

Postoperative Pain Relief After Hepatic Resection in Cirrhotic Patients: The Efficacy of a Single Small Dose of Ketamine Plus Morphine Epidurally

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In cirrhotic patients undergoing hepatic surgery, postoperative analgesia remains a challenge. In this study, we evaluated the efficacy of a single dose of morphine combined with small-dose ketamine given epidurally for postoperative pain relief. One-hundred-four classification "Child A" cirrhotic patients were randomly assigned to two groups: 1) (MKG, $n = 54$): epidural morphine (3.5–5 mg) plus ketamine (20/30 mg); and 2) epidural morphine (3.5/5 mg) (MG, $n = 50$). The level of analgesia, side effects, psychomimetic and neurological disorders, additional analgesic needs, and overall quality of the analgesia were recorded. The mean duration of analgesia was longer in the MKG group (27.2 ± 8 h versus 16.4 ± 10 h; $P < 0.05$). In the MKG group, the

visual analog scale (VAS) score began to be significantly lower from 14 h at rest and 12 h on coughing until the end of the study. The need for additional analgesia was also smaller in the MKG group ($P < 0.05$): at 24 h, only 10% of patients in the MKG group needed complementary analgesia, whereas in the MG group it was 100% ($P = 0.003$). Side effects were similar in both groups. Psychomimetic side effects and neurological disorders were not detected. These results suggest that postoperative analgesia provided by a single dose of epidural morphine with small-dose ketamine is effective in cirrhotic Child's A patients having major upper abdominal surgery.

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Liver resection is used with increasing frequency for treating primary neoplasms of the liver, which are frequently related to liver cirrhosis (1). The remaining liver's capacity to produce substances such as clotting factors is decreased for several days because of loss of hepatic parenchyma and posthepatectomy liver dysfunction (2). In this condition, postoperative analgesia remains a challenge, mainly because of the small range between the analgesic effect and side effects (limited therapeutic index) of conventional opioid IV analgesia in patients who have altered multiple neurotransmitter systems, such as gamma-aminobutyric acid (GABAergic) glutamatergic, opioidergic, and so on (3). Alterations of the endogenous opioid system have been reported in patients with liver disease, and morphine administration

may precipitate episodes of encephalopathy (4). Moreover, after major upper abdominal surgery, some patients continue to experience pain despite patient-controlled analgesia IV morphine administration (5). Continuous epidural analgesia is effective in postoperative pain relief after upper abdominal surgery and, by targeting dorsal root and dorsal horn neurons, may modify some deleterious effects of the stress response (6). The benefits of postoperative pain relief are specifically directed at an improvement of pulmonary function (7), early return of bowel function, and early mobilization (8). However, "Child A" cirrhotic patients, although they have normal coagulation profiles, may develop serious alterations in coagulation with deranged hepatic function during the postoperative period. In this situation, the continuing trauma associated with the presence of an epidural catheter, as well as its removal, could be associated with a serious risk of spinal hematoma (9,10).

Alternative methods should be developed to obtain a long duration and safe postoperative analgesia in patients in whom an epidural catheter may be contraindicated. One possible method could be the combination of different drugs with a known synergistic

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effect (11,12) given epidurally by a single shot. This prospective and controlled study attempted to evaluate the efficacy and safety of a single-dose administration of morphine plus small-dose ketamine given epidurally as the only treatment for postoperative pain relief.

Methods

This prospective and randomized study was approved by the Hospital Clinical Trials Committee. Between July 1998 and February 2001, 107 patients evaluated for the surgical treatment of hepatic resection for hepatocellular carcinoma associated with cirrhosis were considered for entry into the trial. In all patients, hepatic functional assessment was performed according to the classification of Child as modified by Pugh et al. (13), and all patients belonged to the low-risk group, Child's A (five or six points). For this reason, the patient's coagulation status at the time of operation was in normal condition and fulfilled the criteria of the European Consensus (14) for neuraxial block (INR <1.5 and platelet count >80,000). Exclusion criteria for this study included preexisting severe pulmonary, renal, or cardiac disease; history of easy bruising; gingival bleeding; epistaxis; suspicion of anatomical spinal abnormality; psychiatric disease; intraoperative blood loss >15 mL/kg; and the need for postoperative mechanical ventilation. Written, informed consent was obtained from all patients, who were randomly assigned to two groups: a study group in which a single dose of epidural morphine plus ketamine (MKG) (ketamine with 0.01% benzethonium chloride; Parke-Davis) was given and a control group in which epidural morphine (MG) alone was given.

Premedication consisted of oral diazepam 10 mg given 1-2 h before surgery. Anesthesia was induced with midazolam (1-1.5 mg), ketamine (0.5 mg/kg), thiopental (3-4 mg/kg), and fentanyl (150 μ g) and was maintained with isoflurane. Neuromuscular blockade was achieved with atracurium (0.4-0.5 mg $\cdot$ kg⁻¹ $\cdot$ h⁻¹). All patients were mechanically ventilated at a fraction of inspired oxygen of 0.5, and tidal volume was adjusted to maintain end-tidal CO₂ tension between 35 and 40 mm Hg. Fentanyl boluses (100-150 μ g) were given to maintain the level of analgesia. No opiate-antagonistic drugs were used. All patients received 1000 mL of fresh frozen plasma. The circulatory volume and blood loss were substituted only by 5% glucose solution, plasmalyte, and 5% albumin until the hematocrit decreased to 25% (15). Blood loss and blood component requirements during the surgical procedure and the postoperative period were recorded.

The details of the operative procedure have already been published elsewhere (15). In summary, a J-shaped incision was made. Whole mobilization of the liver was performed. It is important to point out the systematic use

of a special retractor (Kent retractor), which maintains a continuous traction and which separates and lifts the rib cage. To produce minimal blood loss, an intermittent Pringle maneuver of 15 min followed by a 5 min rest was performed until completion of the resection.

On completion of the surgical procedure, all patients were tracheally extubated in the operating room. In the recovery room, when patients were wide awake, they were randomly allocated by a computer-generated list to two groups according to the type of analgesia. Patients were placed in the lateral recumbent position, and a thoracic puncture with a 18-gauge Tuohy needle at T10-11 or T11-12 was performed via a midline approach. Failure to achieve a needle placement before three needle passes was considered an exclusion criterion. Patients received a single dose of either MKG or the same dose of MG, administered slowly through the Tuohy needle, given in the same volume (8 mL of 0.125% bupivacaine). The Tuohy needle was withdrawn immediately after drugs were given, and no epidural catheter was placed. The analgesic drug dosages were adjusted for patient age: <50 yr, 5 mg of morphine, with or without 30 mg of ketamine; 50-65 yr, 4 mg of morphine, with or without 20 mg of ketamine; and >65 yr, 3.5 mg of morphine, with or without 20 mg of ketamine.

The duration of analgesia was from the time when the patient was randomized to the time when there was a need for additional analgesia. Additional analgesic treatment was given with IV propacetamol (2 g) if visual analog scale (VAS) ratings of pain were approximately 4 during the previous hour or with subcutaneous methadone (5 mg) if VAS ratings of pain were >5 during the last hour. Each administered dose was recorded. All patients were observed continuously in the recovery room for the first 30 h after surgery.

Efficacy was evaluated as a function of the level of analgesia reported by the patient via the pain score on a graded-scale VAS (0 = no pain, 10 = worst pain imaginable). Determinations were assessed at rest and during cough and were recorded at 2-h intervals for the following 14 h and thereafter at 18, 24, 30, and 40 h after surgery. The analgesia evaluation was recorded by two anesthesiologists who did not know the patient's analgesic treatment.

The safety of the procedure was evaluated by recording side effects such as nausea, vomiting, psychomimetic effects, neurological disorders, sedation (1 = wide awake, 2 = dozing, 3 = asleep, 4 = unrousable), and respiratory depression. Respiratory depression was considered present when Paco₂ increased to a value larger than 50 mm Hg and/or the respiratory rate decreased to less than 8 breaths/min. Hemodynamic and respiratory variables recorded continuously were heart rate, arterial blood pressure, oxyhemoglobin saturation, and respiratory rate. All these

variables and blood gases were recorded at 2, 8, 12, and 18 h after surgery. Patients were observed until hospital discharge for early signs of spinal cord compression, such as radicular back pain, or neurological deficits, such as muscle weakness and sensory deficit.

At 3 days after surgery, patients were asked two questions about the overall quality of the analgesia: 1) How satisfied were you with your analgesia (0 to 4, with 4 being the most satisfied)? and 2) Did you feel more pain than you expected (yes, no, similar)? Postoperative pulmonary complications relating directly or indirectly to analgesia (pneumonia was defined as a persistent temperature greater than 39°C and consolidation on a chest radiograph) and the hospital stay were also recorded.

Liver function tests in terms of serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase, as well as the ratio of prothrombin time (prothrombin time/control prothrombin time) and platelet count, were recorded at 8, 24, 48, and 72 h after surgery.

Where appropriate, results are presented as mean $\pm$ SD. The differences between groups for continuous variables were evaluated with analysis of variance for repeated measures (SPSS; SPSS Inc., Chicago, IL) and the χ^2 test or the Kruskal-Wallis test for the categorical variables and VAS score, respectively. To compare the duration of analgesia, the product-limit survival analysis was used (Kaplan-Meier analysis) followed by Wilcoxon's test. $P < 0.05$ was considered statistically significant.

Results

A total of 107 Child's A cirrhotic patients underwent different types of liver resections. Three patients, one in the MKG group and two in the MG group, were excluded because of a difficult epidural puncture. Fifty-four patients were included in the MKG group and 50 patients in the MG group. The presence of a minute quantity of blood was detected in 14 patients (14%) during needle placement. Demographic and clinical variables for the two groups are presented in Table 1. The mean duration of the surgery and Pringle maneuver and also the operations undertaken were similar in both groups. Blood loss, blood requirements, and the total dose of fentanyl received by each patient were similar between the two groups (Table 1). Total blood loss was similar in both groups. Nineteen patients (19%) required blood transfusions of packed erythrocytes during or after the procedure, as shown in Table 1; the large majority of patients requiring transfusion had alcoholic cirrhosis. Two patients died (both in the MG group) during the early postoperative period (at 8 and 42 postoperative days); both of them had sepsis and multiorgan failure (perioperative mortality rate of 2%). Postoperative morbidity was mainly

Table 1. Clinical Data of the Patients and Surgical Characteristics

Variable	MG patients (n = 50)	MKG patients (n = 54)
Clinical data		
Age (yr)	58.4 $\pm$ 9	60 $\pm$ 7
<50	9	7
50–65	33	37
>65	8	10
Male/female	31/19	37/17
Weight (kg)	69 $\pm$ 12	62.6 $\pm$ 9
Surgical characteristics		
Total anesthesia time (h)	5.2 $\pm$ 0.4	5.4 $\pm$ 1
Time of surgery (h)	3.8 $\pm$ 0.6	4 $\pm$ 0.4
Time of Pringle (min)	64.3 $\pm$ 12	72.2 $\pm$ 15
Blood loss (mL)	1016 $\pm$ 340	944 $\pm$ 382
Total patients transfused	8	11
Alcoholic cirrhosis patients transfused	7	10
Total fentanyl (μ g)	820 $\pm$ 201	862 $\pm$ 190

MG = morphine epidural; MKG = morphine plus ketamine.

related to liver insufficiency in patients who developed moderate renal failure and ascites (76%). No patient developed pneumonia, but 6 patients—2 in the MKG group and 4 in the MG group—had fever with a radiological diagnosis of pulmonary atelectasis. Of all patients, only one developed encephalopathy (in the MG group). No difference in hospital stay was found (6.6 ± 2 days for MKG versus 7.8 ± 3.6 days for MG).

The mean duration of analgesia was significantly longer in patients who received ketamine (27.2 ± 8 h versus 16.4 ± 10 h; $P < 0.05$). Fourteen hours after the completion of surgery, the VAS pain intensity score at rest was significantly lower ($P = 0.04$) in the MKG patients, and this was true for up to 30 h (Fig. 1). When we analyzed VAS score during coughing, the differences were significant at 12 h ($P = 0.02$), and these differences were maintained throughout the study (Fig. 2). The number of doses of complementary analgesia was significantly larger in the MG group (Table 2). Figure 3 shows that at 24 h, only 7% of patients in the MKG group had needed complementary analgesia, whereas in Group MG this was 100% ($P = 0.003$).

Side effects were similarly distributed between the two groups. The incidence of vomiting was infrequent (six patients in Group MG versus nine patients in Group MKG). Psychomimetic effects and neurological disorders were not detected in any patient. We did not find systemic hemodynamic changes either in mean arterial blood pressure or cardiac rate. Finally, there were no differences in respiratory variables and sedation.

The global quality of postoperative analgesia had a significantly better evaluation in MKG patients (Table 3). However, the reply to the question "Did you feel

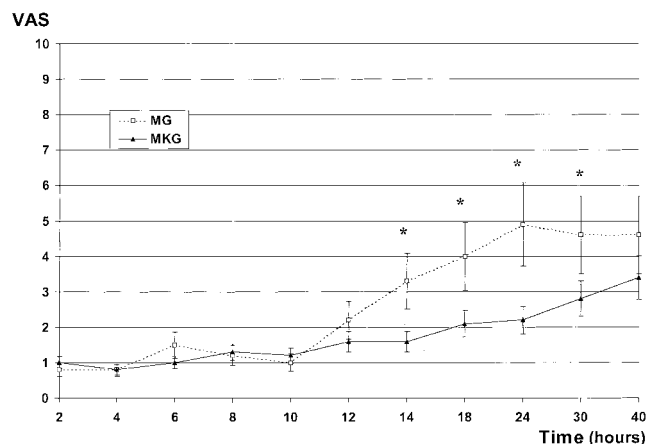


Figure 1. The level of analgesia at rest, reported by the patients after surgery, via the pain score on a graded scale (0 = no pain; 10 = worst pain imaginable). * $P < 0.05$ between groups. MG = epidural morphine; MKG = morphine plus ketamine; VAS = visual analog scale.

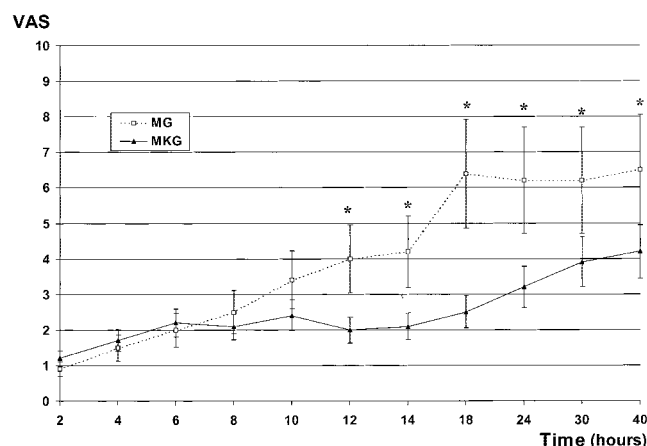


Figure 2. The level of analgesia on coughing, reported by the patients after surgery, via the pain score on a graded scale (0 = no pain; 10 = worst pain imaginable). * $P < 0.05$ between groups. MG = epidural morphine; MKG = morphine plus ketamine; VAS = visual analog scale.

Table 2. Mean Number of Doses of Complementary Analgesics Administered (Propacetamol and Methadone) During the Two Days After Surgery

Day	Propacetamol dose		Methadone dose	
	MG	MKG	MG	MKG
1	2.1 ± 1	—	1.3 ± 0.8	—
2	2.8 ± 1.8	2 ± 0.9	3.5 ± 1.2	1.6 ± 1*

MG = morphine epidural; MKG = morphine plus ketamine.
* $P < 0.05$ between groups.

more pain than you expected?" was similar in both groups (MKG: 42 no and 12 yes, versus MG: 44 no and 6 yes). Postoperative liver function showed a progressively significant increase in enzymes and the ratio of prothrombin time (up to 1.61 ± 0.1 at 48 h) and a

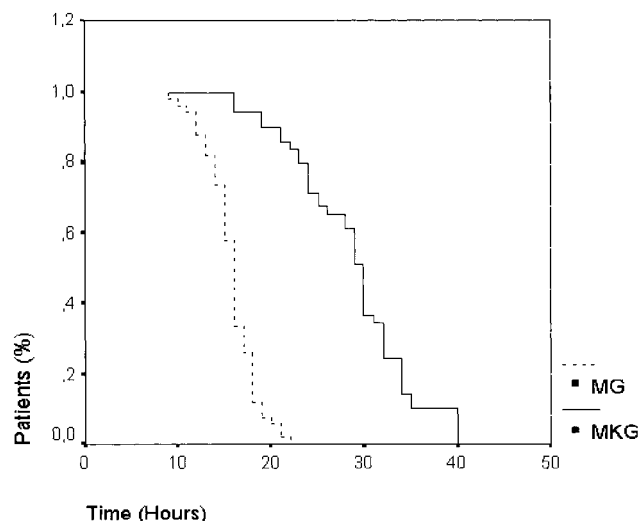


Figure 3. Percentage of patients not requesting additional analgesia after epidural morphine (MG) and morphine plus ketamine (MKG) at various time periods ($P = 0.03$).

Table 3. Overall Quality of the Analgesia: How Satisfied Were You With Your Analgesia (1 = dissatisfied, 2 = moderately dissatisfied, 3 = moderately satisfied, 4 = satisfied)?

Score	MG (n = 50)	MKG (n = 54)	P value
1	—	—	
2	11	5	NS
3	22	16	NS
4	17	33	<0.05

MG = morphine epidural; MKG = morphine plus ketamine; NS = not significant.

Data are numbers of patients.

significant reduction in platelet count during the first 3 days after the operation.

Discussion

Postoperative morbidity and mortality associated with liver resection in patients with compromised liver function has always been very significant (16). Avoidance of nephrotoxic drugs—mainly nonsteroidal antiinflammatory drugs—and early mobilization have proven to be very important in the short-term outcome of these patients. However, early mobilization is difficult with severe pain, and to eliminate this pain, large doses of powerful opiates are needed. Experimental studies have shown that opioidergic neurotransmission (such as μ and δ receptors) may be altered in cirrhotic patients, selectively increasing receptor affinity for opioids. The exogenous or endogenous stimulation of these receptors may lead to impaired mental function.

The use of the epidural route has proven very effective in the postoperative care of high-risk patients.

However, the possibility of a bloody tap from needle or catheter placement or continuing trauma due to the presence of an epidural catheter has been widely described and may occasionally result in spinal bleeding. Although epidural hematoma is a rare event (17), it is always in relation to deranged hemostatic capacity or complete anticoagulation. Although our patients had a normal coagulation state at the time of epidural puncture, there is no doubt that after liver resections, patients usually have a significant derangement in the coagulation profile during the second and third day, and the presence or removal of the epidural catheter at that time constitutes a potential risk.

The possibility of using the epidural route to obtain a decrease in pain threshold for long periods and, at the same time, avoiding the placement of a catheter by the use of a single bolus of an analgesic seems very attractive. However, the decision to perform continuous epidural analgesia should be made on an individual basis, weighing the risk/benefit ratio.

The results of our study showed that 20 or 30 mg of ketamine administered epidurally enhances the analgesic effect of epidural morphine, lengthens pain relief significantly (27.2 ± 8 hours versus 16.4 ± 10 hours; $P < 0.05$), and significantly reduces ($P < 0.05$) the need for complementary analgesia. Probably the more significant result was that, at 24 hours after surgery, only 7% (four patients) in Group MKG had needed complementary analgesia, whereas in Group MG this was 100% ($P = 0.003$).

Different studies have shown that small-dose ketamine plus bupivacaine or morphine administered epidurally produced better and longer pain relief than when the drugs were given alone (11,18,19). Ketamine is a noncompetitive antagonist that blocks the ion channel coupled to the *N*-methyl-D-aspartate (NMDA) receptor; it is capable of depressing the excitation produced by locally applied glutamate (the major excitatory neurotransmitter in the central nervous system) in the dorsal horn by coupling to NMDA receptor (20,21). Small-dose ketamine alone has been administered epidurally for postoperative pain relief in humans; however, its efficacy seems to be limited (11,22,23).

In relation to the longer duration of analgesic action observed in this study (27.2 ± 8 hours), one possible explanation may be that in patients with cirrhosis, profound alterations in glutamatergic neurotransmission have been observed. Although glutamate levels are decreased in the brain (the detoxifying mechanism of ammonia), the levels in the cerebrospinal fluid and extracellular space are increased (24), and, at the same time, the number of NMDA receptors is decreased (25). These alterations affect many cellular functions (interactions between astrocytes and neurons), and they may also facilitate the effectiveness of ketamine analgesia.

Surprisingly, we did not find differences between groups in analgesia level during the first postoperative hours. The study design (preemptive effect of IV ketamine administered before surgery) was probably such that it did not provide a possibility for observing differences between the study groups during the first 12 hours, and the differences appeared only when the ketamine biophase concentration was too small to give a direct pharmacological effect (26). The most likely explanation of our results is that, in patients with cirrhosis, the preemptive effect of IV ketamine was more effective when it was associated with epidural ketamine (MKG patients) than the preemptive effect in the other group (MG patients).

Although no clinical studies have reported neurologic lesions associated with epidural ketamine administration (27), it has to be stated that no proven nonneurotoxic solution of ketamine is currently available for epidural use.

In relation to side effects, no differences between groups were observed. Respiratory rate and $Paco_2$ did not differ between groups. This fact supported the concept that epidural ketamine did not appear to have a marked effect on ventilation. No patients had psychomimetic effects, neurologic disorders, hallucination, headache, or nightmares.

In summary, these results suggest that postoperative analgesia provided by a single shot of epidural morphine combined with small-dose ketamine is effective and safe and represents an alternative technique in cirrhotic Child's A patients undergoing any type of major upper abdominal surgery.

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