EPIDURAL KETAMINE FOR POSTOPERATIVE ANALGESIA IN THE ELDERLY

HANAN M EL SHOBARY*, ZAINAIB M SONBUL**
AND THOMAS P SCHRICKER*

Abstract

Background: We assessed the epidural use of ketamine in elderly patients undergoing major abdominal surgery.

Methods: Patients older than 65 years were randomly allocated to receive preemptive epidural bupivacaine 0.125% (20 ml) combined with either epidural ketamine 40 mg (ketamine group), or epidural morphine 2 mg (morphine group). Postoperatively, boluses of 0.125% bupivacaine (5 ml) supplemented with ketamine (2 mg/ml) or morphine (0.1 mg/ml) were given until a pain score of two was established. Analgesia at rest was assessed by a verbal rating score (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain) at 1h, 2h, 6h, 12h and 24h after surgery. The patient's degree of sedation was assessed using the Ramsay sedation score and episodes of nausea and vomiting (PONV) were recorded.

Results: Patients in the morphine group were more sedated but had significantly lower pain scores and requested less rescue analgesic than patients receiving epidural ketamine ($P<0.05$). In the morphine group three patients were treated for PONV while none of the patients in the ketamine group showed PONV.

Conclusion: Epidural ketamine, when compared to epidural morphine, appears to be associated with less sedation and a smaller risk

* Department of Anesthesia, McGill University Montreal, Canada.
** Department of Anaesthesia, Mansoura University, Egypt.
Correspondence to: Thomas Schricker, Associate Professor, McGill University. Department of Anesthesia, Royal Victoria Hospital, 687 Pine Avenue West, Room C5.20, Montreal, Quebec, Canada H3A 1A1. Phone: 514-9341934-(ext.) 34883, Fax: 514-8431698.
E-mail: thomas.schricker@mcgill.ca.

of PONV, but necessitates more frequent or continuous administration to achieve comparable analgesia.

Key words: elderly, abdominal surgery, postoperative analgesia, epidural ketamine.

Introduction

As a result of a greater life expectancy, anesthesiologists encounter an increasingly elderly patient population in the operating theatre[1]. Altered redistribution kinetics as well as compromised drug clearance capacity render geriatric patients particularly vulnerable to drug-induced complications[2]. For example an increased occurrence of opioid related adverse effects including respiratory depression, nausea, paralytic ileus, and urinary retention have been reported in geriatric patients when compared to their younger counterparts[3]. Consequently, in elderly subjects it may be prudent to limit the use of opioids while ensuring adequate analgesia by administering alternative drugs with lesser side effects[4].

Intravenous ketamine, at subanesthetic doses, has been successfully used to treat pain after surgery and to reduce the incidence of opioid-induced side effects[5-8]. Its analgesic efficacy at the spinal cord level, however remains unclear. According to some reports postoperative pain relief was achieved with epidural ketamine[9,10] while other studies found little or no analgesic effect[11-14]. When added to epidural morphine[11] or local anesthetics ketamine appears to have adjuvant effects[12]. In children undergoing inguinal herniotomy caudal co-administration of ketamine and bupivacaine, produced better analgesia than bupivacaine alone[13]. After total knee arthroplasty epidural ketamine optimized the analgesic effect of ropivacaine[14].

The present study was designed to assess the epidural use ketamine in elderly patients undergoing major abdominal surgery, the hypothesis being that combined epidural ketamine/bupivacaine would provide comparable analgesia with lesser adverse effects than the epidural administration of morphine/bupivacaine.

Methods & Materials

Patients

The study was performed after approval of the Hospital's Research Ethics Board. We approached patients older than 65 years scheduled for elective abdominal surgery. Patients with major systemic illness, contraindications to the use of epidural catheters, mental disorders and chronic intake of narcotics, were excluded from the study.

After obtaining written informed consent, 20 patients equally divided into 2 groups, were randomly allocated to receive epidural bupivacaine combined either with epidural ketamine (ketamine group) or epidural morphine (morphine group). Randomization was done in a double blind fashion using a sealed envelop method.

Anesthetic Care and Outcomes

All patients received oral diazepam 5 mg at 0600 before surgery. Anesthesia was standardized and performed by the same anesthesiologist. On arrival in the operating theatre epidural catheters were inserted between L1 and L2. A test dose of 3 ml 2% lidocaine was injected to exclude intrathecal or intravenous catheter placement. Patients then received a single bolus of 20 ml 0.125% bupivacaine combined with either 40 mg ketamine or 2 mg morphine and the segmentory bilateral sensory level of analgesia was assessed by pin prick.

General anesthesia was induced with intravenous thiopentone and endotracheal intubation was facilitated with suxamethonium. Anesthesia was maintained with isoflurane at end tidal concentrations to keep the arterial pressure and heart rate within 25% of the corresponding baseline values. The lungs were ventilated with a mixture of N_2O: O_2 ($FiO_2 = 0.4$) to normocapnia. Muscle relaxation was maintained with pipecuronium. At the end of surgery, after reversing the residual effects of muscle paralysis with atropine and neotigmine patients were extubated and kept at the surgical intermediate care unit for 24 hours.

Analgesia and sedation were determined immediately after extubation, at 1h, 2h, 6h, 12h and 24 h postoperatively. Analgesia at rest was assessed by an anesthesiologist who was unaware of the patient's group assignment using a verbal rating score (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain). At the patient's request 5 ml boluses of 0.125% bupivacaine supplemented with ketamine (2 mg/ml) or morphine (0.1 mg/ml) were given until a pain score of two was established. If pain persisted after four epidural boluses given within one hour, IV pethidine (1 mg/kg) was administered.

Postoperative sedation was assessed by the sedation score of Ramsay[15] (1 = co-operative, oriented and tranquil, 2 = anxious, agitated and/or restless, 3 = drowsy, responding to commands, 4 = asleep, with brisk response to light glabellar tap or loud auditory stimulus, 5 = asleep with sluggish response to light glabellar tap or loud auditory stimulus, 6 = not responsive).

Episodes of postoperative nausea and vomiting (PONV) requiring treatment and the occurrence of postoperative hallucinations were recorded.

Statistical Analysis

Analysis of power was performed to determine an adequate study group size, anticipating a 40% reduction in sedation score in epidural ketamine group (σ within each group = 0.5, α = 0.05, 1-β= 0.95, effect size = 1.2). Data were analyzed using independent-samples T tests. *P* value of <0.05 was considered statistically significant.

Results

A total of 20 patients were studied (10 in the ketamine group and 10 in the morphine group). The patients' demographic data, duration of surgery and type of surgery, were similar in both group (Table 1). All patients had a midline abdominal incision for removal of intra-abdominal or pelvic tumor. All patients had a documented segmentory bilateral loss of

sensation to pinprick at a level above T10.

Table 1

Biometric data and surgical characteristics in the Morphine-Ketamine groups

	Morphine	**Ketamine**
Age (years)	69 ± 5	69 ± 3
Gender (male/female)	6/4	8/2
Weight (kg)	70 ± 14	66 ± 12
Height (cm)	169 ± 8	169 ± 9
Duration of surgery (min)	180 ± 60	180 ± 24
Cystectomy (n)	3	5
Abdominoperineal resection (n)	4	3
Hysterectomy (n)	3	2

Pain scores immediately till six hours after surgery were significantly higher in the ketamine group than in the morphine group ($p = 0.002$) ($p<0.001$) ($p = 0.001$) (Table 2). None of the patients receiving epidural morphine requested a top up within the first 24 postoperative hours. Eight patients in the ketamine group required additional boluses with one patient receiving six, five patients receiving four and two patients receiving two doses. The total amount of epidural ketamine administered in the first 24 hours after surgery was 70 ± 19 mg.

Table 2

Postoperative Sedation and Pain Score

	Sedation Score			**Pain Score**		
	Morphine	**Ketamine**	**P-Value**	**Morphine**	**Ketamine**	**P-Value**
10 min postoperative	4.1 ± 1.2	2.7 ± 0.5	0.030 ±	0.0 ± 0.0	2.5 ± 2.0	0.002
30 min "	2.1 ± 1.1	2.6 ± 0.5	0.330	0.0 ± 0.0	1.9 ± 1.5	0.002
1h "	1.8 ± 0.7	2.4 ± 0.5	0.070	0.0 ± 0.0	1.6 ± 0.5	<0.001
2h "	1.3 ± 0.5	1.6 ± 0.5	0.140	0.0 ± 0.0	1.1 ± 0.5	<0.001
6h "	1.0 ± 0.0	1.0 ± 0.0	1.000	0.0 ± 0.0	1.8 ± 1.3	0.001
12h "	1.0 ± 0.0	1.0 ± 0.0	1.000	0.0 ± 0.0	0.1 ± 0.3	0.310
24h "	1.0 ± 0.0	1.0 ± 0.0	1.000	0.0 ± 0.0	0.0 ± 0.0	1.000

Value are mean ± SD

Patients in the morphine group were more sedated immediately after surgery as reflected by a higher sedation score ($p = 0.030$). Thirty minutes after the operation, sedation scores were similar in the two groups (Table 2).

In the morphine group three patients had postoperative nausea and vomiting requiring treatment while none of the patients in the ketamine group was treated for PONV. No patient showed signs of hallucinations.

Discussion

We have shown that, in the elderly, a single preemptive dose of epidural ketamine combined with bupivacaine was not as effective in providing postoperative analgesia as epidural morphine. Patients receiving ketamine, however, were less sedated and experienced PONV.

Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, inhibits sodium and potassium channels in nerve membranes, and thus, has local anesthetic properties[16]. Ketmaine also exerts analgesic effects through the interaction with opioid receptors[17]. To avoid the well-known psychomimetic effects of intravenous ketamine, investigators have focused on the use of doses smaller than needed for general anesthesia and alternative administration routes for postoperative analgesia. Neuraxial ketamine administration seems to be especially attractive due to the proximity of the NMDA receptors and the potentially decreased dose requirement. Although little is known about the pharmacokinetics of epidural ketamine in humans, in dogs racemic ketamine was rapidly absorbed from the epidural space into the cerebrospinal fluid and plasma with a longer half-life than if applied intravenously[18]. In humans, a single epidural injection of 5 mg of ketamine entered the systemic circulation with 80% bioavailability[19].

Because ketamine binding to NMDA receptors occurs slowly[20], a single preoperative bolus injection, as performed in the present protocol, most likely did not achieve complete receptor saturation and, hence, adequate analgesia. Continuous ketamine infusion or repeated injections may prove more effective[21] as illustrated by our demonstration that

intermittent postoperative administration of ketamine/bupivacaine resulted in good pain relief with little sedation and PONV.

Alternatively, the amount of ketamine as used in the present study may not have been sufficient to provide longer lasting postoperative pain control. The rationale for using 40 mg of ketamine was based on previous studies showing 24-hours-analgesia with a similar dose following cholecystectomy[22] in adults or with a dose of 0.5 mg/kg in children undergoing inguinal herniotomy[13].

Concern has been expressed about the neurotoxicity of neuraxial ketamine. One case of spinal myelopathy was reported with intrathecal injection of large doses of ketamine[23]. However, single and repeated administration of epidural ketamine diluted in a preservative free solution was found to be devoid of neurotoxic effects[24-26]. Furthermore, a one-year-follow up after combined epidural use of low dose ketamine (containing the preservative benzethonium chloride) and morphine, did not demonstrate adverse neurological sequelae[27].

In agreement with previous observations made in the elderly surgical patient population[28], in the present protocol preemptive epidural administration of 2 mg morphine together with 25 mg bupivacaine provided excellent analgesia over 24 hours following abdominal surgery. None of the patients in the epidural morphine group complained of pain at rest or asked for rescue analgesic during the study period. Although the exact mechanisms are unclear several factors including reduced elimination of epidural morphine through intravertebral foramina resulting in higher intrathecal concentrations[29] and a progressive decline in the number of neurons and opioid receptors with age, may contribute to the enhanced analgesic effectiveness of neuraxial opioids in geriatric subjects[30].

We acknowledge some limitations of this protocol such as the relatively small number of patients studied and the lack of standardization of surgical trauma. Better characterization of postoperative pain by obtaining additional VAS on movement as well as inclusion of control groups receiving intravenous ketamine or morphine, would have further facilitated the interpretation of our observations.

The results of this study suggest that the epidural use of ketamine, when compared to morphine, is associated with less sedation and a smaller risk of PONV in the elderly surgical patient, but necessitates more frequent or continuous administration to achieve comparable analgesia. Future investigations will have to demonstrate whether epidural ketamine is an alternative to opioids for the treatment of pain after major abdominal surgery.

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