Preoperative Epidural Ketamine in Combination with Morphine Does Not Have a Clinically Relevant Intra- and Postoperative Opioid-Sparing Effect

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In this prospective, randomized, and double-blinded clinical trial, we evaluated the efficacy of preincisional administration of epidural ketamine with morphine compared with epidural morphine alone for postoperative pain relief after major upper-abdominal surgery. We studied 50 ASA I and II patients undergoing major upper-abdominal procedures. These patients were randomly allocated to one of the two treatment groups: patients in Group 1 received epidural morphine 50 μg/kg, whereas those in Group 2 received epidural ketamine 1 mg/kg combined with 50 μg/kg of morphine 30 min before incision. Intraoperative analgesia was provided in addition, with IV morphine, and the requirement was noted. A blinded observer using a visual analog scale for pain assessment observed patients for 48 h after surgery. Additional doses of epidural morphine were provided when the visual analog scale score was more than 4. Analgesic requirements and side effects were compared between the two groups. There were no differences between the two groups with respect to age, sex, weight, or duration or type of the surgical procedures. The intraoperative morphine requirement was significantly ($P = 0.018$) less in Group 2 patients (median, 6.8 mg; range, 3–15 mg) compared with patients in Group 1 (median, 8.3 mg; range, 4.5–15 mg). The time for the first requirement of analgesia was significantly ($P = 0.021$) longer (median, 17 h; range, 10–48 h) in Group 2 patients than in Group 1 (median, 12 h; range, 4–36 h). The total number of supplemental doses of epidural morphine required in the first 48 h after surgery was comparable ($P = 0.1977$) in both groups. Sedation scores were similar in both groups. One patient in Group 2 developed hallucinations after study drug administration. None of the patients in either group developed respiratory depression. Other side effects, such as pruritus, nausea, and vomiting, were also similar in both groups. Although the addition of ketamine had synergistic analgesic effects with morphine (reduced intraoperative morphine consumption and prolonged time for first requirement of analgesia), there was no long- lasting preemptive benefit seen with this combination (in terms of reduction in supplemental analgesia) for patients undergoing major upper-abdominal procedures.

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The postoperative pain state results from afferent C-fiber input generated by the tissue injury and the central facilitation from the continuing stimulus (1). Spinal opiates can alter both the processes by reducing the preterminal release of neurotransmitters and hyperpolarizing the postterminal second-order neurons (2). Preemptive analgesia has been advocated as an effective way of managing postoperative pain on the basis of the theory of preventing central sensitization after injury (3,4). *N*-methyl-D-aspartate (NMDA) receptor activation is essential for central facilitation after nociceptive stimulation and is a key factor in the generation and maintenance of persistent pain states (5). Spinal NMDA antagonists might alter postoperative pain by removing the facilitatory component (5). Epidural ketamine alone may be insufficient for adequately reducing the pain state by removing the central facilitation alone (6). Opioid and ketamine combinations can antagonize these two distinct components and provide adequate control of postoperative pain. Spinal potentiation of opiate receptor activity by NMDA antagonism has been reported (7). Wong et al.

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(6) have shown that ketamine potentiates morphine in patients undergoing major joint surgery. Wu et al. (8) have shown that multimodal preincisional analgesia with morphine, bupivacaine, and ketamine is better than their postincisional administration. Choe et al. (9) have shown that preemptive morphine and ketamine administration provides better postoperative analgesia than postsurgical morphine and ketamine in patients undergoing gastrectomy. It is not clear from these studies whether the observed beneficial effects were because of morphine alone or because of the combination of morphine and ketamine. An adequate dose of preemptive epidural ketamine in combination with morphine compared with preemptive epidural morphine alone in major upper-abdominal surgery has not been studied. In this prospective clinical trial, we studied the analgesic efficacy and safety of preincisional epidural ketamine plus morphine compared with preincisional epidural morphine alone after major upper-abdominal surgical procedures.

Methods

After obtaining approval from the institutional ethics committee and written informed consent, we studied 50 ASA physical status I and II adult patients of either sex undergoing major upper-abdominal surgery under balanced general anesthesia. Patients with a history of drug abuse, continuing treatment for chronic pain, major systemic illnesses, a bleeding diathesis, or neurologic dysfunction were excluded from the study. Patients were assigned to one of the two treatment groups by using a table of random numbers. During the preoperative visit, all patients were told about the visual analog scale (VAS) for pain assessment. We used a vertical 100-mm VAS with ends marked as 0 (no pain) and 10 (worst imaginable pain). They were premedicated with diazepam 10 mg in the morning 2 h before the induction of anesthesia. On arrival in the operating theater, an IV cannula was inserted. Patients were placed in the lateral position, and an epidural catheter was inserted in the T12-L1 interspace by an experienced anesthesiologist who used the loss of resistance technique. Instead of the conventional method of a test dose with lidocaine and adrenaline to confirm the catheter placement, we used a catheter advancement technique (CAT) (10). With this technique, after eliciting lack of resistance, the ability to advance 20 cm of a soft epidural catheter without a stylet and with minimal resistance was taken as successful catheterization. After the catheter advancement technique, the catheter was withdrawn up to the 17- to 18-cm mark, and gravity drainage of cerebrospinal fluid or blood was tested. After the epidural catheter was fixed to the back, the patients were placed supine and received epidural morphine 50 μg/kg or epidural ketamine 1 mg/kg combined with morphine 50 μg/kg in a double-blinded manner. General anesthesia was induced after 20 min of study drug administration with thiopentone 5 mg/kg, and the trachea was intubated after vecuronium 0.1 mg/kg IV. Surgical incision was made after 30 min of epidural drug administration. All patients were maintained with N_2O 66% and halothane 0.5% in 33% oxygen. Intraoperative analgesia was provided with IV morphine 3-mg boluses titrated to the clinical variables such as increase in heart rate or blood pressure and the presence of lacrimation and sweating. The total requirement of intraoperative morphine IV was noted. Continuous monitoring of electrocardiogram, automatic noninvasive blood pressure, central venous pressure, Spo_2, and $ETco_2$ were performed. Residual neuromuscular block was reversed with neostigmine 50 μg/kg and atropine 20 μg/kg, and the patients were tracheally extubated at the end of the surgery.

Patients were followed up at 0, 2, 4, 8, 12, 18, 24, 30, 36, 42, and 48 h after surgery for pain with VAS during deep inspiration by an anesthesiologist unaware of the drug given. When VAS on deep inspiration was more than 4, they received morphine 50 μg/kg in 10 mL of normal saline through the epidural catheter. If the patients complained of pain between the 6-h follow ups, the on-call anesthesia resident assessed the patients and administered top-up analgesia if required. The on-call senior residents were aware of the nature of the study but were blinded to the study medication given. The duration of analgesia provided by the first dose and the total number of top-up doses given in the first 48 h were recorded. Sedation was assessed at 2, 6, 12, and 24 h after surgery by using a 5-point scale (4, completely awake and open eyes; 3, drowsy, closed eyes; 2, asleep but responds to verbal commands; 1, asleep but responds to touch or pain; 0, does not respond). Patients were also questioned about side effects, such as hallucinations, pruritus, and nausea and vomiting, in the first 48 h after surgery. Respiratory rate and the patient's response were used to diagnose respiratory depression. If the respiratory rate was $<$10 breaths/min and the patient was not verbally responsive, respiratory depression was diagnosed. If the patient was not responding and the respiratory rate was more than 10 breaths/min, excessive sedation was diagnosed.

Values normally distributed are expressed as mean (SD), and values not normally distributed are expressed as median (range). Age, weight, and duration of surgery were analyzed statistically by unpaired Student's *t*-tests. Intraoperative morphine requirement, time for first requirement of analgesia, and total number of supplemental doses of epidural morphine required in the 48-h postoperative period were compared between the groups by the Mann-Whitney *U*-test. Sedation scores and other side effects were

compared between the groups by Yates' corrected χ^2 test or Fisher's exact tests wherever appropriate. P values <0.05 were considered statistically significant.

Results

Age, sex, weight, and type and duration of surgery were comparable in the two groups (Table 1). All patients underwent extensive upper-abdominal procedures, such as trans-hiatal esophagectomy with gastric or colonic pull-up for esophageal carcinoma; pancreatic and biliary tract surgery such as the Whipple procedure, biliary bypass, and pancreaticojejunostomy; and other surgical procedures, such as radical gastrectomy, hepatic resection for hepatic masses, and colonic resection for colonic carcinoma (Table 2). The intraoperative morphine requirement was significantly ($P = 0.018$) less and the time for first requirement of analgesia was significantly longer ($P = 0.021$) in Group 2 compared with Group 1. The total number of supplemental doses of epidural morphine was comparable in both the groups (Table 3). Sedation and other side effects were similar in both groups (Table 4). None of the patients had a sedation score of 0 during the postoperative follow-up. Four patients in Group 1 and six patients in Group 2 had a sedation score of 1 or 2 in the first 2 h after surgery. One Group 2 patient developed hallucinations after study drug administration. He had no psychomimetic effects after surgery.

Table 1. Demographic Data

Variable	Group 1 ($n = 24$)[a]	Group 2 ($n = 26$)[b]	P value[c]
Age (yr)	47.6 ± 18.6	44.9 ± 14.2	0.575
Weight (kg)	52.5 ± 13.6	53.9 ± 7.3	0.661
Sex (male/female)	17/7	20/6	0.867
Duration of surgery (h)	4.4 ± 1.4	3.8 ± 1.5	0.113

Values are expressed as mean ± SD.
[a] Group 1 = morphine.
[b] Group 2 = morphine plus ketamine.
[c] $P < 0.05$ is considered significant.

Table 2. Type of Surgery

Variable	Group 1 ($n = 24$)[a]	Group 2 ($n = 26$)[b]
Trans-hiatal esophagectomy (gastric or colonic pull-up)	9	8
Pancreatic and biliary tract surgery (Whipple's surgery, biliary bypass)	8	8
Radical gastrectomy	2	4
Colonic resection	2	4
Hepatic resection	3	2

Values are expressed as n.
[a] Group 1 = morphine.
[b] Group 2 = morphine plus ketamine.

Table 3. Analgesic Data

Variable	Group 1 ($n = 24$)[a]	Group 2 ($n = 26$)[b]	P value[c]
Intraoperative morphine dose (mg)	8.3 (4.5–15)	6.8 (3–15)	0.018
Time for first analgesia (h)	12 (4–36)	17 (10–48)	0.021
No. postoperative epidural supplements (n)	2.5 (1–4)	2 (0–4)	0.198

Values are expressed as median (range).
[a] Group 1 = morphine.
[b] Group 2 = morphine plus ketamine.
[c] $P < 0.05$ is considered significant.

Table 4. Side Effects

Variable	Group 1 ($n = 24$)[a]	Group 2 ($n = 26$)[b]
Excessive sedation (scores 1 and 2, first 2 h)	4 (17%)	6 (23%)
Pruritus	7 (29%)	8 (31%)
Nausea and vomiting	11 (46%)	11 (42%)
Psychomimetic effects	0	1
Respiratory depression	0	0

Values expressed as number of patients, n (%).
[a] Group 1 = morphine.
[b] Group 2 = morphine plus ketamine.

Discussion

In our study, the preincisional administration of epidural ketamine plus morphine decreased intraoperative IV morphine requirements and prolonged the time for first analgesic request compared with preincisional epidural morphine alone after major upper-abdominal surgery. NMDA receptor activation by morphine initiates intracellular events that induce tolerance and hyper-responsiveness (11). Ketamine, an antagonist of NMDA receptors, prevents the development of tolerance and brings out the full potential of opioid analgesia. It also produces analgesia by stereospecific binding to opiate receptors (12), direct action on the dorsal horn (13) and within descending inhibitory systems (14), and interaction with cholinergic, adrenergic, and 5-hydroxytryptamine antagonists (15). It also brings out this potential by its local anesthetic property (16).

NMDA receptors play an important role in the central sensitization of peripheral nociceptive stimulation and the wind-up phenomenon (5). Ketamine thus should prevent the central sensitization and decrease postoperative analgesic requirements beyond its duration of action. In our study, this effect was seen briefly until the first requirement for postoperative analgesia in the Ketamine-Plus-Morphine group. However, this beneficial effect did not last long, because we did not find any difference in the median

number of supplemental doses between the two groups. The decrease in intraoperative morphine requirement from 8.3 to 6.8 mg is also not clinically relevant. This is similar to the findings of Royblat et al. (17), who observed the beneficial effect of adding small-dose ketamine to a general anesthetic only in the first six hours after open cholecystectomy. There are several explanations for this finding.

Ketamine acts mainly on the opened ionic channels and prevents neuroplasticity (18). When the drug is given before surgery, the channels are not in an open state, because there is no noxious stimulus to open it. Hence, the drug does not bind to these channels during the preincisional period. However, it stops the barrage of noxious stimuli once the incision is made, and the effect lasts only for the duration of action of epidural ketamine. Menigaux et al. (19) have shown that the timing of ketamine administration was not important in achieving the benefits of intraoperative small-dose ketamine on postoperative pain after anterior cruciate ligament repair.

Yashpal et al. (20) have shown that a short-lasting intrathecal lidocaine block in rats could produce a preemptive effect only with a weak nociceptive stimulus. When the intensity of the stimulus was increased, even with larger concentrations of lidocaine, the preemptive effect profoundly declined. A single bolus dose of epidural ketamine and morphine is probably not adequate to block the entire intraoperative noxious stimuli in major surgery such as upper-abdominal surgery. Hence, insufficient afferent blockade might be the other reason why we could not show a significant difference between the groups over 48 hours.

Fu et al. (21) infused ketamine after a bolus dose throughout abdominal surgery when they compared preemptive ketamine with a single bolus dose of postsurgical ketamine. They demonstrated a beneficial effect over the next 48 hours. Aida et al. (22) have shown the preemptive effects of IV infusion of ketamine with epidural morphine. Therefore, it is possible that ketamine, because of its short duration of action, needs to be given as a continuous infusion to block the entire intraoperative noxious stimuli and to prevent the development of central nervous system (CNS) plasticity. Probably a single bolus dose of epidural ketamine was insufficient to block all the noxious stimuli.

In upper-abdominal surgery, there could be additional routes of transmission of noxious stimuli to the CNS through the phrenic nerve (23) and the vagus nerve (24). Aida et al. (22) suggested that IV ketamine might have some advantages over extradural ketamine when administered with epidural morphine in blocking this heterosegmental nociception sensitization. This could be another factor in our study for the failure to demonstrate a significant opioid-sparing effect. However, definite conclusions cannot be made until direct comparisons are made between epidural and IV ketamine as an adjuvant to epidural morphine. Pharmacokinetic studies have shown that the plasma half-life of ketamine after extradural administration was significantly longer than that by IV administration. The peak concentration of ketamine was found in the brainstem after lumbar epidural administration in dogs. Slow systemic absorption of ketamine from the spinal cord leads to the termination of its pharmacologic effects. This may explain the prolonged maintenance of analgesic effects after epidural ketamine (25,26). Koinig et al. (27) compared epidural and IM ketamine and reported that despite similar plasma concentrations, caudal epidural ketamine provided superior analgesia in children during most of the postoperative period. Alam et al. (28) evaluated the antinociceptive effects of epidural and IV ketamine in rats and have shown that both epidural and IV ketamine produced greater antinociceptive effects with visceral than with somatic stimulation and that epidural ketamine had an infrequent incidence of emergence reactions.

Wong et al. (6) showed that epidural ketamine pretreatment potentiates the analgesic effect of morphine in postoperative pain control after major joint replacement surgery. In their study, all the patients received epidural ketamine along with lidocaine before and during surgery. Preemptive multimodal analgesia with ketamine, morphine, and local anesthetics improves postoperative analgesia (8,29,30). In our study we compared morphine and ketamine pretreatment versus morphine alone without the confounding effect of local anesthetics.

Stubhaug et al. (31) have shown that ketamine reduces wound hyperalgesia (which we have not examined in our study) after surgery, though this does not equate to the decreased pain reported by the patients. Probably it decreased the wound hyperalgesia only, without decreasing the postoperative pain.

The use of IV opioids may have undermined the preemptive effect of epidural ketamine, although the preemptive analgesic effect of an intraoperative opioid is controversial (3). Intraoperative IV morphine was administered because we considered that epidural morphine alone may not have provided adequate intraoperative analgesia, and it is unethical not to provide analgesics for the purposes of study. Our aim was to see whether the addition of epidural ketamine made any difference to the regimen of preincisional epidural morphine with intraoperative IV morphine, which is routine in our clinical practice (32).

Choe et al. (9) used 60 mg of ketamine (mean weight, 59 ± 10 kg) with 2 mg of morphine while demonstrating the preemptive effects of this combination in patients undergoing radical subtotal gastrectomy. Naguib et al. (33) have shown that 30 mg of ketamine provided adequate postoperative analgesia

in patients undergoing lower abdominal surgery. This dose may not be adequate to block the intense noxious stimuli of major upper-abdominal surgery. Schmid et al. (34) reviewed the clinical trials of ketamine analgesia and concluded that small-dose ketamine (defined as <1 mg/kg for the epidural route) may play an important role in postoperative pain when used as an adjunct to local anesthetics, opioids, or other analgesics. We chose the larger end of this small dose of ketamine because we wanted to look at the effectiveness of combining a single bolus dose of ketamine with morphine on decreasing postoperative pain. We need dose-finding studies for ketamine as an adjunct to opioids.

Intrathecal ketamine has been associated with significant CNS side effects (35). None of the previous studies on epidural ketamine reported adverse events, such as psychomimetic reactions or emergence phenomena (6–9). In this study, one patient developed hallucinations after preemptive ketamine plus morphine, although the other side effects, such as nausea and vomiting, pruritus, and respiratory depression, were not increased by the addition of ketamine.

We used preservative-free ketamine in our study, and ketamine concentration was <1% in all patients. The neurotoxic effects of ketamine have been attributed to its preservative (chlorbutanol), and intrathecal preservative-free ketamine up to 1% is devoid of neurotoxic effect (36). De Lima et al. (37), while reviewing the neural toxicity of ketamine, have encouraged the continued study of small doses (in small concentrations) of preservative-free ketamine through the epidural route.

In conclusion, although the addition of ketamine to preincisional epidural morphine reduced the intraoperative narcotic requirement and increased the time for first requirement of analgesia, the effect was not sustained, and further use of narcotic supplements was not significantly reduced. The decreased requirement of intraoperative morphine and the prolonged first-dose effect were not associated with a decrease in opioid-related side effects. A single-bolus dose of epidural ketamine added to epidural morphine before surgery does not lead to significant postoperative pain relief.

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