

Sedation for the Conduct of Lumbar Epidural Anaesthesia: A Study Using Subanaesthetic Dose of Ketamine in Combination with Midazolam

C C Loo,**MBBS, FRCA*, E Thomas,***MBBS (Cal), M Med (Anaes), FFARACS*, H M Tan,***MBBS, M Med (Anaes)*,
S W Yeo,***MBBS, M Med (Anaes)*, T H Sia,**MBBS, M Med (Anaes)*

Abstract

We gave sedation for the conduct of lumbar epidural analgesia using intravenous ketamine 0.3 mg.kg^{-1} with intravenous midazolam 2 mg . Forty adult Chinese females undergoing major gynaecological laparotomies had epidural catheter inserted before general anaesthesia, 20 of whom were given ketamine and midazolam (study group) and the other 20 acted as control. During the conduct of the epidural, the pain and anxiety scores in the study group were significantly less than the control group ($P < 0.05$). Patients were significantly more sedated in the study group ($P < 0.05$). All the patients in the study group were satisfied and would consent to future epidural versus 75% in the control group (significant at $P < 0.05$). Ninety per cent of patients in the study group had amnesia but none in the control group. Pain experienced during the epidural was the reason for refusal of future epidural. We did not observe any emergence phenomenon or cardiovascular stimulation. There was a statistically significant decrease in the pulse oximetry oxygen saturation (SpO_2) in the study group but none required oxygen supplementation. We concluded that pain caused by the conduct of epidural did decrease the patient's acceptance rate to future epidural, and the combined use of intravenous ketamine 0.3 mg.kg^{-1} and midazolam 2 mg provided adequate sedation, analgesia, anxiolysis and amnesia to significantly increase the acceptance rate without any significant side effects.

Ann Acad Med Singapore 1997; 26:200-4

Key words: Amnesia, Analgesia, Anxiolytics, Benzodiazepine, Gynaecological

Introduction

Epidural analgesia is commonly employed in surgery either as the sole anaesthetic or to provide intra and postoperative pain relief during and after general anaesthesia. However, some patients may be apprehensive of the injection pain (however slight) that inevitably accompanies the insertion of epidural catheter. This may result in a lower acceptance rate of epidurals.

To provide optimal conditions for the conduct of the epidural, not only do we need to sedate them but also at the same time provide anxiolysis, analgesia and amnesia. Opioids, benzodiazepines, ketamine, propofol, droperidol and nitrous oxide have all been satisfactorily employed. We decided to use ketamine and midazolam because the combination has several advantages. Subanaesthetic doses of ketamine (i.v. 0.2 to 0.5 mg.kg^{-1}) are short acting, provide good analgesia and sedation.¹ Ketamine is a mild respiratory depressant,² but oxygen supplementation is usually not required at subanaesthetic doses. Midazolam is also short acting and provides good sedation, anxiolysis, amnesia and prevents emergence phenomenon^{3,4} and cardiovascu-

lar stimulation³ due to ketamine. The aim of this study were to show that there is a need to provide adequate sedation and analgesia for the pain inflicted during the insertion of epidural catheters and the use of ketamine and midazolam could be satisfactorily employed to achieve greater patients' satisfaction and acceptance of epidural analgesia.

Materials and Methods

Forty adult (aged 30 to 60 years) Chinese female patients, ASA (American Society of Anesthesiologists) 1, undergoing major gynaecological laparotomies (hysterectomy $\pm$ salphingo-oophorectomy, Wertheim's and staging laparotomy for ovarian carcinoma) were offered lumbar epidural analgesia before general anaesthesia. This study was approved by the ethics committee of our hospital.

The patients were randomly allocated to 2 groups. No sedation was given in the control group ($n = 20$). Intravenous ketamine 0.3 mg.kg^{-1} and intravenous midazolam 2 mg bolus were given 2 minutes before the commencement of the epidural in the study group ($n = 20$).

*Registrar

** Consultant

Department of Anaesthesia
Kandang Kerbau Hospital

Address for Reprints: Dr Loo Chee Chuen, Department of Anaesthesia, Kandang Kerbau Hospital, 2 Hampshire Road, Singapore 219428.

The anaesthetic management was as follows:

No premedication was given. Patients were assessed for degree of anxiety and sedation before the epidural. The anxiety scores were as follows:

- 0 = not at all anxious,
- 1 = mild, no sedation required,
- 2 = moderate, supplemental sedation desirable but not an absolute necessity,
- 3 = severe, will require sedation if procedure lasts longer than 10 minutes, and
- 4 = extreme, will require immediate sedation.

The sedation scores were as follows:

- 0 = alert,
- 1 = drowsy but orientated,
- 2 = drowsy and confused, and
- 3 = unarousable.

Non invasive blood pressure monitoring was recorded every 5 minutes, pulse oximetry for oxygen saturation and pulse rate were recorded every minute. Patients were only given oxygen supplementation if the pulse oximetry oxygen saturation (SpO_2) was less than 95%. The anxiety and sedation scores were repeated in the study group 2 minutes after administering ketamine and midazolam. The epidural was performed with skin infiltration with 3 ml of lignocaine 1.5% with both 27G and 23G needles, followed by a 16G Tuohy needle. A test dose of 3 ml of lignocaine 1.5% was given. Only those with single attempt and duration of <10 minutes (from local anaesthetic infiltration to completion of insertion of catheter) were included in the study. Patients were assessed for pain during the epidural.

The pain scores were as follows:

- 0 = no pain,
- 1 = mild, no analgesia required,
- 2 = moderate, supplemental analgesia desirable but

not an absolute necessity,

3 = severe, will require analgesia if procedure lasts longer than 10 minutes, and

4 = extreme, will require immediate analgesia.

The patients were assessed after the epidural (10 minutes after intravenous ketamine and midazolam) for anxiety, sedation, amnesia (any recall of injection being performed at the back) and emergence phenomenon (hallucinations, dreams, visual disturbance and delirium). The patients were then put under general anaesthesia (intravenous fentanyl $1 \mu\text{g.kg}^{-1}$ and propofol 2 mg.kg^{-1} for induction, atracurium for intubation and nitrous oxide in oxygen with isoflurane for maintenance, and epidural morphine 3 mg). Patients were assessed in the ward 24 hours postoperatively for amnesia, emergence phenomenon and degree of satisfaction. All assessments were done by the same observer blinded to the study. All the epidural analgesia were performed by the same person blinded to the study. The results were analyzed by t-test, Fisher's exact test and Wilcoxon rank sum test. A *P* value of <0.05 was taken as significant.

Results

The 2 groups were comparable in weight, age and duration of epidural catheter insertion (Table I, unpaired t-test).

Table II shows the anxiety scores in the control and study groups. There was no difference in the anxiety score between the control and study groups before the conduct of epidural (Wilcoxon rank sum unpaired test). Majority of patients had some degree of anxiety (70% in the control and 80% in the study group). In the control group, the anxiety score pre and post-epidural was not significantly different (Wilcoxon signed rank paired test). Two minutes after administering the intravenous ketamine and midazolam in the study group, majority of the patients showed no anxiety (75%). Wilcoxon signed rank test (paired) showed that the decrease in the anxiety score between pre-epidural and 2 minutes post-sedation in the study group was significant. Post-epidurally in the study group, only one patient experienced mild anxiety while the rest had no anxiety. However the difference in the anxiety score 2 minutes post-sedation and post-epidurally in the study group was not statistically significant (Wilcoxon signed rank paired test).

TABLE I: PATIENTS CHARACTERISTICS

	Age(y) mean $\pm$ SD	Weight (kg) mean $\pm$ SD	Duration of epidural (min) mean $\pm$ SD
Control	47 $\pm$ 7.9	59 $\pm$ 10.4	3.6 $\pm$ 2.4
Study	45 $\pm$ 5.9	61 $\pm$ 11.5	3.5 $\pm$ 2.0

TABLE II: ANXIETY SCORES

Anxiety score		0	1	2	3	4
Control	Pre-epidural	6 (30%)	6 (30%)	2 (10%)	6 (30%)	0 (0%)
	Post-epidural	10 (50%)	6 (30%)	1 (5%)	3 (15%)	0 (0%)
Study	Pre-epidural	4 (20%)	8 (40%)	6 (30%)	2 (10%)	0 (0%)
	Two min post-sedation	15 (75%)	5 (25%)	0 (0%)	0 (0%)	0 (0%)
	Post-epidural	19 (95%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)

TABLE III: SEDATION SCORES IN THE STUDY GROUP

Sedation score		0	1	2	3
Study	Two min post sedation	0 (0%)	9 (45%)	8 (40%)	3 (15%)
	Post-epidural	1 (5%)	16 (80%)	3 (15%)	0 (0%)

Wilcoxon signed rank test (paired) showed that the difference in the sedation score is significant (*P* < 0.05)

Table III shows the sedation score in the study group. All patients were fully alert before sedation. Patients were significantly more sedated 2 minutes post-sedation than before sedation (Wilcoxon signed rank paired test). Comparing the sedation score between 2 minutes post-sedation and post-epidurally in the study group, the sedation score was significantly less post-epidurally (Wilcoxon signed rank paired test). No patients were unarousable in the study group post-epidurally, whereas 15% of patients were unarousable 2 minutes post-sedation.

Table IV shows the blood pressure, pulse rate and SpO₂ in the study group before and during the conduct of the epidural. As ketamine has cardiovascular stimulatory and respiratory depressant properties, the greatest increase in blood pressure and pulse rate, and greatest reduction in SpO₂ were taken as representative of the parameters during the conduct of the epidural. However, if the blood pressure or pulse rate decreased instead, the greatest reduction was taken instead. After administration of intravenous ketamine and midazolam, there was a statistically significant decrease in systolic blood pressure and SpO₂. The greatest reduction in SpO₂ was observed within 2 minutes after administration of the drugs in 85% of patients. Five minutes after administration of the drugs none of the patients had respiratory depression. No patients required supplemental oxygen as the lowest SpO₂ recorded was 95%. There was a slight decrease in diastolic blood pressure and slight increase in pulse rate but they were not significant at *P* < 0.05. There were no differences in the systolic and diastolic blood pressure, pulse rate and SpO₂ in the control group before and during the conduct of the epidural.

The pain scores during the conduct of the epidural were analyzed by Wilcoxon rank sum test (unpaired) and showed that the study group had significantly less pain than the control group (Table V). In the control

TABLE IV: BLOOD PRESSURE (BP), PULSE RATE (PR) AND OXYGEN SATURATION (SpO₂) IN THE 2 GROUPS BEFORE AND DURING THE CONDUCT OF THE EPIDURAL

	Systolic BP (mmHg) mean ± SD	Diastolic BP (mmHg) mean ± SD	PR (beats per min) mean ± SD	SpO ₂ (%) mean ± SD
Pre- epidural (control)	138.4 ± 24.1	73.7 ± 13.1	80.1 ± 14.9	98.5 ± 1.4
During epidural (control)	139.6 ± 23.2	74.1 ± 9.5	78.8 ± 15.8	98.3 ± 1.86
Pre- epidural (study)	133.6 ± 21.7	77.5 ± 13.6	79.9 ± 11.1	98.5 ± 1.5
During epidural (study)	125.4 ± 20.3*	72.8 ± 14.8	82.8 ± 11.2	96.6 ± 2.1*

* t-test (paired) analysis showed that the difference was significant.

TABLE V: PAIN SCORES DURING THE CONDUCT OF THE EPIDURAL

Pain score	0	1	2	3	4
Control	0 (0%)	13 (65%)	1 (5%)	6 (30%)	0 (0%)
Study	12 (60%)	3 (15%)	4 (20%)	1 (5%)	0 (0%)

Wilcoxon rank sum test (unpaired) analysis showed that the difference was significant

group, all patients experienced some degree of pain, of which 65% and 30% had mild and severe pain, respectively. In the study group, 60% of patients were pain free and only 5% of patients had severe pain. No involuntary movements were observed during the epidural.

The patients were assessed after the completion of the epidural (10 minutes after the start of the epidural) for amnesia and emergence phenomenon. In the study group 55% of patients had no recollection of the epidural injection whereas none of those in the control group had amnesia (the difference was significant using Fisher's exact test analysis). No patients experienced any emergence phenomenon.

The patients were assessed 24 hours postoperatively for amnesia, emergence phenomenon and degree of satisfaction. In the study group there was a significant increase in proportion of patients having amnesia 24 hours postoperatively compared to post epidurally (90% versus 55%, Fisher's exact test). All patients in the control group had recollection of the epidural. No patients experienced any emergence phenomenon. In the study group, all patients were satisfied with the epidural and would consent to future epidural. In the control group, 75% of patients were satisfied with the epidural and would consent to future epidural due to good postoperative pain relief. The other 25% of patients, despite also having good pain relief from the epidural postoperatively, felt that the pain experienced during the conduct of the epidural was unacceptable and would refuse future epidural if possible. The difference between the 2 groups was significant (Fisher's exact test). In the control group, 6 patients (30%) had pain score of 3, of which 2 were satisfied and 4 were not satisfied; 14 patients (70%) had pain score of 0, 1 or 2, of which 13 were satisfied and 1 were not satisfied. Of the 5 patients who were not satisfied, 4 had a pain score of 3. Fisher's exact test analysis showed that more patients were likely to be dissatisfied if they had a higher pain score. Anxiety was not a factor in dissatisfaction.

Discussion

We have shown in this study that there is a need to provide adequate sedation and analgesia during the conduct of epidurals, and a combination of ketamine and midazolam can be satisfactory employed to achieve greater patient satisfaction and acceptance. All the patients in the study group were satisfied and would

consent to future epidurals. Whereas 25% of patients in the control group despite having good pain relief from the epidural postoperatively, felt that the pain experienced during the conduct of the epidural was unacceptable and would refuse future epidural if possible.

Ketamine is chemically related to phencyclidine and cyclohexamine. Its lipid solubility is 10 times that of thiopentone, and after intravenous injection, onset is within 30 to 60 seconds and duration is within 10 to 15 minutes. Ketamine's distribution half-life is 24.1 seconds, redistribution half-life is 4.68 minutes and elimination half-life is 2.17 hours.⁵ The intravenous induction dose is 0.5 to 1.5 mg.kg⁻¹ and the sedation and analgesic dose (subanaesthetic dose) by the same route is 0.2 to 0.75 mg.kg⁻¹.⁶ We employed a dose of 0.3 mg.kg⁻¹. This dose was not sufficient for complete pain relief as only 60% were completely pain free during the epidural. However, with the help of midazolam, 90% of patients were rendered amnesic to the "traumatic" experience. Increasing the dose would certainly improve the analgesia but at the expense of greater incidence of emergence phenomenon,⁶ cardiovascular stimulation,^{7,8} respiratory depression² and airway obstruction.

Kortilla and Levanen¹ administered ketamine with diazepam to patients receiving regional anaesthesia. They found that intravenous ketamine 0.5 mg.kg⁻¹ was not associated with significant side effects whereas intravenous 1.5 and 3 mg.kg⁻¹ were associated with greater incidence of emergence phenomenon. Subanaesthetic doses of ketamine (0.2 to 0.5 mg.kg⁻¹) were also found to be adequate for analgesia during routine vaginal deliveries with high patient acceptance.^{9,10} The analgesia produced by ketamine is probably due to the antagonism of N-methyl-D-aspartate (NMDA) receptors which are a subgroup of the sigma opiate receptors. Emergence phenomenon due to ketamine is most troublesome as it can occur even at subanaesthetic doses¹¹ and may persist for 24 hours or longer. The interaction of ketamine with sigma opiate receptors might be a plausible theory to explain dysphoric emergence reactions.¹² The emergence phenomenon following ketamine vary in incidence from less than 5%¹³ to greater than 30%.¹⁴ This phenomenon is more common in patients over the age of 16 years (less in children and the elderly), in females, larger doses of ketamine (>intravenous 2 mg.kg⁻¹), rapid intravenous administration (>intravenous 40 mg.min⁻¹) or a history of personality problems.⁶ It has been described as floating sensations, vivid dreams (pleasant or unpleasant), hallucinations, and delirium. Benzodiazepines have proven to be the most effective agents for prevention of these phenomena.³ Midazolam had been found to be superior to diazepam in this respect.⁴ Contrary to common beliefs, there is no evidence that covering the eyes

during the operative and postoperative periods or allowing patients to emerge in a quiet area alter the incidence of emergence reactions.¹⁵ Ketamine exists in two enantiomers: s(+) and r(-). Commercially available racemic preparations contain equal concentrations of the two enantiomers. The s(+) enantiomer has greater anaesthetic, hypnotic and analgesic potency, whilst the r(-) enantiomer produces more emergence phenomenon. Thus if commercially prepared s(+) ketamines are available, we might expect a reduction in the incidence of emergence phenomena.

Ketamine also causes dose-related cardiovascular stimulation.^{7,8} It causes central sympathetic stimulation and the circulating catecholamines are increased at least partially by an inhibition of re-uptake. In the study group, after the administration of ketamine and midazolam, there was a significant decrease (instead of the expected increase) in the systolic blood pressure (133.6 ± 21.7 mmHg versus 125.4 ± 20.3 mmHg). There was a slight decrease in the diastolic blood pressure and slight increase in the pulse rate but they were not significant. However, we cannot make any conclusions here because the blood pressure was only recorded every 5 minutes. More frequent recordings especially by an intra-arterial blood pressure monitoring should be able to detect the blood pressure changes more accurately. The blood pressure would also be affected by the concomitant administration of midazolam. Midazolam decreases both blood pressure and pulse rate. The benzodiazepines are the most efficacious agents for attenuating the cardiovascular effects of ketamine.³

Ketamine is a mild respiratory depressant. Bourke et al² found dose-related respiratory depression with incremental doses of ketamine. They found that ketamine alone caused the CO₂ response curve to shift to the right, but did not change the slope of the curve, similar to opioids. Midazolam also causes respiratory depression in a dose-dependant manner. In our study group, after the administration of ketamine and midazolam, there was a statistically significant decrease in the SpO₂ (98.5 ± 1.5 versus 96.6 ± 2.1). The greatest decrease was observed within 2 minutes after administration of the drugs in 85% of the patients. Five minutes after administration of the drugs none of the patients had respiratory depression. None of the patients required oxygen supplementation as the lowest SpO₂ recorded was 95%. The respiratory depression caused by intravenous ketamine 0.3 mg.kg⁻¹ and midazolam 2 mg appeared to be mild and transient and not clinically significant. However, caution needs to be taken in the elderly, patients with respiratory diseases and ASA 3 or 4 patients. Ketamine can cause excessive salivation, and if anaesthetic doses were to be administered, an antisialagogue agent should be given concomitantly. However, a subanaesthetic dose does not usually require an

antisialogue.^{10,16,17} We did not have any problems with excessive salivation.

Midazolam is a short-acting benzodiazepine. Its distribution half-life ($t_{1/2\alpha}$) is 6 to 20 minutes and elimination half-life ($t_{1/2\beta}$) is 1 to 4 hours. Following intravenous administration, the onset of sedative, anxiolytic and amnesic action usually occurs within 1 to 5 minutes. The duration of action is dose dependent and lasts from 20 minutes to 2 hours. The dose should preferably be titrated according to the response and not according to the weight of the patient. The drug company recommends i.v. 2 mg bolus, followed by 0.5 mg to 1 mg every 2 minutes until the desired response. In our study, there was a significant decrease in anxiety and increase in sedation after administration of ketamine and midazolam. Ten minutes later, there was a significant decrease in sedation demonstrating the short duration of action of ketamine and midazolam. However, the amnesic action of midazolam was certainly longer than 10 minutes because there was a significant increase in proportion of patients having amnesia 24 hours postoperatively compared to post-epidurally (90% versus 55%).

In an ideal setting, the patient should be completely pain free, slightly drowsy but orientated, calm, amnesic of the procedure, requiring no or minimal monitoring, no side effects and quick recovery. Sixty per cent of the patients did not experience any pain during the conduct of the epidural. Forty-five per cent of the patients were slightly drowsy but orientated and 75% of the patients were not anxious during the conduct of the epidural. Ninety per cent of the patients had no recollection of the epidural injection. We did not observe any significant side effects and patients were significantly more alert 10 minutes after administration of the drugs, as both ketamine and midazolam have short duration of action. Despite not being able to achieve the "ideal", all patients in the study group were satisfied with the epidural. Although all patients in the control group had some degree of pain during the epidural, 75% still found the epidural to be satisfactory due to the good postoperative pain relief. Of the 5 patients (25%) who were not satisfied, 4 had a pain score of 3. Fisher's exact test analysis showed that more patients were likely to be dissatisfied if they had a higher pain score.

Midazolam has powerful amnesic properties as 90% of patients were rendered amnesic in our study. So why not use it alone for sedation, instead of using it in combination with ketamine? Midazolam in adequate doses could certainly achieve the same objective but at the expense of possibly causing more confusion and

restlessness, and delayed recovery. Midazolam has no analgesic properties and patients if confused, may not be able to cooperate and remain still for the conduct of the epidural if they feel pain. In patients who are in pain e.g. fracture of the lower limbs, turning the patient to perform epidural or spinal anaesthesia is most unpleasant. Ketamine would certainly be useful in this situation.

We concluded that pain caused by the conduct of epidural did decrease the patient's acceptance rate to future epidural, and the use of intravenous ketamine 0.3 mg.kg⁻¹ and midazolam 2 mg provided adequate sedation, analgesia, anxiolysis and amnesia to significantly increase the acceptance rate without any significant side effects.

REFERENCES

1. Korttila K, Levanen J. Untoward effects of ketamine combine with diazepam for supplementing conduction anaesthesia in young and middle aged adults. *Acta Anaesth Scand* 1978; **22**:640-8.
2. Bourke D L, Malit L A, Smith T C. Respiratory interactions of ketamine and morphine. *Anesthesiology* 1987; **66**:153-6.
3. White P F. Pharmacologic interactions of midazolam and ketamine in surgical patients [abstract]. *Clin Pharmacol Ther* 1982; **31**:280-1.
4. Cartwright P D, Pingel S M. Midazolam and diazepam in ketamine anaesthesia. *Anaesthesia* 1984; **59**:439-42.
5. Domino EF, Domino SE, Smith RE, Domino LE, Goulet JR, Domino KE, et al. Ketamine kinetics in unpremedicated and diazepam-premedicated subjects. *Clin Pharmacol Ther* 1984; **36**:645-53.
6. White P F, Way W L, Trevor A J. Ketamine—its pharmacology and therapeutic uses. *Anesthesiology* 1982; **56**:119-36.
7. Tweed W A, Minuck M S, Mymin D. Circulatory responses to ketamine anaesthesia. *Anesthesiology* 1972; **37**:613-9.
8. Idvall J, Ahlgren I, Aronsen K F, Stenberg I. Ketamine infusions: Pharmacokinetics and clinical effects. *Br J Anaesth* 1979; **51**:1167-72.
9. Chodoff I, Stella J C. Use of CI-581, a phencyclidine derivative for obstetric anaesthesia. *Anesth Analg (Cleve)* 1966; **45**:527-30.
10. Akamatsu T J, Boreca J J, Rehmet R. Experiences with the use of ketamine for parturition. 1. Primary anaesthetic for vagina delivery. *Anesth Analg (Cleve)* 1974; **53**:284-7.
11. Harris J A, Biersner R J, Edwards D, Bailey L W. Attention, learning and personality during ketamine emergence. *Anesth Analg (Cleve)* 1975; **54**:169-72.
12. Smith D J, Westfall D P, Adams J D. Ketamine interacts with opiate receptors as an agonist. *Anesthesiology* 1980; **53**:S5.
13. Oduntan S A, Gool R Y. Clinical trial of ketamine (CI-581). *Anaesth Soc J* 1970; **17**:411-6.
14. Knox J W D, Bovill J G, Clarke R S J, Dundee J W. Clinical study of induction agents-ketamine. *Br J Anaesth* 1970; **42**:875-85.
15. Heijja P, Galon S. A consideration of ketamine dreams. *Anaesth Soc J* 1975; **22**:100-5.
16. Sadove M S, Shulman M, Hotano S, Fevold N. Analgesic effects of ketamine administered in subdissociative doses. *Anesth Analg* 1971; **50**:452-7.
17. Slogoff S, Allen G W, Wessels J V, Cheney D H. Clinical experience with subanaesthetic ketamine. *Anesth Analg* 1974; **53**:354-8.