory rate, and peripheral oxygen saturation (SpO2) by Nihon Kohden (Japan).

- Equipment and devices used in circulatory and respiratory emergencies.

2.3. Study procedure

2.3.1. Anesthesia and PCEA procedure

Patients underwent pre-anesthetic examination, including assessment of ASA classification. Epidural catheter placement was performed pre-induction in the lateral decubitus position, primarily at the L2 - L3 intervertebral space. The catheter was advanced 5 - 7 cm into the epidural space, targeting the tip position at T10 - T11 for adequate surgical coverage. General anesthesia with endotracheal intubation (ETT) was induced using Propofol, Fentanyl, and Rocuronium, and maintained with sevoflurane (1 MAC).

The PCEA regimen was initiated post-surgery once the patient was fully awake (Aldrete ≥ 9), reported a VAS score > 4, had not received any other postoperative analgesics (H_0), and immediately prior to administration of the first dose through the epidural catheter. The mixture contained 0.1% Levobupivacaine and 2 µg/ml Fentanyl (100 ml total volume) PCEA parameters were set as follows:

• Initial dose volume (calculated based on height): (height in cm - 100) ÷ 10

• Bolus dose: 3 ml.

• Lockout interval: 10 minutes.

• Background infusion rate: 3 ml/hour.

• 4-hour limit: 30 ml.

Pain relief onset time was measured as the time until VAS < 4. Pain rescue was administered (5 ml of 1% Lidocaine epidurally) if the VAS remained ≥ 4 after two consecutive successful demand presses.

2.3.2. Analgesic efficacy assessment

Data was collected at H0 (baseline) and subsequent intervals up to H72.

• Efficacy: VAS scores (at rest and during movement/coughing). Effective pain relief is defined as VAS ≤ 3 cm at rest and ≤ 5 cm during movement. PCEA performance was assessed via the A/D ratio (Actual successful presses/Total Demand presses), with A/D > 75% considered acceptable.

• Safety: Hemodynamic parameters (HR, SBP, DBP, MAP) and respiratory parameters (RR, SpO_2) were monitored. Sedation level was assessed using the Observer's Assessment of Alertness/Sedation (OAA/S) scale. Motor blockade was assessed using the Bromage scale.

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• ADRs: Included nausea, vomiting, and itching.

• Patient satisfaction: Very satisfied, satisfied, neutral, dissatified, very dissatisfied.

Table 2.1. Data collection time points

H_0	**Just before injecting the anesthetic mixture**	**H_{16}**	**16 hours after injection**
$H_{0.25}$	15 minutes after injection	H_{24}	24 hours after injection
$H_{0.5}$	30 minutes after injection	H_{36}	36 hours after injection
H_1	1 hour after injection	H_{48}	48 hours after injection
H_4	4 hours after injection	H_{72}	72 hours after injection
H_8	8 hours after injection		

2.3. Data analysis

The data was collected and entered into a computer for processing using the SPSS 26.0 statistical software. The data were presented as mean standard deviation $(\overline{X} \pm SD)$, percentages (%). Comparison of means was performed using the T - student test. A p-value of < 0.05 was considered statistically significant.

2.4. Research ethics

The research protocol received approval according to official document number 256/HĐĐĐ dated August 9, 2023, by the Ethical Review Board (ERB) of 103 Military Hospital. Written informed consent was obtained from all patients, who were informed of their right to withdraw at any time.

3. RESULTS

3.1. Characteristics of the study patients

The study involved 50 patients, with an average age of 40.12 ± 11.86 years. Males predominated (68.0%). The majority of patients were classified as ASA III (86.0%), with 14.0% classified as ASA IV. The most common comorbidity was hypertension (92.0%). The average surgical duration was 136.2 ± 14.65 minutes. Post-transplant biochemical parameters confirmed early recipient kidney function, with serum creatinine decreasing significantly from 680.45 ± 25.3 µmol/L before surgery to 146.78 ± 140.6 µmol/L at 48 hours post-transplant.

3.2. Postoperative pain relief effectiveness

3.2.1. Analgesic onset and block extent

Table 3.1. Injection volume of the initial dose and onset time of analgesic effect

Indicator	$\overline{X} \pm SD$	Min	Max
Injection volume of the initial dose (ml)	6.34 ± 0.45	4.5	8.2
Onset time of analgesic effect (minutes)	8.66 ± 1.80	7	14

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e-ISSN 3030 - 4008

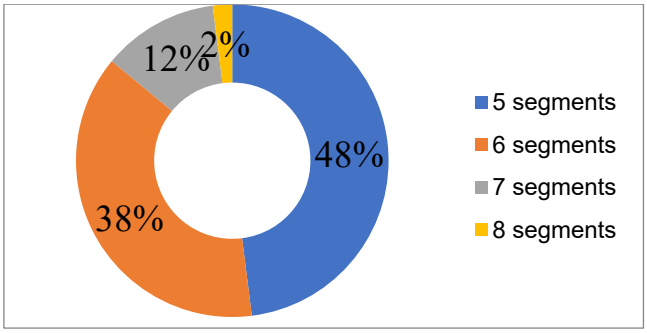

Chart 3.1. Number of blocked segments (n=50)

The mean onset time for effective pain relief (VAS < 4) was 8.66 ± 1.80 minutes. The sensory block extended across 5 to 8 spinal segments, with 5 segments being the most frequently inhibited (48% of patients).

3.2.2. VAS scores

Pain intensity showed a rapid and highly significant reduction ($p < 0.001$) at all monitored time points compared to baseline (H_0: 7.1 ± 1.08).

Table 3.2. Average VAS score at time points

Time point	VAS at rest ($\bar{X} \pm SD$)	VAS during movement (coughing) ($\bar{X} \pm SD$)
H_0	7.1 ± 1.08	7.1 ± 1.08
$H_{0.25}$	3.24 ± 0.98*	4.85 ± 0.76*
H_4	1.84 ± 0.34*	2.46 ± 0.89*
H_{24}	0.79 ± 0.55*	1.36 ± 0.45*
H_{72}	0.26 ± 0.29*	0.65 ± 0.49*

Note: (*) Comparison of values with the H_0 time point shows a statistically significant difference with p<0.001

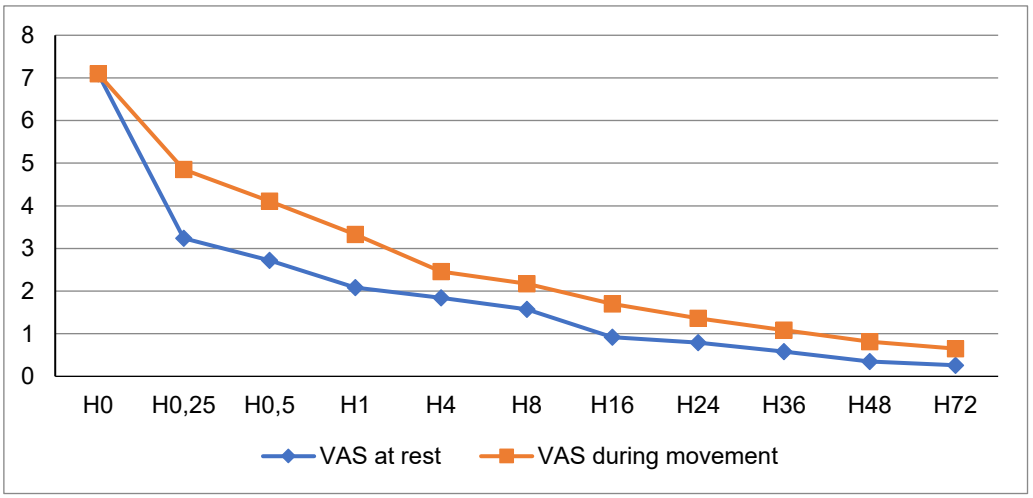

Chart 3.2. Average VAS score at rest and during movement at different time points

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3.2.3. PCEA usage and drug consumption

Table 3.3. PCEA usage and drug consumption

Indicator	0 - 24h $\bar{X} \pm SD$ (min - max)	24 - 48h $\bar{X} \pm SD$ (min - max)	48 - 72h $\bar{X} \pm SD$ (min - max)	Total $\bar{X} \pm SD$ (min - max)
Demand request	15.64±1.14 (13-17)	6.04±1.16 (3-9)	0±0 (0-0)	21.68 ±1.86 (17-26)
Actual request	13.18±1.02 (11-15)	5.32±1.24 (3-7)	0±0 (0-0)	18.50±1.52 (11-29)
A/D ratio (%)	85.46±6.20 (75-100)	89.46 ±8.56 (75-100)	0±0 (0-0)	85.53±5.48 (77,27-100)
Levobupivacaine (mg)	111.54±3.07 (105-117)	87.96±3.71 (81-93)	72.00±0.00 (72-72)	271.50±4.55 (261-282)
Fentanyl (µg)	223.08±6.14 (210-234)	175.92±7.42 (162-186)	144.00±0.00 (144-144)	741.74±37.72 (681-861)

The mean total Demand requests over 72 hours was 21.68±1.86. The mean overall A/D ratio was 85.53±5.48%, suggesting optimal settings.

Drug consumption was highest in the first 24 hours: Levobupivacaine consumption averaged 111.54 ± 3.07 mg and Fentanyl averaged 223.08 ± 6.14µg. Consumption steadily decreased on subsequent days.

A total of 13 patients required pain rescue, all occurring within the first 24 hours. The average time to the first required rescue dose was 12.00 ± 2.55 hours.

3.2.4. Patient satisfaction

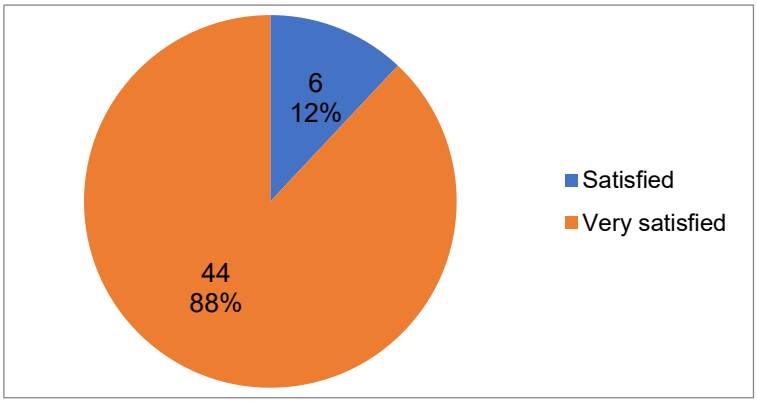

Chart 3.3. Patient satisfaction level

Patient satisfaction was excellent, with 88% reporting being very satisfied and 12.0% satisfied with the PCEA method.

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3.3. Effects on circulatory and respiratory parameters

Table 3.4. Hemodynamic parameters at time points

Time point	Heart rate (bpm) $\bar{X} \pm SD$	SBP (mmHg) $\bar{X} \pm SD$	DPB (mmHg) $\bar{X} \pm SD$	MAP (mmHg) $\bar{X} \pm SD$
H_0	101.32± 6.10	149.70±7.70	89.54±9.15	108.79±10.08
$H_{0.25}$	92.98± 5.32*	139.92±4.37*	83.08±6.76*	102.03±5.55*
H_4	86.30±3.95 *	132.92±5.02*	77.60±6.82*	96.04±5.70*
H_{24}	84.78±3.71*	128.68±4.99*	74.38±6.37*	92.48±5.15*
H_{72}	83.54±3.67*	125.58±7.36*	73.36±6.44*	90.77±6.11*

Note: (*) Comparison of values with the H_0 time point shows a statistically significant difference with $p < 0.001$

All hemodynamic parameters showed a statistically significant decrease compared to H0 ($p < 0.001$) but remained stable within the allowed range.

The respiratory rate (RR) decreased significantly from H0 (23.90 ± 2.49 breaths/min) to H72 (14.64 ± 1.60 breaths/min) ($p < 0.001$). No case of respiratory depression (RR < 10 breaths/min) or severe hypoxia (SpO_2 < 92%) was reported.

3.4. Adverse effects

Table 3.5. The incidence of adverse effects

Adverse effect	Rate (%)
Nausea and vomiting	16.0
Itching	12.0
Motor blockade (Bromage M_0)	100
Sedation (OAA/S 5)	100

The most common adverse effects were nausea and vomiting (16.0%) and itching (12.0%). Importantly, no patient experienced significant motor blockade (100% Bromage M0) or deep sedation (100% OAA/S 5).

4. DISCUSSION

The study population's characteristics underscore the need for a highly effective and safe regional technique. The average age of patients was approximately 40 years, and a high proportion were classified as ASA III (86.0%), often accompanied by comorbidities such as hypertension (92.0%).

The management of postoperative pain following renal transplantation presents unique challenges due to the special physiological status of the recipients. Our findings demonstrate that the PCEA mixture of levobupivacaine 0.1% and fentanyl 2 µg/ml delivered sustained analgesia. VAS scores were consistently low, remaining below 1 cm at rest and below 2 cm during movement from H_{24} onward, meeting the criteria for effective postoperative pain control (VAS ≤ 3 at rest and ≤ 5 during movement) [6] (Table 3.2, chart 3.2). These results align with findings from other studies both nationally and internationally [5], [6], [7].

The extent of sensory blockade achieved by the initial epidural dose was crucial for providing effective coverage for renal transplantation surgery. Our results indicated that the number of inhibited

p-ISSN 1859 - 3461
e-ISSN 3030 - 4008

dermatomes ranged from 5 to 8 spinal segments, with 5 segments being the most frequently observed block (48% of patients) (Chart 3.1). For pain control following kidney transplantation a procedure involving the iliac fossa it is necessary to achieve sensory block extending up to the T10 spinal segment, which innervates the umbilical region. Given that the epidural catheter was primarily inserted at the L2-L3 intervertebral space and the medication tends to spread approximately 3-4 vertebral segments from the injection site, achieving a 5 to 8 segment block confirmed successful coverage of the surgical region required for profound analgesia. The average initial dose of 6.34±0.45 ml was calculated based on patient height to meet this requirement, consistent with literature suggesting 1-1.5 ml of local anesthetic per spinal segment [8]. This reliable segmental blockade is fundamental to the highly effective reduction in VAS scores observed throughout the 72-hour period.

The highly potent nature of the regimen is reflected in the rapid onset time of 8.66±1.80 minutes (Table 3.1). This quick relief is largely attributed to the high lipid solubility of fentanyl, which ensures rapid penetration into the spinal cord's opioid receptors [6].

Additionally, the effectiveness of the patient-controlled mechanism was demonstrated by the overall high A/D ratio of 85.53 ± 5.48%. This ratio, which exceeds the acceptable threshold of 75% [9], validates that the programmed PCEA settings (3 ml bolus, 10-minute lockout, 3 ml/h background infusion) were optimized to meet the patients' fluctuating analgesic demands. The highest analgesic consumption (Levobupivacaine 111.54 ± 3.07 mg in the first 24h) and all rescue doses (13 patients) occurred during the first 24 hours, correlating with the peak phase of acute postoperative pain [1], [7] (Table 3.3).

The high patient satisfaction rate (100% satisfied or very satisfied) confirms that PCEA provides superior comfort and flexibility, allowing patients to self-manage their pain effectively (Chart 3.3).

Safety analysis demonstrated minimal impact on vital functions. Renal transplant patients frequently suffer from hypertension (92.0% in our study). Severe pain triggers sympathetic activation, leading to hypertension and increased myocardial workload. The PCEA technique effectively blocked this sympathetic response, leading to a statistically significant decrease in heart rate and blood pressure from H_0 to H_{72} (Table 3.4). This hemodynamic stabilization is therapeutically beneficial for transplant recipients.

Furthermore, combining levobupivacaine (an agent with demonstrated reduced cardiotoxicity compared to its racemic counterpart, bupivacaine) with a low concentration of fentanyl (2 µg/ml) allowed us to achieve pain relief while maintaining neuromuscular and respiratory integrity [6]. The absence of motor blockade (100% Bromage M0) and deep sedation (100% OAA/S 5) confirms the safety of the regimen and is crucial for early patient mobilization (Table 3.5). While opioid use carries a risk of respiratory depression, the monitored RR remained safe, and no respiratory complications were observed.

Pain management in this group must mitigate the risk of pain-induced sympathetic overstimulation, which can lead to hypertension and potentially compromise the vascular integrity of the transplanted kidney [1]. Furthermore, the study confirms that the PCEA method is

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e-ISSN 3030 - 4008

appropriate for RT patients, as postoperative creatinine and urea levels showed the expected rapid improvement, indicating that the technique did not negatively interfere with early graft function. The mean surgical duration of 136.2±14.65 minutes is within the expected range for RT, yet the successful pain control demonstrated that the PCEA regimen was sufficient to manage the pain associated with this type of procedure.

Adverse effects (nausea/vomiting 16.0%, itching 12.0%) (Table 3.5) were low and manageable. These rates are comparable to those reported in other surgical pain studies utilizing epidural opioids, commonly linked to histamine release or systemic opioid action, and did not require specific intervention outside of standard care [10].

5. CONCLUSION

The study on 50 patients undergoing renal transplantation concluded that the mixture of 0.1% levobupivacaine and 2 µg/ml fentanyl administered via PCEA over 72 hours provided highly effective pain relief, satisfying 100% of the patients. The method demonstrated a favorable safety profile, minimally affecting circulatory and respiratory parameters, and resulted in no cases of motor blockade or respiratory depression.

6. LIMITATIONS

The study has several limitations. First, it did not include a comparative control group. In addition, it was conducted at a single center, which may limit the generalizability of the findings.

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