

LOW-DOSE KETAMINE INFUSION DURING SURGERY DECREASES ACUTE PAIN AFTER ORTHOPEDIC SURGERY. OUR ANESTHETIST-ORTHOPEDIC SURGEON JOINT EXPERIENCE

Luai K. Aldaklalah MD*, Mohanad A. Odat MD, Sami A. Alwashdeh MD, Eyas M. Alzuqaili MD and Deyaaldeen I. A. Alrashdan MD.

*Corresponding Author: Dr. Luai K. Aldaklalah MD

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ABSTRACT

Background: Pain attitude is various according to type of operative intervention. Some relief methods for pain after surgery are: Pre-emptive analgesics, multimodal analgesics, epidural analgesia, nerve block, patient controlled analgesia and oral analgesics. **Aim:** To assess the influence of low-dose ketamine infusion during surgery with general anesthesia on pain after orthopedic surgery. **Methods:** Our prospective, randomized and double blind investigation included 111 patients, of both sexes, aged 29-71 yrs and scheduled for orthopedic surgery during the year 2018 at Haya military hospital, Ajlun, JORDAN. Patients were divided into two groups. Group I patients (GI, n=55) were administered ketamine hydrochloride infusion (5 mcg/kg/minute) and group II patients (GII, n=56) were administered normal saline 0.9%, both immediately after intubation and maintaining till wound closure. A visual analogue scale (0 = no pain to 10 = most intense pain) was used to record patient's score of pain at rest at 1, 2, 8 and 24 hours postoperatively. First analgesic demand and morphine use after surgery were recorded. General anesthesia was induced in which intravenous fentanyl 3 mcg/kg was administered. Immediately before wound closure, all patients were administered intravenous 3 mg morphine. Analgesia in the recovery room was performed using morphine in increments of 3 mg every 10 minutes until the VAS pain score was 3. **Statistics:** For comparison of parameters other than gender between the two groups, the t-test was used. For comparison of gender, Chi square test was used. Morphine use and VAS pain scores were compared using variance. P-value less than 0.05 was considered statistically significant. **Results:** Low-dose ketamine infusion increased the time to first analgesic demand and decreased morphine use after surgery at 1, 2, 8 and 24 hours ($P < 0.05$). VAS scores were significantly less in group I than in group II, after surgery ($P < 0.05$). **Conclusion:** Low-dose ketamine infusion during surgery decreased pain and analgesic use after surgery.

KEYWORDS: During surgery: ketamine; After surgery: pain, morphine; Orthopedic surgery; general anesthesia.

INTRODUCTION

Pain attitude is various according to type of operative intervention. Orthopedic patients experience intense immediate after surgery pain more than laparotomy patients, demanding more analgesia.^[1] Some relief methods for pain after surgery are: Pre-emptive analgesics, multimodal analgesics, epidural analgesia, nerve block, patient controlled analgesia and oral analgesics.^[2]

Tissue response to surgery causes production of inflammatory mediators, activating peripheral nociceptors. Nociceptive data are transmitted to the central nervous system. Severe noxious input causes central sensitization and pain hypersensitivity. Production of inflammatory mediators in the periphery releases latent nociceptors. Pre-emptive analgesics precluding central sensitization can decrease acute postoperative pain. Ketamine diminishes central

sensitization by depression of N-methyl-D-aspartate amino acid receptors.^[3] Ketamine during surgery may possess pain relief profile after surgery^[4] or not.^[5] Ketamine was efficient with different methods of anesthesia, decreased pain after various types of operative procedures and reduced needs for opiates, after abdominal surgery.^[6] Ketamine has a morphine-sparing action after total hip arthroplasty, even when morphine was used with a systemic multimodal analgesic protocol such as paracetamol and non-steroidal anti-inflammatory drugs.^[7]

Infusion of ketamine in abdominal surgery was more efficient in reducing the requirements for opioids after surgery than after wound closure use of ketamine. Ketamine infusion during knee arthroplasty showed that more patients were pain-free than in the placebo group^[8], but anesthesia technique was both general and intrathecal.

Our investigation assessed the influence of low-dose ketamine infusion during surgery with general anesthesia on pain after orthopedic surgery.

METHODS

Our prospective, randomized and double blind investigation included 111 patients, of both sexes, aged 29-71 yrs and assigned for orthopedic surgery under general anesthesia during the year 2018 at Haya military hospital, Ajlun, JORDAN, after obtaining written informed consent from all patients and approval from our local ethical and research board review committee of the Royal medical services. Patients were divided into two groups. Group I patients (GI, n=55) were administered ketamine hydrochloride infusion (5 mcg/kg/minute) and group II patients (GII, n=56) were administered normal saline 0.9%, both immediately after intubation and maintaining till wound closure. A visual analogue scale (0 = no pain to 10 = most intense pain) was used to record patient's score of pain at rest at 1, 2, 8 and 24 hours postoperatively. First analgesic demand and morphine use after surgery were recorded. Patients with poor cardiovascular stability and contraindications to general anesthesia were ruled out.

General anesthesia was induced in which intravenous fentanyl 3 mcg/kg was administered; immediately before wound closure, all patients were administered

intravenous 3 mg morphine. Analgesia in the recovery room was performed using morphine in increments of 3 mg every 10 minutes until the VAS pain score was 3.^[2]

Statistics

For comparison of age, height, weight, period of anesthesia and first morphine demand between the two groups, the t-test was used. For comparison of gender, Chi square test was used. Morphine use and VAS pain scores were compared using variance. P-value less than 0.05 was considered statistically significant.

RESULTS

There were no significant discrepancies in characteristics between the groups. There were no discrepancies between the groups regarding the period of anesthesia. Table 1.

Morphine use after surgery was significantly less in group I than in group II at 1, 2, 8 and 24 hours ($P < 0.05$). Table 2. In group I, the first morphine demand was at 25 minutes, while it was at 15 minutes in group II with statistically significant difference ($P < 0.05$). Group I patients needed less morphine use (6 mg) than group II patients (15 mg) but with statistically insignificant difference ($P > 0.05$). Table 1. VAS scores after surgery at all times were significantly less in group I than in group II ($P < 0.05$). Table 2.

Table 1: Patients data.

	GI	GII
N=	55	56
Age(yrs) median	46	47
Sex M	23	26
F	28	30
Period of anesthesia(min)median	145	140

Table 2: Overall Morphine use and VAS pain scores during recovery room and the first day after surgery.

Recovery room	GI		GII		P
Time to first morphine demand(min)median	25		15		<0.05
Morphine use(mg)in recovery room	6		15		>0.05
	Morphine use(mg)		VAS pain scores		
First day intervals	GI	GII	GI	GII	
At 1hr	4	12	2	5	<0.05
At 2hr	11	29	1	4	
At 8 hr	23	58	0.0	4	
At 24hr	35	73	0.0	2	

DISCUSSION

Our investigation showed that low-dose infusion of ketamine during surgery decreased pain and morphine use within the first day after orthopedic surgery and time to the first analgesic demand was lengthened.

Ketamine, an N-methyl-d-aspartate receptor antagonist, obstructs central pain sensitization at sub-anesthetic doses (0.3 mg/kg). At sub-anesthetic doses, ketamine has a reduced physiologic impact and has centrally mediated analgesic characteristics. Sub-anesthetic ketamine

enhances pain scores and decreases perioperative opioid use in different surgical techniques.^[9,10] Ketamine is beneficial in avoiding chronic postsurgical pain. Ketamine, a phencyclidine derivative originally known as CI-581, at anesthetic dose (more than 1.0 mg/kg) has effects in the central nervous system that cause a dissociative anesthetic state. Sub-anesthetic ketamine is an analgesic, mainly for perioperative acute pain.^[11,12]

Continuous intravenous ketamine infusion of 1 - 10 mcg/kg/hour decreased morphine use of up to 55%.^[4,13]

In our investigation, although intravenous bolus ketamine was not administered before skin incision but infusion continued till wound closure, not as in other investigations^[4,13], but with a comparable analgesic action. Ketamine attains more analgesia after surgery than general or extradural anesthesia only, when used as a bolus of 0.5 mg/kg before incision with 0.2 mg/kg at 20 minute intervals during surgery.^[14] Use of ketamine at repeated intervals may be as efficient as continuous infusion. When ketamine is used during surgery, continuous or at repeated intervals, less morphine is needed within the early after surgery duration, because of the ketamine's depressive influence on peripheral and central sensitization.^[3] In our investigation, the infusion of ketamine before incision and continued until wound closure may have avoided pathological pain.

The pain-prophylactic mechanisms of ketamine are: depression of sensitization of the nociceptive pathways, avoiding stimulation of the pronociceptive system with opiates and avoiding opiate tolerance.^[3] To avoid pathological pain after intense tissue insult, ketamine must be used during the period of increased-severity noxious and inflammatory activation and not during the primary insult alone.^[3] ketamine infusion during knee arthroplasty under general and spinal anesthesia, using a ketamine bolus of 0.5 mg/kg followed by ketamine infusion of 4 mcg/kg/minute, with an infusion initiated before the incision was made and remained until the wound closure, resulted in more patients pain-free at 6 months after surgery in the ketamine group.^[7] In our investigation, patients were administered general anesthesia with ketamine infusion but the study group was larger and pain was recorded only during the first day of surgery. Ketamine's influence was assessed when combined with multimodal analgesia on pain after total hip arthroplasty.^[7] Intravenous ketamine before incision (0.5 mg/kg) and one day infusion (2 mcg/kg/minute) was initiated. They concluded that ketamine decreased morphine use within the first day after surgery by 28%.

Subanesthetic ketamine may have an antihyperalgesic or analgesic influence after surgery.^[6] An intravenous ketamine bolus dose of 0.5 mg/kg then an infusion of 0.25 mg/kg/hour was used.

Hyperalgesia and the morphine PCA need were significantly decreased, with less residual pain up to the sixth month after surgery.^[14] Subanesthetic intravenous ketamine used within anesthesia decreased wound hyperalgesia and is a beneficial in perioperative balanced analgesia.^[15,16]

Our investigation limitation is that VAS scores were not registered after the first day after surgery.

CONCLUSION

Ketamine infusion during surgery decreased morphine use and ameliorated analgesia after surgery. Ketamine

infusion during surgery must be included as an adjuvant to opiates for pain control after orthopedic surgery.

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