

Small-Dose Ketamine Improves the Postoperative State of Depressed Patients

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We investigated whether ketamine is suitable for depressed patients who had undergone orthopedic surgery. We studied 70 patients with major depression and 25 patients as the control (Group C). The depressed patients were divided randomly into two groups; patients in Group A ($n = 35$) were induced with propofol, fentanyl, and ketamine and patients in Group B ($n = 35$) were induced with propofol and fentanyl, and all patients were maintained with 1.5%–2.0% isoflurane plus nitrous oxide. The mean Hamilton Depression Rating (HDR) score was 12.7 ± 5.4 for Group A and 12.3 ± 6.0 for Group B 2 days before surgery and 9.9 ± 4.1 for Group A and 14.4 ± 3.8 for Group B 1 day after surgery. The HDR

score in Group A 1 day after surgery was significantly ($P < 0.05$) lower than that in Group B. The HDR score in Group C was 4.2 ± 1.7 2 days before surgery and 4.8 ± 1.6 1 day after surgery. Depressed mood, suicidal tendencies, somatic anxiety, and hypochondriasis significantly decreased in Group A as compared with Group B. Postoperative pain scores in Group A at 8 and 16 h after the end of anesthesia were 26.6 ± 8.7 and 24.9 ± 8.2 , respectively, which were significantly ($P < 0.05$) lower than 34.3 ± 12.0 and 31.1 ± 8.8 in Group B. In conclusion, small-dose ketamine improved the postoperative depressive state and relieved postoperative pain in depressed patients.

(Anesth Analg 2002;95:114–8)

The N-methyl-D-aspartate (NMDA) of glutamate systems is involved in the pathophysiology of major depression and the mechanism of action of antidepressants (1). NMDA receptor antagonists are effective for improving depression (2). Ketamine is a NMDA receptor antagonist. Barman et al. (3) showed that the administration of 0.5 mg/kg of ketamine significantly improved the symptoms of depressed patients for 72 h after the ketamine infusion. However, depressed patients have increased clinical pain problems. Patients with symptoms of depression have increased postoperative pain (4). Ketamine has an analgesic action that modulates central sensitization to nociceptive stimulation and is useful for the prevention and treatment of acute postoperative pain (5). Roytblat et al. (6) found improvement in postoperative pain with a single preemptive dose of 0.25 mg/kg of ketamine in patients undergoing gallbladder surgery. Thus, ketamine may be suitable for depressed patients, but its use for depressed patients remains unclear.

Ketamine may theoretically produce an adverse response when administered in the presence of tricyclic antidepressants because both ketamine and tricyclic antidepressants inhibit norepinephrine reuptake and may produce dangerous cardiovascular complications (7). Ketamine produces posthypnotic emergence reactions, such as hallucinations or delirium, after surgery (8). The incidence of postoperative confusion in patients with depression is more frequent than that of patients without psychiatric disease (9). The purpose of this study was to investigate the effect of ketamine on postoperative outcomes in depressed patients with a chronic administration of antidepressants.

Patients and Methods

This study was performed in Hakodate Watanabe Hospital, Japan, and Hirosaki National Hospital, Aomori, Japan. The protocol for the study was approved by the institutional ethical committee, and informed consent was obtained from all patients.

We studied 70 patients ranging in age from 35 to 63 yr who were diagnosed as having major depression by psychiatrists according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria (10) and 25 patients ranging in age from 30 to 64 yr selected randomly as the control (Group C). The depressed patients were divided randomly into two

Accepted for publication March 12, 2002.

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DOI: 10.1213/01.ANE.0000020693.65934.B7

groups; patients in Group A ($n = 35$) were anesthetized with propofol, fentanyl, and ketamine and patients in Group B ($n = 35$) were anesthetized with propofol and fentanyl. The randomization was performed on computer-generated codes. All depressed patients were medicated by antidepressants (imipramine, clomipramine, maprotiline, and mianserin) for more than a year. The state of depression was quantitatively estimated 2 days before and 1 and 3 days after surgery by means of the Hamilton Depression Rating (HDR) score. This score is a useful self-report measure for the diagnosis of depression (11). The test consists of 21 items with a cumulative scoring system based on common symptoms of depression, such as sleep disturbance, weight change, fatigue factors, sexual dysfunction, and cognitive components of depressive illness. A larger number indicates a more depressed state. All patients had orthopedic surgery, including elective reduction of arm or lower limb fracture, under general anesthesia. All patients with a history of anemia (Hemoglobin <10 g/dL), dysfunction of the immune system, marked cardiovascular disease, respiratory disease, or endocrine disorders were excluded. All control patients were free of medical illness and did not have a negative past, present, or family history of psychiatric disease and were not treated with psychotropic drugs.

For patients in Groups A and C, anesthesia was induced with 1.0 mg/kg of ketamine, 1.5 mg/kg of propofol, and 2 μ g/kg of fentanyl; tracheal intubation was then facilitated by vecuronium 0.1 mg/kg IV. Anesthesia was maintained with 1.5%–2.0% isoflurane in nitrous oxide (70%) and oxygen according to response to vital signs, such as systolic blood pressure and heart rate, which were controlled within 20% of preoperative values. For Group B, anesthesia was induced with 1.5 mg/kg of propofol and 2 μ g/kg of fentanyl; tracheal intubation was then facilitated by vecuronium 0.1 mg/kg IV. Anesthesia was maintained with 1.5%–2.0% isoflurane in nitrous oxide (70%) and oxygen according to response to vital signs, such as systolic blood pressure and heart rate, which were controlled within 20% of preoperative values. The end-expiratory concentration of oxygen, carbon dioxide, and anesthetics were monitored throughout the anesthesia period. The lungs were mechanically ventilated to maintain PETCO₂ at 35–40 mm Hg. No patient received packed red blood cells. Nasopharyngeal temperature was monitored continuously with an electric thermistor and maintained at 36.0°C–37.0°C using a warming blanket and by controlling the temperature in the operating room. After surgery, all patients were treated with a nonsteroidal analgesic (Diclofenac sodium 50 mg suppository) every 6 h for incisional pain.

Postoperative confusion was assessed using the confusion assessment method (CAM). The sensitivity

Table 1. Profile of Patients, Clinical Data During Anesthesia in this Study, and Antidepressants Treatment

No.	Group A ($n = 35$)	Group B ($n = 35$)	Group C ($n = 25$)
Age (yr)	46.9 $\pm$ 8.8	48.2 $\pm$ 7.4	46.2 $\pm$ 10.3
Weight (kg)*	56.0 $\pm$ 13.3	55.2 $\pm$ 13.2	63.0 $\pm$ 15.7
Duration of surgery (min)	112.6 $\pm$ 28.7	116.0 $\pm$ 32.3	104.9 $\pm$ 37.5
Duration of anesthesia (min)	135.6 $\pm$ 40.0	141.5 $\pm$ 43.7	122.8 $\pm$ 46.1
Blood loss (g)	95.1 $\pm$ 25.2	100.3 $\pm$ 31.8	93.6 $\pm$ 27.4
Antidepressants			
Imipramine	13	14	–
Clomipramine	8	4	–
Maprotiline	7	9	–
Mianserin	7	8	–

Values are mean $\pm$ SD or number of patients.

* $P < 0.05$ for Group A versus B or C.

was 100%, and positive and negative predictive accuracy was 91% and 100%, respectively (12); the CAM is a sensitive and reliable method for the assessment of confusion. The patients were examined at least once daily with CAM diagnostic criteria for confusion until the seventh day after surgery, and the assessment of confusion was performed whenever a patient was found by the nursing staff to be changed mentally. The nurses were not aware of the purpose of the study. Haloperidol 5 mg was administered for treatment of the postoperative confusion.

Pain scores were evaluated by nurses every 8 h for the first 24 h after the end of surgery and every 24 h after that time. Pain was estimated using a 100 mm visual analog scale (0 mm representing no pain and 100 mm representing the worst imaginable pain).

Data were expressed as mean $\pm$ SD. Comparisons between groups in the visual analog scale pain score, blood pressure, heart rate, mean duration of anesthesia and surgery, mean volume of blood loss, and HDR score before and after the operation were analyzed by analysis of variance followed by Dunnett's test. The incidence of psychosis emergence or confusion was analyzed by χ^2 testing. $P < 0.05$ were considered significant.

Results

There were no significant differences in age, mean duration of anesthesia and surgery, mean volume of blood loss, and total fentanyl consumption among the groups, but the average weight in Group C was significantly heavier than that of Groups A and B (Table 1).

One patient (3%) of 35 in Group A, two patients (6%) of 35 in Group B, and one patient (4%) of 25 in Group C developed ventricular ectopic rhythm and returned to sinus rhythm without any treatment. One patient (3%) in Group A and two patients (6%) in

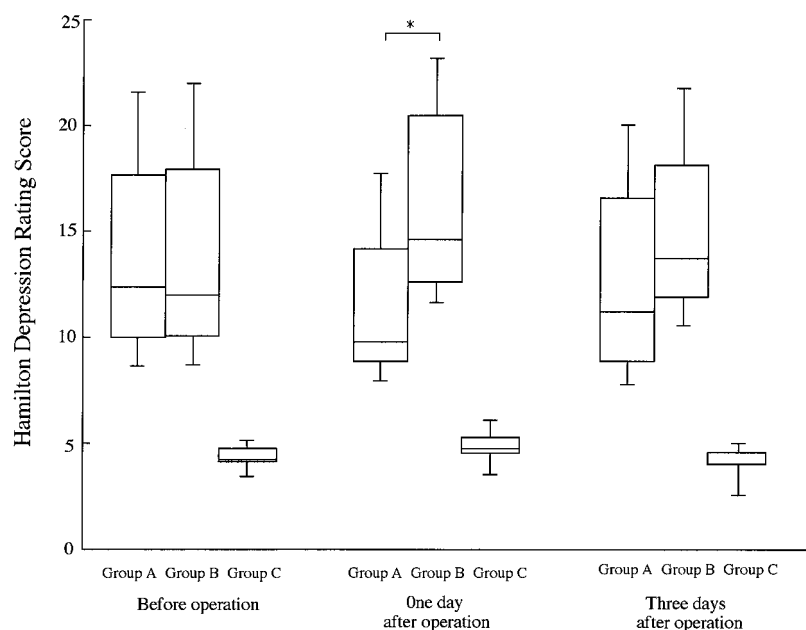


Figure 1. Hamilton Depression Rating (HDR) score before and after surgery. Box and whisker plots indicating median, 25th, 50th, and 75th percentile (box), and 10th and 90th percentile (whiskers). * $P < 0.05$ between Group A and B.

Group B had a history of postural hypotension. Hemodynamic changes immediately after the induction of anesthesia were observed in both groups. Two patients (6%) of 35 in Group A and two patients (6%) of 35 in Group B had episodes of hypotension <70 mm Hg in systolic blood pressure during the induction. Ephedrine and the infusion of acetate Ringer's solution were effective for all patients who developed hypotension.

Eight (23%) of 35 patients in Group B were up more than 5 points in HDR score after surgery, but there were no patients who were up more than 5 points in HDR score after surgery in Group A. The mean HDR score was 12.7 ± 5.4 for Group A and 12.3 ± 6.0 for Group B 2 days before surgery and 9.9 ± 4.1 for Group A and 14.4 ± 3.8 for Group B 1 day after surgery (Fig. 1). The HDR score in Group A was significantly lower than that in Group B 1 day after surgery, but there was no significant difference in the score between Groups A and B 3 days after surgery. The score of individual HDR items before and after surgery were compared. Depressed mood, suicidal tendencies, somatic anxiety, and hypochondriasis significantly ($P < 0.001$) decreased in Group A as compared with Group B (Table 1). The HDR score in Group C was 4.2 ± 1.7 2 days before surgery and was 4.8 ± 1.6 24 h after surgery.

Postoperative pain scores in Group A at 8 and 16 h after the end of anesthesia were significantly lower than those in Group B. However, there were no significant differences in the other postoperative pain scores between the two groups for 4 days after surgery. Postoperative pain scores of patients in Group C at 8, 16, 24, 48, and 72 h after the end of anesthesia were 20.2 ± 8.4 , 18.4 ± 7.5 , 11.9 ± 6.1 , 8.7 ± 5.5 , and 5.2 ± 3.2 , respectively (Fig. 2).

Postoperative confusion occurred in 5 patients (14%) of Group A and in 8 patients (23%) of Group B. There was no significant difference in the incidence of postoperative confusion between Group A and B. No patients in Group C developed confusion.

Discussion

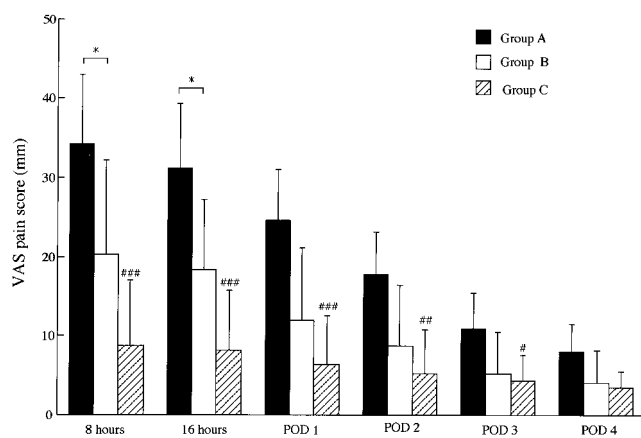
The present study showed that the depressive state of depressed patients administered ketamine improved after surgery. Ketamine is a high-affinity NMDA receptor antagonist. This result is consistent with reports that NMDA antagonists mimic the effects of clinically effective antidepressants (2). NMDA receptor antagonists show similar behavioral and neurochemical profiles to antidepressants. MK-801, which is a noncompetitive NMDA antagonist, and AP7, which is a competitive NMDA antagonist, exhibited antidepressant-like activity (13). MK-801 showed down-regulation of β -cortical adrenoceptors, and the down-regulation was similar in magnitude to that produced by the antidepressant imipramine (14). Therefore, ketamine seems to exert a postoperative antidepressive effect in depressed patients, probably through the NMDA receptor.

Patients with symptoms of depression have increased postoperative pain (4). Approximately 50% of patients with major depression complain of pain such as facial pain, headache, cervical pain, abdominal pain, back pain, and lower limb pain (15). Because pain is closely associated with the pathology of depression, postoperative pain relief may contribute to an improvement in the depressed state. Ketamine is known to have analgesic action, which is linked to an antagonism to NMDA (5). Clements and Nimmo (16)

Table 2. Individual Hamilton Depression Rating Items Score Before and After Surgery

Symptoms	HDR scores 2 days before surgery			HDR scores next day after surgery			P-values (Group A vs B after surgery)
	Group A	Group B	Group C	Group A	Group B	Group C	
Depressed mode	2.2 ± 1.2	2.0 ± 1.0	0.6 ± 0.3	0.8 ± 0.8	2.1 ± 1.0	0.6 ± 0.4	P < 0.001
Guilt	1.3 ± 1.2	1.2 ± 1.3	0.2 ± 0.1	1.4 ± 1.6	1.4 ± 1.6	0.2 ± 0.1	P = NS
Suicide	1.3 ± 0.7	1.1 ± 1.1	0.1 ± 0.0	0.3 ± 0.5	1.1 ± 0.8	0.1 ± 0.1	P < 0.001
Insomnia initial	0.7 ± 0.6	0.8 ± 0.4	0.5 ± 0.3	0.7 ± 0.6	0.9 ± 0.6	0.7 ± 0.5	P = NS
Insomnia middle	0.6 ± 0.4	0.5 ± 0.6	0.4 ± 0.3	0.6 ± 0.4	0.7 ± 0.8	0.4 ± 0.3	P = NS
Insomnia delayed	0.6 ± 0.3	0.5 ± 0.5	0.4 ± 0.2	0.6 ± 0.3	0.5 ± 0.5	0.4 ± 0.2	P = NS
Work and interests	0.7 ± 0.8	0.8 ± 1.0	0.4 ± 0.3	0.7 ± 0.7	0.8 ± 0.9	0.5 ± 0.3	P = NS
Retardation	0.4 ± 0.3	0.3 ± 0.4	0.0 ± 0.0	0.4 ± 0.4	0.3 ± 0.3	0.0 ± 0.0	P = NS
Agitation	0.2 ± 0.1	0.4 ± 0.2	0.0 ± 0.0	0.2 ± 0.1	0.4 ± 0.2	0.0 ± 0.0	P = NS
Anxiety, psychic	0.8 ± 0.9	0.6 ± 0.9	0.4 ± 0.3	0.8 ± 0.9	0.9 ± 1.1	0.4 ± 0.3	P = NS
Anxiety, somatic	1.1 ± 1.2	0.9 ± 1.0	0.5 ± 0.3	1.3 ± 0.7	1.9 ± 0.9	0.5 ± 0.4	P < 0.001
Somatic symptoms, gastrointestinal	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.2	0.4 ± 0.2	0.6 ± 0.5	0.4 ± 0.2	P = NS
Somatic symptoms, general	0.2 ± 0.3	0.2 ± 0.2	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	P = NS
Genital symptoms	0.2 ± 0.2	0.2 ± 0.2	0.0 ± 0.0	0.2 ± 0.2	0.2 ± 0.2	0.0 ± 0.0	P = NS
Hypochondriasis	0.8 ± 1.1	0.5 ± 0.4	0.2 ± 0.1	1.2 ± 1.0	1.6 ± 0.9	0.3 ± 0.2	P = NS
Loss of weight	0.2 ± 0.1	0.2 ± 0.1	0.0 ± 0.0	0.2 ± 0.1	0.2 ± 0.1	0.0 ± 0.0	P = NS
Insight	0.5 ± 0.4	0.6 ± 0.6	0.0 ± 0.0	0.3 ± 0.3	0.3 ± 0.3	0.0 ± 0.0	P = NS
Diurnal variation	0.1 ± 0.1	0.1 ± 0.1	0.0 ± 0.0	0.1 ± 0.1	0.1 ± 0.1	0.0 ± 0.0	P = NS
Depersonalization and derealization	0.2 ± 0.1	0.1 ± 0.1	0.0 ± 0.0	0.2 ± 0.1	0.1 ± 0.1	0.0 ± 0.0	P = NS
Paranoid symptoms	0.1 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	P = NS
Obsessional symptoms	0.2 ± 0.1	0.1 ± 0.0	0.0 ± 0.0	0.2 ± 0.1	0.1 ± 0.0	0.0 ± 0.0	P = NS

HDR = hamilton depression rating; NS = not significant.

**Figure 2.** Visual analog scale (VAS) score at 8 and 16 h after the end of anesthesia, the first day (POD 1), the second day (POD 2), the third day (POD 3), and the fourth day (POD 4) after surgery. Data are expressed as mean ± SD. **P* < 0.05 between Group A and B. ##*P* < 0.05, ###*P* < 0.01, and ####*P* < 0.001 versus Group A.

found that analgesic effects with ketamine were achieved at a low level of 100 ng/mL in plasma. The plasma level could be achieved with an initial dose of 1 mg/kg (17). In this study, patients in Group A received 1 mg/kg of ketamine, and the postoperative pain score of Group A was significantly lower than that of Group B. Thus, ketamine has a beneficial effect on the postoperative depressive state and on pain

relief for depressed patients who underwent orthopedic surgery.

We could not find a significant difference in the incidence of confusion between patients with and without ketamine. The incidence of confusion, such as hallucinations, after large-dose ketamine (>2 mg/kg) is 5%–30% (18). However, small-dose ketamine given at an infusion rate $<2.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ does not cause hallucinations or impairment of cognitive functioning (19). In this study, we used the dose in the upper end (1 mg/kg) of the small-dose range to avoid the risk of psychotomimetic, cardiovascular, or respiratory effects. Thus, small-dose ketamine does not seem to influence the incidence of emergence reactions of chronically depressed patients. However, the incidence of confusion was frequent in both groups of depressed patients as compared with that of control patients. Gustafson et al. (9) reported that the incidence of postoperative confusion in patients with preoperative depression was 88%. The administration of antidepressants is also one of the causes of postoperative confusion. Antidepressants have moderate anticholinergic effects. The regular use of drugs with anticholinergic effects is the most important predictor for postoperative mental confusion (20). Although chronically depressed patients tend to develop postoperative confusion, this study suggests that ketamine is not likely to enhance it.

Only one patient in Group A and two patients in Group B developed arrhythmia during the induction. The incidence of the arrhythmias was not significantly different between Group A and B and was not significantly increased as compared with the Control group. Antidepressants initially increase noradrenergic synaptic activity, thereby promoting arrhythmogenesis, but their chronic administration ultimately results in a decrease in noradrenergic transmission because of down-regulation of β -adrenergic receptors (21). The chronic administration of antidepressants can create hypotension and decreased myocardial contractility (22). Therefore, patients treated with chronic antidepressants often develop hypotension during anesthesia (23). In this study, four of 75 patients had profound hypotension, and there were no patients with severe hypotension resistant to vasopressor therapy. The cardiovascular response to small-dose ketamine causes minimal changes in heart rate and blood pressure (24). Thus, small-dose ketamine seems to be safely used for depressed patients treated with antidepressants.

In conclusion, small-dose ketamine improved the postoperative depressive state and relieved postoperative pain in depressed patients who underwent orthopedic surgery.

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