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# Epidural ketamine for postoperative analgesia

*Thirty-four patients of ASA physical status I or II scheduled for gall bladder surgery were studied in a comparative prospective trial to evaluate the efficacy of epidural and intramuscular ketamine for postoperative pain relief. They were divided randomly into three groups. Group I (11 patients) received 30 mg intramuscular ketamine. Group II (10 patients) and Group III (13 patients) received 10 and 30 mg ketamine in 10 ml saline respectively, through epidural catheters. Pain was evaluated every two hours for the first 24 hours postoperatively by using a linear analogue pain scale from 0–10. Ketamine was given on the patient's request and whenever the pain score exceeded three. Ketamine produced analgesia in all patients studied. The reduction of pain score after two and four hours in Group I and III was significant when compared to Group II. Seven patients (54 per cent) in Group III did not require further analgesia after the initial injection. However, following 10 mg epidural ketamine or 30 mg IM ketamine, postoperative pain was more frequent. Four patients who received epidural ketamine complained of transient burning pain in the back during injection. No patient developed respiratory depression, psychic disturbance, cardiovascular instability, bladder dysfunction or neurologic deficit. It is concluded that 30 mg epidural ketamine is a safe and effective method for postoperative analgesia.*

**Key words**
ANALGESICS: ketamine; ANAESTHETIC TECHNIQUES: epidural; PAIN: postoperative.

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Following the identification of opiate receptors in the spinal cord,[1] the epidural and intrathecal use of opioids has increased. However, these methods of pain relief are not without side-effects,[2] the most serious of which is delayed respiratory depression.[3]

Ketamine [2-(O-Chlorophenyl)-2-(methylamino) cyclohexanone HCl] is a potent analgesic.[4] Recent studies indicate that analgesia produced by ketamine is mediated by opiate receptors.[5,6] Since ketamine administered systemically is unlikely to produce respiratory depression,[7] it seemed to offer an obvious advantage over the opiates.

The demonstration of the safety of intrathecal ketamine with preservatives in baboons by Brock-Utne *et al.*[8] led Makowitz *et al.*[9] to administer ketamine with preservative into the extradural space to humans suffering from chronic pain, in an uncontrolled study.

This paper reports a prospective randomized study with two different doses of epidural ketamine to determine the analgesic and side effects of this technique while employing intramuscular (IM) ketamine as a control, in patients undergoing gallbladder surgery.

## Methods

Thirty-four patients of ASA physical status I or II undergoing gallbladder surgery with a subcostal incision were studied. Patients with a previous history of hypertension, hyperthyroidism or psychiatric disorders were excluded. This study was approved by the institutional review committee and informed consent was obtained.

Diazepam 10 mg was given orally as premedication to all patients. In the operating room an intravenous (IV) line was established, the electrocardiograph (ECG) was monitored continuously and arterial blood pressure was monitored every five minutes by an electronic oscillotonometer (Dinamap).

A standard anaesthetic was administered to all

patients. This consisted of phenoperidine 2 mg, thiopentone 5 mg·kg$^{-1}$ and succinylcholine 1 mg·kg$^{-1}$ IV. After intubation, anaesthesia was maintained with 70 per cent nitrous oxide in oxygen, halothane 0.5 per cent and pancuronium 0.1 mg·kg$^{-1}$. Ventilation was controlled with a Manley Servovent to maintain normocapnia and end tidal $CO_2$ was monitored by Datex infrared $CO_2$ analyser.

Ketamine with benzethonium chloride as the preservative was used. Patients were randomly allocated to one of three groups. Patients in Group I (control group) received 30 mg ketamine intramuscularly (IM) for postoperative analgesia, whereas patients in Groups II and III received 10 and 30 mg ketamine in 10 ml saline respectively through epidural catheters for postoperative pain relief. The epidural catheters were inserted at the end of the operation using aseptic technique, at the lumbar vertebral level of L1-2 and advanced cephalad for 3–5 cm. Nothing was given through the catheters until the patients were fully recovered from the general anaesthetic and complained of pain.

Pain was evaluated initialy in the recovery room and then every two hours for the first 24 hours postoperatively by using the linear analogue pain scale from 0–10. The scale was explained to every patient preoperatively. "Zero" corresponds to "no pain" and "ten" corresponds to "severe unbearable pain." Ketamine was given on the patient's request and whenever the pain score exceeded three. The onset and the degree of pain relief were recorded. The data were collected by one of the investigators.

Pulse, blood pressure and respiratory rate were recorded before the administration of ketamine. These observations were repeated at 5, 10, 15 and 30 minutes after ketamine administration. Hypertension was considered to be present if the systolic blood pressure increased by more than 15 mmHg above its previous level. Respiratory depression was considered to be present if respiratory rate fell to eight or less per minute. Arterial blood gases were performed before and 30 minutes after ketamine administration in a few patients in each group at the beginning of the trial but were discontinued because no changes in blood gases were observed.

In addition, all patients were observed for nausea, vomiting, disturbed micturition, hallucination and any other side effects.

Changes in sensory and motor functions were looked for and the patient's general condition was observed during the trial.

Within 48 hours of ketamine injection, and before discharge from the hospital, all patients were interviewed and a detailed neurological examination was carried out and the results were recorded.

TABLE I Patient data

| | *Group I Intramuscular ketamine (30 mg) n = 11* | *Group II Epidural ketamine (10 mg) n = 10* | *Group III Epidural ketamine (30 mg) n = 13* |
|---|---|---|---|
| Age (yr) (mean ± SD) | 38.2 ± 10.6 | 37.2 ± 11.2 | 38.6 ± 11.4 |
| Sex (male/female) | 4/7 | 3/7 | 4/9 |
| Body Weight (kg) (mean ± SD) | 67.5 ± 11.8 | 62.8 ± 13.9 | 68.9 ± 6.0 |

## Statistical methods

The Mann-Whitney Test was used to compare the medians of two independent samples. It was utilized to test the difference between the groups with respect to the reduction in pain score after two and four hours, also to test the difference between the median times until the second dose of ketamine was needed and lastly to compare the medians of the number of injections needed in 24 hours. The difference was considered significant when $p < 0.05$.

Fisher's exact test was performed to test the homogeneity between groups in terms of the proportion of patients who needed only one dose of ketamine versus those who received more than one injection during the first 24 hours postoperatively.

## Results

Patients in each of three groups were comparable in age, sex and body weight (Table I). The mean pain score and the total dose of ketamine administered to each patient during 24-hour period are shown in Tables II and III respectively. The time intervals (mean ± S.D.) after the procedure at which the first dose of ketamine was given to the patients were 34.5 ± 7.5, 36.5 ± 11.6 and 36.1 ± 9.8 minutes in Groups I, II and III respectively. Ketamine gave pain relief in all patients. In the first two hours, after the administration of ketamine, Group III had a significantly greater reduction in pain score than

TABLE II Mean pain score (±SD) during first 24 hours following operation

| *Postoperative period* | *Group I IM ketamine (30 mg) Pain score n = 11* | *Group II Epidural ketamine (10 mg) Pain score n = 10* | *Group III Epidural ketamine (30 mg) Pain score n = 13* |
|---|---|---|---|
| Initial pain score | 6.1 ± 0.9 | 5.9 ± 0.9 | 6.1 ± 1.0 |
| 2 hours | 1.8 ± 0.3 | 2.7 ± 1.4 | 1.3 ± 0.4 |
| 4 hours | 2.7 ± 1.1 | 3.3 ± 2.6 | 1.8 ± 1.4 |
| 6 hours | 2.1 ± 0.5 | 3.1 ± 2.5 | 1.7 ± 1.2 |
| 8 hours | 1.8 ± 0.9 | 2.6 ± 1.4 | 1.4 ± 1.3 |
| 10 hours | 1.9 ± 0.8 | 2.4 ± 2.2 | 1.1 ± 1.1 |
| 12 hours | 2.0 ± 0.9 | 1.6 ± 0.8 | 0.7 ± 0.6 |
| 14 hours | 1.7 ± 0.9 | 2.0 ± 1.7 | 0.5 ± 0.8 |
| 16 hours | 1.2 ± 0.9 | 1.9 ± 1.0 | 0.4 ± 0.7 |
| 18 hours | 1.0 ± 0.6 | 2.1 ± 1.9 | 0.3 ± 0.8 |
| 20 hours | 0.8 ± 0.5 | 0.6 ± 0.4 | 0.2 ± 0.4 |
| 22 hours | 0.9 ± 0.6 | 0.9 ± 0.8 | 0.2 ± 0.4 |
| 24 hours | 0.8 ± 0.5 | 0.6 ± 0.4 | 0.2 ± 0.4 |

Group II ($p < 0.001$). The reduction of pain score was also significantly greater in Group I when compared to Group II ($p = 0.025$), but the difference was not significant when compared with Group III.

After four hours, the reduction of pain score was significantly greater in Groups I ($p < 0.01$) and III ($p < 0.01$) each as compared to Group II. Although the reduction of pain score in Group III was greater than Group I after four hours, this difference was not statistically significant ($p < 0.1$).

Regarding the time until a second injection was needed, this was significantly longer in Group III when compared with either Group I ($p = 0.001$) or Group II ($p < 0.001$), and it was longer but not statistically significant in Group I when compared to Group II.

The number of injections needed in 24 hours in Group I was greater than in Group III ($p < 0.005$) but it was less than that of Group II ($p < 0.05$). Furthermore, the number of injections was significantly less in Group III than in Group II ($p < 0.001$).

Fisher's exact test (Table IV) showed that the proportion of patients who needed only one dose of ketamine during the first 24 hours postoperatively was much higher and significant in Group III when compared with either Group I ($p = 0.005$) or Group II ($p = 0.007$), but the difference was not significant between Group I and II.

Four of the patients in Group II and III complained of burning pain during the introduction of the ketamine solution into the epidural space. Patients in Group II and III tended to doze off after the epidural injection but were easily rousable and mentally alert.

No changes in heart rate, blood pressure or

TABLE III Total dose and frequency of administration of ketamine per patient during the first 24 hours postoperatively

| | *Group I (n = 11) IM ketamine (30 mg)* | | | *Group II (n = 10) Epidural ketamine (10 mg)* | | | | |
|---|---|---|---|---|---|---|---|---|
| Number of patients (%) | 2(18.1%) | 6(54.5%) | 3(27.2%) | 1(10%) | 3(30%) | 2(20%) | 3(30%) | 1(10%) |
| Number of injections per patient | 2 | 3 | 4 | 2 | 3 | 4 | 5 | 8 |
| Total dose of ketamine (mg) given in 24 hours per patient | 60 | 90 | 120 | 20 | 30 | 40 | 50 | 80 |

| | *Group III (n = 13) Epidural ketamine (30 mg)* | | | |
|---|---|---|---|---|
| Number of patients (%) | 7(53.8%) | 3(25%) | 1(7.6%) | 2(15.5%) |
| Number of injections per patient | 1 | 2 | 3 | 4 |
| Total dose of ketamine (mg) given in 24 hours per patient | 30 | 60 | 90 | 120 |

TABLE IV Analgesic requirements in the postoperative period

| | *Group I* $n = 11$ | *Group II* $n = 10$ | *Group III* $n = 13$ |
|---|---|---|---|
| Number of patients who received one dose of ketamine only in 24 hour period | 0 | 0 | 7 |
| Number of patients who received more than one dose of ketamine in 24 hour period | 11 | 10 | 6 |

The proportion of patients who needed only one dose of ketamine during 24 hours was highly significant in Group III when compared with either Group I ($p = 0.005$) or Group II ($p = 0.007$), but the difference was not significant between Group I and II (Fisher's exact test).

respiration rate were noted and there was no impairment of sensory or motor function. In no case was ketamine associated with bladder dysfunction, vivid dreams or hallucinations. One patient in Group III vomited in the postoperative period.

Epidural ketamine was not associated with any neurological deficit.

## Discussion

Ketamine, a phencyclidine derivative with marked analgesic properties, probably acts as an agonist on the opiate receptors in the central nervous system.[5,6] Ryder *et al.*[10] further speculated that ketamine might produce analgesia by releasing or potentiating endogenous opioid peptides, whose action is then antagonized by naloxone. *In vitro* studies have shown that ketamine is able to displace radioactively labeled narcotic agonist, etrophine, from the opiate receptors in regional areas of the mouse brain in infant animals.[6]

In recent years intrathecal opioids have been used to provide good pain relief in clinical practice, but this method is still subject to certain drawbacks,[2] the most serious of which appears to be delayed respiratory depression.[2,3]

Ketamine produces potent analgesia[4] without respiratory depression[7] and would therefore seem to be a suitable drug for pain relief. Brock-Utne *et al.*[8] demonstrated that the administration of ketamine with preservative intrathecally into baboons was not associated with any evidence of macroscopic or microscopic abnormalities in the spinal cord. Mankowitz *et al.*[9] studied the effects of epidural ketamine in seven patients with chronic pain.

Gallbladder surgery is associated with severe postoperative pain[11] and in the present study ketamine produced analgesia in all patients studied, whether administered by IM or epidural route. However, there were considerable differences in the duration of analgesia between these three groups. Group III had by far the longest duration, 54 per cent of the patients in this group were completely pain-free after a single injection of 30 mg ketamine (Table IV). The reduction of pain score after two and four hours in Group I and III was significant when compared to Group II and this was probably due to the lower dose used in the latter group. The time until the second dose was given in Group III was significantly longer when compared with either Group I or II. Furthermore, the number of injections given in 24 hours in Group III was significantly less than that given to patients in Group I or II.

The duration of analgesia following repeated doses of ketamine was variable as demonstrated by the wide range of doses used (Table III). In some patients the duration of analgesia bore little relation to the dose given. This variability in response was more marked in patients in Group II and this observation has been reported by Mankowitz *et al.*[9] although they used a smaller dose. They administered 4 mg ketamine in 10 ml five per cent dextrose epidurally to seven patients suffering from chronic pain and noted that the duration of analgesia varied from 30 minutes to more than six hours. This variability may be related to ketamine-receptor affinity or the development of tachyphylaxis due to the acidity of the solution used, similar to that observed after repeated administration of local anaesthetics through the epidural space.[12] For instance, ketamine has a pH of 3.5–5.5, molecular weight of 238 and a pKa of 7.5, while lidocaine has a molecular weight of 234, a pKa of 7.7. The pH of solutions containing adrenaline is 4.2.

Because of the lack of blinding in this study, an unknown placebo effect may exist. A double blind trial, when neither the patient nor the observer is aware of the route and dose of ketamine given will reduce bias to minimum. However, the data (pain scores) was collected by a single observer in order to avoid variations in the assessment.

The psychic disturbances following ketamine

anaesthesia vary in incidence from less than five per cent[13] to greater than 30 per cent.[14] In this study no patient had any psychic disturbance or vivid dreams.

The analgesic doses of ketamine used given by different routes were not associated with any changes in cardiovascular parameters in this study. In constrast, general anaesthesia with ketamine produces a dose-related rise in the heart rate–systolic pressure product (often in excess of 100 per cent) with a transient rise in cardiac index but without altering the stroke index[15] through a central adrenergic stimulation.[16] However, this effect was not observed with low-dose infusions used for analgesia (approximately 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$).[17]

In this study, ketamine analgesia was not associated with any respiratory depression. Soliman *et al.*[18] demonstrated that ketamine did not produce any significant respiratory depression and the respiratory response to $CO_2$ challenge was maintained during ketamine anaesthesia. In contrast, respiratory depression after epidural narcotics has been described by many authors.[2,3] In addition, disturbances of micturition and pruritus have been frequently reported with epidural opioids,[2,19] but these side effects were not encountered in this study.

Although Mankowitz *et al.*[9] did not report any pain on injection in their patients, we had four patients in Group II and III who complained of transient burning pain in the back during injection of ketamine into the epidural space. Pain was not severe enough to withhold injection.

We found that epidural ketamine was not associated with motor block and active mobilization was possible earlier and this is in accordance with reports by Mankowitz *et al.*[9] No patient developed any neurologic deficit after epidural ketamine, and this was expected after the safety of epidural ketamine has been established.[8,9]

Our study demonstrated that administration of 30 mg ketamine epidurally was a better method for pain relief compared to the other methods employed in this study. The stability of the cardiovascular system and absence of respiratory depression, motor block and any other significant side effects provided a safe technique for postoperative analgesia. Epidural ketamine may be considered as an alternative to epidural opioids. However, because of the variability in the duration of analgesia produced by epidural ketamine in some patients, the use of this technique for postoperative pain relief will require further controlled clinical trials.

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## Résumé

*Trente-quatre patients classe ASA I et II devant subir une cholécystectomie ont été étudiés d'une façon comparative et prospective afin d'évaluer l'action de la kétamine par voie épidurale ou intra-musculaire pour le soulagement de la douleur dans la période post-opératoire. Les patients ont été divisés au hasard en trois groupes, le groupe I (11 patients) ont reçu 30 mg de kétamine intra-musculaire, le groupe II (10 patients) et le groupe III (13 patients) ont reçu 10 et 30 mg de kétamine dans 10 ml de saline respectivement en injection épidurale. La douleur post-opératoire a été évaluée chaque deux heures pour les premiers 24 heures utilisant une échelle linéaire de douleur de 0 à 10. La kétamine était administrée à la demande du patient et quand le degré de la douleur dans l'échelle a dépassé trois. La kétamine a produit l'analgésie chez tous les patients étudiés. La diminution de la douleur après deux et quatre heures pour le group I et III était significative quant elle est comparée au groupe II. Sept patients (54 pour cent) dans le groupe III n'ont pas requis d'autres analgésiques. Cependant après 10 mg de kétamine en injection épidurale ou 30 mg en injection intra-musculaire la douleur post-opératoire était plus fréquente. Quatre des patients ayant reçu la kétamine épidurale se sont plaint d'une douleur transitoire dans le dos lors de l'injection. Aucun patient a démontré une dépression respiratoire, des perturbations psychologiques, une instabilité cardiovasculaire, une dysfonction de la vessie ou des problèmes neurologiques. On conclut que 30 mg de kétamine en injection épidurale représente une méthode sécuritaire et efficace pour l'analgésie post-opératoire.*