Comparison of Low Dose Ketamine versus Ilioinguinal-Iliohypogastric Nerve Block for Post-Operative Pain Relief in Inguinal Hernia Repair Surgery: A Randomized Controlled Trial

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Abstract

Introduction: Lately ketamine has gained acceptance with studies showing its analgesic benefit in a low-dose form in various surgical operations. Our goal was to compare the post-operative analgesic effect of intravenous low-dose ketamine (IV ketamine) versus ilioinguinal-iliohypogastric nerve block (IINB) in inguinal hernia repair surgery.
Method: This was a prospective randomized clinical trial of 75 patients who were randomly allocated into three groups and received either intravenous normal saline solution (placebo group) (N=25); IV ketamine 0.25 mg/kg (N=25); or IINB (N=25) using 0.25% bupivacaine 20 ml under ultrasound (US) guidance, after having their inguinal hernia surgically repaired. Visual Analog Scale (VAS) scores were recorded at 0, 2, 6, 12, and 24 hours post-operatively. The time-first analgesic request, total opioid consumption, and post-operative complications were also evaluated.
Result: VAS scores were significantly lower in the IV ketamine and IINB groups compared to the placebo group at the 6th, 12th, and 24th hour of the post-operative period. Total opioid consumption was lower in the IINB group (56%) and the IV ketamine group (34%) compared to the placebo group. There was no significant difference among the three groups relating to time- first analgesic requirement, and no post-operative complications.
Conclusion: Both low-dose IV ketamine, and IINB, given provide effective pain control after inguinal hernia repair surgery, but IV ketamine showed inferior analgesia reflected by greater opioid consumption compared to IINB.

Keywords: Ketamine; ilioinguinal/iliohypogastric nerve; hernia; analgesic.

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Introduction

Ketamine is a dominant NMDA (N-methyl-D-aspartate) receptor antagonist playing an important role in the pain processing phenomenon. Intravenous (IV) ketamine is considered a good alternative to opioids for acute pain management. Multiple trials have shown that IV ketamine provides effective post-operative analgesia [1]. IV ketamine is simple, safe and cost-effective yet is has some related adverse effects [2].

Ilioinguinal-Iliohypogastric nerve block (IINB) has been successfully used for post-operative pain management in herniorrhaphy providing effective pain relief and prolonged analgesic effect. However, several complications have been reported [3–5].

Previous studies have shown that low-dose ketamine provides effective analgesia by reducing the rate of opioid consumption, similar to IINB, especially in cesarean section [6-7]. Unfortunately, no trials have been carried out to investigate this approach within herniorrhaphy.

Therefore, our objectives were to assess the efficacy of IV ketamine compared to IINB in achieving adequate pain control and reducing opioid consumption in herniorrhaphy.

Materials and Methods

This randomized control trial was conducted at our hospital, during January 2020 to March 2020, after obtaining approval from the Ethics Committee of Health Center [EC.81/62] and was registered with Thai clinical trial registry [Approval number: T CTR20200409010]. The study was a randomized and double blind design. Before the study began, 75 opaque envelopes were prepared and coded by a nurse anesthesiologist, not involved in the study. Seventy-five patients undergoing inguinal hernia repair surgery gave their informed consent to participate in this study. Patients in American Society Anesthesia classification I – III, between the ages of 18 – 80 years old were included. Exclusion criteria were if patient had any of the following: 1) obstructed/strangulated inguinal hernia; 2) contraindication to spinal anesthesia; 3) treatment with other NMDA receptor antagonists; 4) allergy to any of the study medication; and 5) severe psychological disorders.

The enrolled patients were randomized into 3 groups, with 25 patients in each group: 1) Normal saline solution (placebo), 2) intravenous ketamine group (IV ketamine), 3) Ilioinguinal - Iliohypogastric nerve block group (IINB). Standard monitors were applied to record heart rate (HR) and rhythm (ECG), arterial blood pressure (BP), and oxygen saturation values (O2). All patients received spinal anesthesia with hyperbaric bupivacaine 12.5 mg from the anesthesiologist who did not know to which group the patient was allocated. The block level was assessed using cold sensation and controlled within T6. Before skin incision, the intervention as shown in Figure 1 was given.

Patients received either: 1) normal saline volume 10 ml (placebo); 2) low dose ketamine intravenous 0.25 mg/kg diluted with normal saline in 10 ml (IV ketamine); or 3) ultrasound-guided ilioinguinal-iliohypogastric nerve block that contained 0.25% bupivacaine 20 ml (IINB). All the study agents were prepared by a nurse anesthesiologist whom not participating in this study.

After transferring patients to the ward, the Visual Analog Scale (VAS) score was used to access the patient's severity of pain within the first

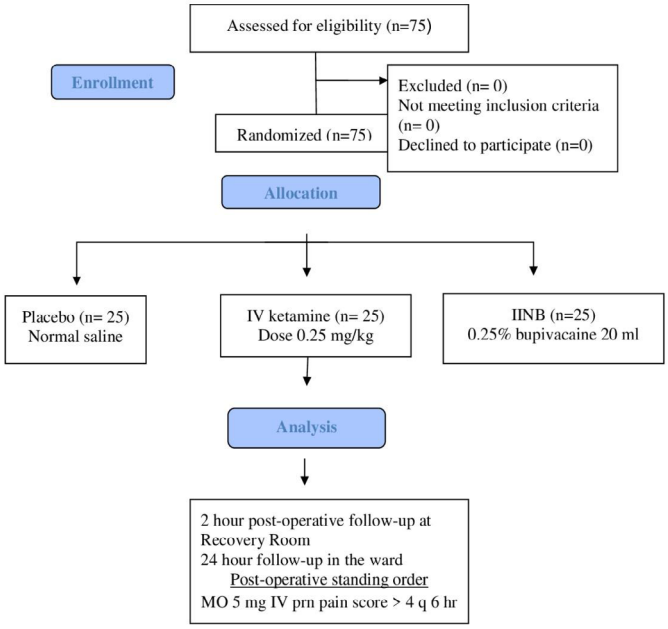

Figure 1 Study diagram.

24 hours by a ward nurse not participating in this study. The VAS score was assessed from the time of intervention administration. Supplementary morphine 5 mg intravenous was administered when patients reported their VAS > 4.

The primary outcome was the VAS score which was evaluated in the post-operative period at 0, 2, 6, 12 and 24 hours. T0 was time zero at post anesthetic care unit. Secondary outcomes were the duration of time from T0 to first analgesic pain requirement, total opioid consumption, the number of patients who needed analgesic medication, and adverse effects.

The sample size was calculated using the different between VAS scores (Delta) of 1.1 and the S.D. of 1.2 and 1.3 for the treatment and control group, respectively. Using the power of 80% and significance level of 0.05, as used in the study carried out by Ismail et al., a sample size of 21 patients per group was generated. We recruited an additional 4 patients per group to account for a 20% dropout, hence the sample size was increased to 25 patients per group.

The VAS scores were analyzed using mean and standard deviation (SD). One-way ANOVA and post-hoc pairwise t-tests with Bonferroni-correction were used to compare the VAS scores across the intervention groups at each time point. The level of significance was $P < 0.05$. The statistical analyses were conducted using Microsoft R Open 3.5.3 software.

Results

A total 75 patients were enrolled in this study, 25 patients in each group were analyzed. There was no significant difference between groups in terms of age, body weight, ASA classification, and operating time [Table 1].

The VAS scores were the lowest in the IINB group at all time points compared to the other two groups, and significantly lower at the 6th, 12th and 24th hour compared to the placebo group, but there was no significant difference between the IINB group and the IV ketamine group [Tables 2, 4, 5]. The VAS scores were lower in the IV ketamine group compared with the placebo group at the 6th, 12th and 24th hour, but only significantly different at the 6th hour [Tables 2, 4, 5]. At 0 and 2 hours, there was no statistically significant difference between the three groups.

Table 1 Evaluation of patient expectations in our cohort.

Characteristics	Placebo	IV ketamine	IINB	*P* value
Age (yr)	63.52±9.00	60.12±16.10	64.28±11.85	0.47
Weight (kg)	57.04±10.26	59.44±9.09	56.40±12.09	0.56
Body mass index (kg/m^2)	21.02±2.49)	21.97±2.96	20.84±3.09	0.33
ASA physical status (I/II/III)	10/12/3	12/13/0	5/19/1	
Operating time (min)	48.56±12.61	47.40±12.82	47.80±11.44	0.94

Table 2 Comparison of VAS score at movement.

VAS (at movement)	Placebo	IV ketamine	IINB
0 hour	0.00 ±0.00	0.08 ±0.40	0.00±0.00
2nd hour	2.64±2.23	3.12±2.11	2.12±1.62
6th hour	5.48±1.50	4.28±1.74	4.08±1.75
12th hour	5.20±1.53	4.40±1.63	3.68±1.31
24th hour	3.24±1.39	2.44±1.04	2.36±1.08

Table 3 Analgesic requirements and complications.

	Placebo	IV ketamine	IINB	*P*
Time to first analgesia (min)	279.76±211.03	273.64±168.00	344.71±172.89	0.31
Total opioid requirement (mg)	8.80±3.31	5.80±3.44	3.80±2.98	0.00*
No. post-operative analgesia	1.80±0.71	1.16±0.69	0.76±0.60	0.00*
Complications	1	1	2	

Table 4 One-way ANOVA.

VAS score	Df	Sum Square	F-value	P-value
0 hour	2	0.11	1.00	0.37
2nd hour	2	12.51	1.56	0.22
6th hour	2	28.67	5.13	0.01*
12th hour	2	28.91	6.45	0.00*
24th hour	2	11.84	4.24	0.02*
Analgesic requirement	**Df**	**Sum Square**	**F-value**	**P-value**
Time to first analgesia (min)	2	57,848	0.83	0.44
Total opioid requirement (mg)	2	31,667	14.96	0.01*
No. patient who request analgesia	2	13.76	6.88	0.01*

Table 5 Post-hoc ANOVA.

VAS	P-value	Placebo	IV ketamine
VAS at 6th hour	IV ketamine	0.04*	-
	IINB	0.01*	1.00
VAS at 12th hour	IV ketamine	0.19	-
	IINB	0.001*	0.28
VAS at 24th hour	IV ketamine	0.06	-
	IINB	0.03*	1.00
Analgesic requirement			
Total opioid requirement (mg)	IV ketamine	0.01*	-
	IINB	0.001*	0.01*
No. patients who requested analgesic	IV ketamine	0.01*	-
	IINB	0.01*	0.11

Our result showed that total opioid consumption was significantly lower in the IINB group (3.80±2.98 mg) compared to the IV ketamine group (5.80±3.44 mg) and the placebo group (8.80±3.31 mg). The total opioid consumption in the IV ketamine group (5.8 ±3.44mg) was significantly lower than the placebo group (8.80±3.31mg) [Tables 3-5]. (near here) Even after adjusting the p-value using Bonferroni's p-value correction, the difference in opioid consumption between the IV ketamine group and placebo group remained statistically significant [Tables 4–5]. The IINB group and IV ketamine group produced opioid sparing effects of 56% and 34% respectively compared to the placebo group during the first 24 hours.

A lower number of patients requested analgesic medication in the IINB group compared to the other groups, but only significantly different to the placebo group. The number of patients who requested analgesic medication was also significantly less in the IV ketamine group compared to the placebo group [Tables 3–5].

The time to first opioid request was 344.70 min in the IINB group, 273.64 min in the IV ketamine group, and 279.76 min in placebo group, with no statistically significant difference between the 3 groups. There was not a significant number of patients requesting analgesia, nor who had adverse effects [Table 3].

Discussion

Inguinal hernia repair surgery continues to be one of the most common operations causing moderate to severe pain particularly within the first 24 hour period. Adequate pain control can provide patient satisfaction, early ambulation and a shortened hospital stay.

Ketamine is a dominant NMDA receptor antagonist as well as a Mu receptor, GABA, and dopaminergic receptor agonist. NMDA receptor antagonist medication, inhibiting central sensitization induced by noxious stimuli, has played an important role in both acute and chronic pain management [8].

Inguinal hernia repair is the surgical incision of the T11-12 dermatomes which are innervated by the ilioinguinal-iliohypogastric nerve. Therefore, ultrasound-guided IINB has become a useful and common procedure for providing effective post-operative analgesia [9].

In recent years, IV ketamine has been of interest for use in treating acute moderate to severe pain as well as chronic pain. The use of ultrasound-guided IINB or IV ketamine are both attractive techniques because of their simplicity and safety.

The present study is the first randomized control trial to evaluate the efficacy of ultrasound-guided IINB and IV ketamine for post-operative pain control in patients undergoing elective inguinal hernia repair surgery.

In the present study, the VAS scores were similar between the placebo, ketamine and IINB groups within the first 2 hours due to

the prolonged analgesic effect of spinal anesthesia. However, the VAS scores were lower in the IINB group at all time points compared to the IV ketamine and placebo groups. The VAS scores in the IINB group were also lower than the placebo group in other studies [10-12]. Sakali et al., for example, showed that the mean VAS scores were lower in the IINB group compared with the placebo group at the 6th, 8th, 12th and 24th hour in patients undergoing elective cesarean section under general anesthesia. [12]

The present study VAS scores were also lower in the IV ketamine group when compared with the placebo group at the 6th, 12th and 24th hour post-operatively. This is similar to the findings in others trials that demonstrated lower VAS scores using low-dose ketamine [13-15]. A similar trial in 2017, using low-dose ketamine 0.25 mg/kg and a placebo, compared pain scores in the first 24 hours of the post-operative period of patients undergoing cesarean section under spinal anesthesia. The pain scores were significantly lower in the ketamine group compared to the placebo group [15].

In the present study, the time to first opioid request was 344.70 min in the IINB group which was longer compared to the other groups. This might be due to the prolonged analgesic effect after peripheral nerve block. This result was in accordance with a trial carried out by Dorreya et al. in which 42 patients, undergoing herniorrhaphy using ultrasound-guided IINB (20 ml 0.25% buvipacaine), showed a prolonged duration until first dose of analgesic medication request compared with the placebo group. The present study also found that the duration of time to first opioid request was similar between IV ketamine and placebo groups. This is in contrast to a previous study which demonstrated that ketamine (0.25mg/kg) could significantly delay the time to first analgesic request compared with the placebo in patients undergoing cesarean section under spinal anesthesia [17].

Total opioid consumption within the first 24 hours post-operatively in the IINB group was significantly lower compared with the other two groups (a 56% opioid sparing effect). The IV ketamine group also showed significantly lower total opioid consumption than the placebo group (a 34% opioid sparing effect). Moreover, both the IINB and IV ketamine groups showed a lower number of patients who requested analgesic medication. These results were similar to the findings in a number of previous studies [11, 18, 19].

Currently, it is preferred to carry out inguinal hernia repair surgery as ambulatory surgery. Therefore, the selection of anesthetic techniques that can provide adequate post-operative pain control, as well as early ambulation and cost effectiveness, is essential. This study has demonstrated that the two simple techniques of IV ketamine and IINB, that do not require a lot of special equipment or technical skill, can provide better post-operative analgesia than a patient receiving only spinal anesthesia.

In summary, 0.25 mg/kg dose of intravenous ketamine or ultrasound-guided IINB given before surgery provides effective post-operative analgesia and reduces the VAS score within the first 24 hours after inguinal hernia repair surgery.

There are limitations of the current study. The VAS scores and level of opioid consumption were assessed only during the first 24 hours of the post-operative period. Other treatments, for example the combination of systemic analgesic drugs, have not been compared with IINB.

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Conflicts of interest There are no conflicts of interest.

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