PERIOPERATIVE KETAMINE FOR PREVENTING PHANTOM LIMB PAIN AFTER AMPUTATION IN PATIENTS WITH LIMB ISCHEMIA: A PILOT STUDY

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Phantom pain after limb amputation (PLP) remains a challenge to prevent and manage due to its complex mechanism involving peripheral, neural, central and psychogenic mechanisms. In patients with limb ischemia who have frequent long history of ischemic pain and opioid consumption, the incidence of PLP seems to be soaring and more severe. Although advances in the management and treatment of vascular diseases have reduced the need for amputation in this population, managing postoperative pain remains a significant challenge and necessitates effective preventive strategies. Ketamine, which is not only an anesthetic but also a potential medication for the treatment of chronic pain, neuropathic pain, and phantom pain, is anticipated to prevent PLP. This is a prospective study conducted on six patients (63 - 77 years old) with limb ischemia undergoing amputation surgery. The results showed that PLP occurred in 3 patients (50%), with the average visual analog score (VAS) of 1 (range of 0-7 on day 3, 0-4 on day 5). Phantom sensation was also recorded early in 3 patients (50%) and two of these 3 patients developed phantom pain later, suggesting that patients with postoperative phantom sensation should be observed thoroughly. Stump pain after amputation gradually decreased from day 1 (median 2.5, range 0-7) to 2.5 (range 0-4, day 2) and 2 on day 5 (range 0-3) without morphine rescue. Intraoperative ketamine infusion in this study has demonstrated its effectiveness in reducing PLP severity and postoperative stump pain without side effects. However, longer follow-up with a larger dataset is needed to further evaluate the long-term effects of ketamine on PLP.

Keywords: Phantom limb pain (PLP), stump pain, ketamine infusion, phantom sensation, amputation surgery, limb ischemia.

I. INTRODUCTION

Phantom sensation, showing any sensation except pain in the absent body part of an amputated limb, was described first by a French surgeon, Ambroise Paré, in 1551, followed by the “phantom pain” known during the American Civil War by a neurologist, Silas Mitchell.[1-3] The incidence of phantom limb pain after amputation ranges from 42.2% to 78.8%, with varying pain intensity.[4] Most cases involve moderate to severe pain, significantly impacting quality of life. The risk factors of postoperative phantom pain include female sex, upper extremity amputation, pre-amputation pain, residual pain in the remaining limb, and pain severity. Therefore, patients with limb ischemia

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who are indicated for amputation have a higher risk of suffering phantom pain postoperatively and need a more critical pain management strategy.

Phantom limb pain is classified as a type of neuropathic pain but has a combined mechanism of peripheral, central neural, and psychogenic mechanisms, making it difficult to treat once it develops.[1,5] Various pain management methods have been proposed to control postoperative phantom limb pain, including epidural analgesia, regional anesthesia, and oral neuropathic pain medications; however, none have achieved optimal effectiveness.

Ketamine, a dissociative anesthetic, has also been used for the treatment of both acute and severe chronic pain, with efficacy comparable to morphine.[4] In recent years, ketamine has gained increasing attention as an alternative to opioids for managing chronic pain conditions, particularly neuropathic pain, complex regional pain syndrome, cancer-related pain, and, especially, in the treatment and prevention of phantom limb pain following amputation. However, there have not been many studies on perioperative intravenous ketamine infusion to prevent phantom pain.[6] This study is believed to be a first step in evaluating the effectiveness of ketamine infusion in a high- risk group of patients.[6-8]

II. MATERIALS AND METHODS

1. Subjects

Inclusion criteria

Patients with limb ischemia (Rutherford stage 6 or Fontaine stage IV) indicated and scheduled for elective amputation surgery of the lower limb below the knee.[9]

Exclusion criteria

- Patients with liver or kidney failure.
- Patients with unstable cardiovascular conditions.
- Patients with impaired consciousness or uncooperative behavior.
- Patients who do not consent to participate in the study.
- Patients with a known allergy to ketamine.
- Patients with contraindications to ketamine.

2. Methods

Study design

This is a prospective study conducted on patients with limb ischemia who had an indication of amputation at Ha Noi Medical University from May of 2024 to February of 2025.

Research sampling

Convenience sampling. All patients who met selection criteria were included in this study. Six patients were eligible.

Anesthesia protocol

Patients who were selected would receive information and be prepared perioperatively as follows:

Preoperative Assessment and Patient Education

Conduct a comprehensive preoperative evaluation.

Assess the patient's pain status.

Educate the patient on the risks of phantom limb pain (PLP) and stump pain following amputation.

Explain the differences between these pain types and the available treatment options.

Preoperative Analgesic Catheter Placement

Place the analgesic catheter before surgery.

Evaluate the catheter's effectiveness based on sensory distribution.

Administer an initial bolus of local anesthetic (ropivacaine 1 mg/kg at least 20 minutes prior to surgery).

Intraoperative and Postoperative Regional Analgesia

Continuous infusion of ropivacaine (Anaropin) 0.1% at a beginning rate of 5 mL/h during operation and titration for 5 days postoperatively.

Catheter Placement:

Sciatic nerve catheter at the popliteal fossa for below-knee amputations.

Brachial plexus catheter for upper limb amputations.

Ketamine Administration

Administer ketamine at a dose of 0.45 mg/kg/3 hours intraoperatively and postoperatively.

Intraoperative Monitoring and Data Collection

Perform standard intraoperative monitoring every 5 minutes, including heart rate (HR); blood pressure (mean, systolic, diastolic); oxygen saturation (SpO_2); respiratory rate; electrocardiography (ECG), and body temperature.

All monitoring parameters were documented on the patient's study sheet.

General Anesthesia for Amputation Surgery

Induction Protocol: Propofol (1.5 – 2 mg/kg) and Fentanyl (2 – 5 mcg/kg).

Intraoperative Medications: Antiemetics: Dexamethasone (4mg) and Ondansetron (8mg).

Intravenous Analgesics: Paracetamol (15 – 20 mg/kg) and Ketorolac (30mg).

Postoperative Monitoring and Assessment

Conduct a consciousness assessment and assess the side effects of ketamine (hallucination, nausea, dizziness) 30 minutes after laryngeal mask removal.

Continue postoperative pain management and evaluate pain control efficacy.

Statistical analysis

All data were collected and analyzed by Excel and SPSS 20.0 version.

3. Research ethics

The study was designed to protect patients and improve patients' quality of life. It was performed under patient's approval, and the collected information is used for medical research only. The study is a part of a larger study approved by the Ethical Committee of Ha Noi Medical University (approval no.: 1396/GCN-HMUIRB issued on 22nd of April, 2024).

III. RESULTS

1. Clinical characteristic of patients:

Table 1. Clinical characteristic of the patients

	Patient1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Value
Gender							
Male, n (%)	+	+	+	+		+	5 (83.3%)
Female, n (%)					+		1 (16.7%)
Age, Median (Min-Max)	77	72	56	63	75	69	70.5 (63 - 77)
ASA score	3		3	3	3	3	5 (83.3)
		2					1 (16.7%)

Among 6 patients in the study, there are 5 male patients accounting for 83.3% and 1 female patient (16.7%). All patients were elderly with the age range of 63 to 77 years old (median age is 70.5 years old). Five out of six cases were ASA -3 which indicated severe system disease (83.3%), one patient was ASA-2 indicating mild system disease (16.7%).

Table 2. Risk factor of phantom pain

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Value
Opioid used before surgery, n (%)			+		+		2(33.3%)
No history of opioid before surgery, n (%)	+	+		+		+	4 (66.7%)
Ischemic limb pain before surgery (VAS), Median (Min - Max)	7	5	7	5	7	5	6 (5 - 7)
Infection of limb amputated, n (%)	+	+	+	+	+	+	6 (100%)
Time of surgery (minute), Median (Min - Max)	30	60	60	90	90	30	60 (30 - 90)
Lower limb amputation, n (%)	+	+	+	+	+	+	6 (100%)

Table 2 shows there are two patients (33.3%) treated with opioid for limb pain before amputation and four patients (66.7%) were not treated with opioid before surgery. The median ischemic limb pain was 6 (range from 5 to 7) indicating a moderate limb pain. All patients had signs of ischemic limb infection which is known as a risk factor for peripheral sensitization. Time of surgery ranged from 30 minutes to 90 minutes with the median time of 60 minutes. 100% percent of patients had lower limbs amputated.

2. Intraoperative changes

Chart 1 shows mean heart rate and mean blood pressure during surgery. Both heart rate and mean blood pressure changed slightly during operation. The changes were not statistically significant indicating a stable state during the whole procedure.

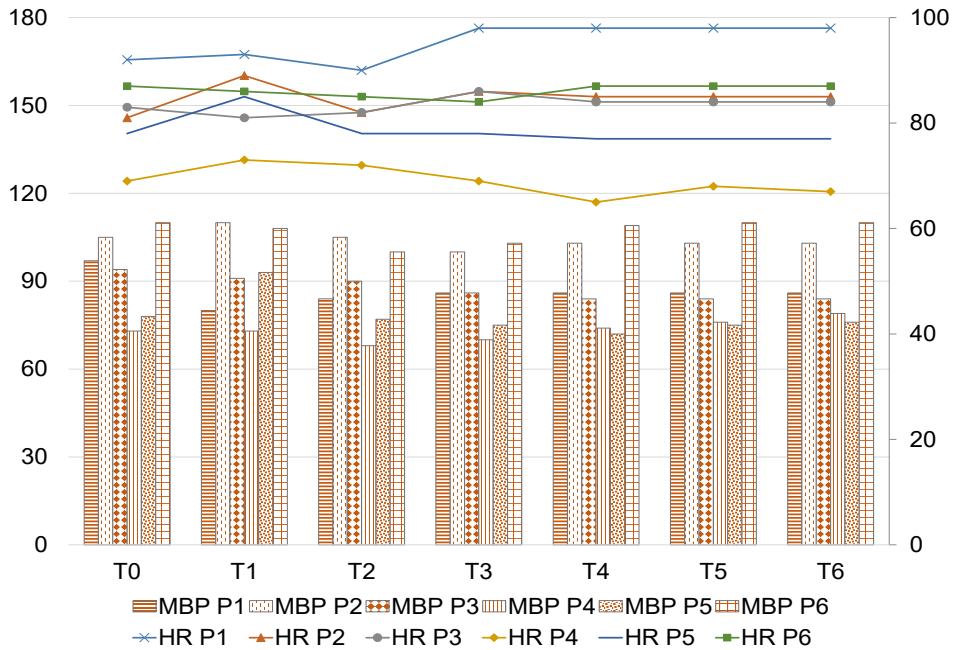

Chart 1. Intraoperative Heart rate and Mean Blood Pressure

(MBP P1: Mean Blood Pressure patient 1; HR P1: Heart rate patient 1

T0- Pre anesthesia time, T1- Time of skin incision, T2- 10 minutes after incision, T3- 20 minute after incision, T4- 30 minute after incision, T5- 40 minute after incision, T6- 50 minute after incision)

3. Postoperative assessment

Table 3. Phantom sensation after amputation surgery

	Patient1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Value, n (%)
Phantom sensation	+		+		+		3 (50%)
Day 0 postop	+		+		+		3 (50%)
Day 1 postop	+		+		+		3 (50%)
Day2 postop	+						1 (16.7%)
Day 3 postop	+						1 (16.7%)
Day 4 postop	+						1 (16.7%)

Table 3 shows the incidence of phantom sensation defined as any sensation in the absent limb except pain. Patient 1 felt the amputated limb and this sensation appears from day 0 (day of surgery) to day 4 with unchanged characteristic. Patient 3 and patient 5 had phantom sensation on the day of surgery and a day after.

Table 4. Stump pain after amputation surgery

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Value
Stump pain (VAS), n (%)	+	+	+	+	+	+	6 (100%)
Day 0 (day of surgery)	0	0	0	0	0	0	0
Day 1 postop, Median (Min - Max)	1	2	3	3	7	0	2.5 (0 - 7)
Day 3 postop. Median (Min - Max)	1	2	3	3	4	0	2.5 (0 - 4)
Day 5 postop	0	2	3	2	3	2	2 (0 - 3)
Morphin rescue, n (%)	0	0	0	0	0	0	0%

Stump pain is described in table 4 which shows that the average pain according to visual analog scale (VAS) on the day of surgery (Day 0) was zero. Then there was a slight increase in stump pain in day 1, day 3, day 5 postoperation which was 2.5 (0 - 7); 2.5 (0 - 4); 2 (0 - 3) respectively, indicating a stable state of patients and no morphine rescue needed.

Table 5. Phantom pain after amputation surgery (VAS score)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Value
Phantom Pain (VAS), n (%)			+	+	+		3 (50%)
Day 0 postop	0	0	0	0	0	0	0
Day 1 postop, Median (Min - Max)	0	0	0	3	0	0	0 (0 - 3)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Value
Day3 postop, Median (Min - Max)	0	0	2	3	7	0	1 (0 - 7)
Day 5 postop, Median (Min - Max)	0	0	2	2	4	0	1 (0 - 4)

Table 5 shows the incidence of phantom pain is 50% (3 patients). The phantom pain appeared quite early in patient 3 (1 day after surgery) and later in patient 4 and patient 5 (day 3 after surgery). The average postoperative VAS score in day 1, day 3, day 5 was 0 (0 - 3); 1 (0 - 7); 1 (0 - 4) respectively.

The study did not record any symptoms of nausea, hallucination or dizziness in any patient during the study period.

IV. DISCUSSION

This study aimed to evaluate the effectiveness of perioperative intravenous ketamine infusion in preventing phantom limb pain (PLP) after amputation in patients with limb ischemia. The findings suggest that ketamine may contribute to a reduction in both the incidence and severity of phantom pain while maintaining hemodynamic stability and minimizing adverse effects.

The incidence of phantom limb pain in our study was 50%, which aligns with previous reports indicating a prevalence ranging from 42.2% to 78.8% post-amputation.[4,6] Especially, patients receiving ketamine exhibited relatively low pain intensity, with median postoperative VAS scores remaining low across the study period (Day 1: 0 (0 - 3); Day 3: 1 (0 - 7); Day 5: 1 (0 - 4)). This supports the hypothesis that perioperative ketamine administration may attenuate the development of central sensitization, a key mechanism implicated in phantom limb pain. The presence of preoperative ischemic limb pain (median VAS = 6) may have contributed to central sensitization, which is a known risk factor for the development of PLP.

Opioid use prior to surgery was observed in 33.3% of patients, while 66.7% had no opioid exposure. Although prior opioid usage has been suggested as a potential risk factor for PLP, our sample size was too small to establish a statistically significant correlation. However, the lower-than-expected incidence of phantom pain in our study suggests that ketamine may play a role in mitigating central sensitization and subsequent neuropathic pain development.

Stump pain postoperatively was shown to be low in this study during the first five days. It is known that the pain in the surrounding areas of an amputated limb or in the opposite limb could be a trigger for the phantom pain.[8,10] Therefore, with the combination of ketamine infusion during operation and perioperative regional blocks, stump pain is well controlled, leading to less severity of postoperative phantom pain.

When comparing our findings with the randomized controlled trial conducted by Hayes et al. (2004), which assessed ketamine for post-amputation pain prevention, we observe key similarities and differences. In their study,

the incidence of phantom pain at six months was 47% in the ketamine group and 71% in the control group, though this difference did not reach statistical significance (p = 0.28). In contrast, our study found a 50% incidence of PLP, but due to the absence of a control group, a direct comparative analysis was not possible. Moreover, Hayes et al. did not find a significant reduction in pain severity or opioid consumption with ketamine infusion, whereas our results suggest that ketamine contributed to stable postoperative pain scores without the need for morphine rescue.[6]

One of the most notable findings of this study was there were no significant side effects associated with ketamine administration. All patients tolerated ketamine infusion well, with no record of nausea, dizziness, or hallucinations. This is consistent with studies that suggest low-dose ketamine, when administered in a controlled perioperative setting, has a favorable safety profile.[6]

Another important observation was the stability of intraoperative hemodynamic parameters, including heart rate and mean blood pressure, further reinforcing the safety of ketamine infusion in this patient population. Additionally, the absence of morphine rescue analgesia postoperatively suggests effective pain control with multimodal analgesia, including ketamine and regional anesthesia.

Despite these promising findings, the study has several limitations. The sample size was small, limiting the generalizability of the results. Additionally, the study lacked a control group receiving standard analgesia without ketamine, which would have provided a stronger comparative analysis. Further randomized controlled trials with larger sample sizes are necessary to confirm the benefits of perioperative ketamine infusion in preventing phantom limb pain.

V. CONCLUSION

Our study provides preliminary evidence that perioperative intravenous ketamine infusion may reduce the incidence and severity of phantom limb pain in high-risk patients undergoing limb amputation. The administration of ketamine was well tolerated, with no reported adverse effects, and was associated with stable intraoperative hemodynamics. Although these findings are promising, further large-scale, randomized controlled trials are needed to validate the efficacy and safety of ketamine as a preventive strategy for phantom limb pain.

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