Reports of Investigation

Epidural ketamine reduces post-operative epidural PCA consumption of fentanyl/bupivacaine

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Purpose: To study the analgesic effect of epidural ketamine on postoperative pain and epidural PCA consumption after total abdominal hysterectomy.

Methods: Sixty-one ASA I-II patients, 34–60 yr were randomly assigned into three groups. Epidural catheters were inserted before induction of anaesthesia. Patients in group I and II received 30 mg ketamine epidurally before induction of anaesthesia or 20 min after skin incision: group III received placebo. Postoperatively, on first analgesia request, sedation score, Visual Analogue Scale (VAS), Prince Henry Score (PHS) and Bromage motor weakness score were taken and followed by an epidural bolus of 9 ml bupivacaine 0.25% + 50 μg fentanyl. Analgesia was maintained by PCA with a mixture of bupivacaine 0.1% + fentanyl 0.001% epidurally. Measurements were repeated at 1, 2, 4, 8, 12 and 24 hr.

Results: First analgesia request was 17 ± 6.8 min in the control group compared with 31.4 ± 23.8 and 44 ± 23.1 min for groups I and II respectively. The differences between group III and group I ($P < 0.05$) and between group III and group II ($P < 0.01$) were statistically significant. Twenty four hour PCA consumption was 101.2 ± 47.2, 87 ± 27 and 162 ± 38 ml for groups I, II and III respectively. The differences between group III and group I and that between group III and group II were statistically significant ($P < 0.001$).

Conclusion: Epidural ketamine 30 mg reduces post hysterectomy pain as evidenced by prolongation of time to first analgesia request and reduction in postoperative epidural PCA consumption. This effect is manifest whether ketamine is given before induction or 20 min after skin incision.

Objectif : Étudier l'effet analgésique de l'administration péridurale de kétamine sur la douleur post-opératoire et la consommation d'analgésique par ACP péridurale après hystérectomie abdominale totale.

Méthodes : 61 patientes, ASA I et II, âgées de 34 à 60 ans ont été attribuées au hasard à trois groupes. Les cathéters périduraux ont été installés avant l'induction de l'anesthésie. Les patientes des groupes I et II ont reçu 30 mg de kétamine par voie péridurale avant l'induction ou 20 minutes après l'incision cutanée, alors que le groupe III recevait un placebo. Après l'opération, lors de la première demande d'analgésie, on a enregistré le score de sédation, l'échelle visuelle analogue (EVA), le score Prince Henry (PHS) et le score de faiblesse motrice de Bromage pour ensuite administrer un bolus péridural de 9 ml de bupivacaïne 0,25% + 50 mcg de fentanyl. L'analgésie a été maintenue par ACP péridurale avec une solution de bupivacaïne 0,1% + fentanyl 0,001%. Les mesures ont été répétées à 1, 2, 4, 8, 12 et 24 heures.

Résultats : La première demande d'analgésie est survenue à 17 ± 6,8 min dans le groupe contrôle et à 31,4 ± 23,8 min et 44 ± 23,1 min pour les groupes I et II respectivement. Les différences entre le groupe III et le groupe I ($P < 0,05$) et entre le groupe III et le groupe II ($P < 0,01$) sont statistiquement significatives. La consommation de 24 heures de solution analgésique épidurale a été de 101,2 ± 47,2, 87 ± 27 et 162 ± 38 ml pour les groupes I, II et III respectivement. Les différences entre le groupe III et les groupes I et II étaient statistiquement significatives ($P < 0,001$).

Conclusion : La kétamine 30 mg administrée par voie péridurale réduit la douleur post hystérectomie tel que démontré par une prolongation de la période précédant la première demande d'analgésie et par la réduciton de l'utilisation de l'ACP péridurale. Cet effet existe, que la kétamine soit donnée avant l'induction ou 20 minutes après l'incision cutanée.

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RECENT clinical and experimental evidence suggests that trauma or surgical stimuli provoke sustained changes in the function of the central nervous system that outlasts the original stimulus and markedly affects CNS subsequent response to pain.[1–3] The induction of central sensitisation involves the activation of NMDA (N-Methyl D-Aspartic acid) receptors in the spinal cord.[4] These receptors seem to be receptors of pain memory and for optimum pain relief, it is necessary to prevent any change occurring at the NMDA receptor complex.[4] The rationale behind the different strategies for preemptive analgesia has been to prevent the central sensitising effects of the surgical procedure by reducing the signal traffic in the nociceptive primary afferents and central nociceptive pathways. On the other hand, blockade of NMDA receptors may inhibit the sensitisation process itself. Ketamine has been shown to block non-competitively the NMDA receptors by binding to the PCP recognition site in the NMDA receptor channel.[5] As pointed out in a recent editorial,[6] a correct definition of preemptive analgesia should emphasise the importance of treatment that prevents the development of central hyperexcitability, *even if it occurs after surgery*. The emphasis should not be on the timing of treatment initiation but on the pathophysiological phenomenon it should prevent: central hyperexcitability. Intravenous ketamine has been shown to have a preemptive effect in decreasing postoperative pain and wound hyperalgesia following total abdominal hysterectomy (TAH).[7]

This study compares in a prospective, randomised, double blinded, placebo controlled design the preemptive effect of epidural ketamine given either before induction of general anaesthesia or 20 min after skin incision with that of placebo on postoperative pain scores and epidural PCA consumption of fentanyl/bupivacaine mixture in patients undergoing TAH.

Patients and methods

Following departmental research committee approval and informed patient consent, 63 ASA I or II patients between the ages of 34 and 60 yr, undergoing elective total abdominal hysterectomy (TAH), through a transverse lower abdominal incision were randomly assigned to one of three equal treatment groups using a table of random numbers. One patient in group II was excluded from the study because of a dural puncture. Another patient in group III was excluded because of technical difficulty localising the epidural space. All personnel taking care of the patients were unaware of the group assignment. Exclusion criteria included narcotic abuse, prolonged sedative or opioid drug use or presence of any neurological or psychological disease. All patients were visited the day before surgery and introduced to the Visual Analogue Scale (VAS) and Prince Henry Score (PHS) of pain and instructed in the use of Patient Controlled Analgesia (PCA) pump. All patients were premedicated with 10 mg diazepam *po* one and half hours before surgery. In the operating room an *iv* line was started and ECG, automatic NIBP, and SpO_2 were continuously monitored using Cardiocap II (Datex). A T_{12}-L_1 epidural catheter G16 was inserted under local infiltration anaesthesia using loss of resistance technique. Then, all patients received the first dose of the test drug epidurally, which was 30 mg ketamine in 10 ml 0.9 N saline for group I or 10 ml 0.9 N saline for groups II and III. The drug was administered by an anaesthetist, unaware of its nature, but immediate access to that information was available in case of emergency. Immediately after the epidural injection, anaesthesia was induced with 7 $mg \cdot kg^{-1}$ thiopentone muscle relaxation was produced with 0.5 $mg \cdot kg^{-1}$ atracurium *iv*. Mask ventilation was continued with O_2/N_2O 50/50 + 2% isoflurane until full paralysis, which was followed by direct laryngoscopy and orotracheal intubation. Anaesthesia was maintained with O_2/N_2O 30/70% + 1–2% isoflurane. Ventilation was controlled to maintain end tidal CO_2 30–35 mmHg.

Twenty minutes after skin incision, a second dose of the test drug was given epidurally. The test dose was 10 ml 0.9 N saline for groups I and III and 30 mg ketamine diluted in 10 ml 0.9 N saline for group II. The second dose was given by the same anaesthetist. If patients were judged to have inadequate analgesia (↑ HR > 30% or ↑ in MABP > 20% of preinduction values), 7 $\mu g \cdot kg^{-1}$ alfentanil *iv* were given and repeated as required.

At the end of surgery anaesthesia was discontinued, the trachea was extubated and patients were transferred to the recovery room. Post operative pain management started in the recovery room. When patients first requested analgesia, assessment of sedation, visual analogue, Prince Henry and Bromage scores were done (see appendix).

These assessments were repeated every 15 min until the patient was discharged to the ward where these were repeated at 1, 2, 4, 8, 12 and 24 hr. After this initial assessment all patients were given an epidural bolus of 9 ml bupivacaine 0.25% + fentanyl 50 µg and the epidural catheter was connected to a PCA (Patient Controlled Analgesia) pump (Graseby 3300 PCA pump). Each ml of PCA solution contained 1 mg bupivacaine + 1 µg fentanyl. The pump was programmed to give: PCA bolus = 5 ml; Lockout interval = 10 min; Maximum in four hours = 60 ml; Continuous infusion rate 0.00 $ml \cdot hr^{-1}$.

Vital signs were recorded before giving the epidural bolus and every 15 min until the patient was discharged to the ward. Pain assessment, cumulative PCA volume

consumed and vital signs were recorded 1, 2, 4, 8, 12 and 24 hr post operatively by a member of the anaesthesia team who was unaware of the patient group assignment. Side effects (nausea, vomiting, pruritus, hypotension, excessive sedation or inadequate pain relief) were recorded. Inadequate pain relief was managed by a physician override bolus of 5 ml and repeated every 10 min until pain was relieved.

Statistical analysis

Continuous data are presented as mean ± standard deviation (SD). Discrete data are presented as median and range. ANOVA with post Hoc multiple comparisons using Student-Newman-Keuls test were used for continuous data (e.g., PCA volume, VAS, weight and blood pressure). Kruskal Wallis test was used for discrete data (e.g., sedation score, PHS and Bromage score). A P value of < 0.05 was considered statistically significant. Statistical Package for Social Sciences for Windows (SPSSWIN) was used for data analysis.

Results

The three treatment groups were matched for age, weight, duration of surgery and preoperative values of heart rate, blood pressure and alfentanil requirements (Table I).

Postoperatively patients in group III (placebo) requested pain relief after 17 ± 6.8 min compared with 31.4 ± 23.8 and 44 ± 23.1 min for groups I and II respectively (mean ± SD). The differences between group III and either group I ($P < 0.05$) or group II (0.01) were statistically significant (Table I). At the time of first request of postoperative analgesia, patients in the three groups had similar sedation scores (Table I).

At this time, Prince Henry (PHS) and Visual Analogue (VAS) pain scores were high for the three groups (Table II, Figure 1). Following the injection of the epidural bolus dose and the start of the PCA pump, both VAS and PHS pain scores were lower than control values and continued to be so for the whole study period (Table II, Figure 1). Some degree of motor weakness

TABLE I Patient demographic data and clinical variables

	Group I (Ketamine before induction) (n = 21)	*Group II (Ketamine 20 min. post-incision) (n = 20)*	*Group III (placebo) (n = 20)*
Age (yr.)	46.9 ± 6.4	41.7 ± 6.6	47.6 ± 6.0
Weight (kg)	70.4 ± 11.6	74.9 ± 13.3	68.5 ± 10.5
Duration of surgery (min)	124.0 ± 34.7	114.5 ± 32.4	132.5 ± 36.0
Range (min)	75–195	80–195	85–195
Alfentanil requirements (μg)	511.9 ± 390.4	250.0 ± 344.1	400.0 ± 383.9
Range (μg)	0–1000	0–1000	0–1000
Time to first request of analgesia (min)*	31.4 ± 23.8	44.0 ± 23.1	17.0 ± 6.8
Preoperative heart rate (beats/min)	96.6 ± 11.9	87.6 ± 21.7	90.4 ± 15.9
Preoperative systolic blood pressure (mmHg)	126.5 ± 20.7	130.2 ± 21.5	137.0 ± 15.1
Preoperative diastolic blood pressure (mmHg)	82.7 ± 13.1	82.2 ± 14.7	83.7 ± 11.5
Sedation score at time of first request of analgesia†	1	0	0
Range	0–1	0–1	0–1

Data are mean ± SD

*GP III vs GP I ($P < 0.05$), GP III *vs* GP II ($P < 0.01$).

†Values are median

TABLE II Changes in the Prince Henry Score (PHS) in the three groups during the study period

Time (hr)	*Group I (ketamine before induction)*		*Group II (ketamine 20 min. post-incision)*		*Group III (placebo)*	
	Median	*Range*	*Median*	*Range*	*Median*	*Range*
0	4	3–4	4	3–4	4	3–4
1	0	0–2	0	0–2	0	0–2
2	0	0–1	0	0–1	0	0–1
4	1	0–1	0	0–1	0	0–1
8	1	0–2	1	0–2	1	0–2
12	1	0–2	1	0–2	1	0–2
24	0	0–1	0	0–1	0	0–1

P = NS.

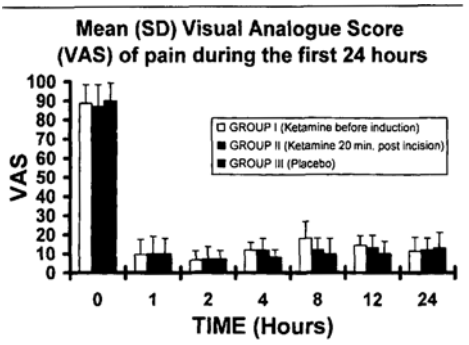

FIGURE 1 Postoperative mean ± SD VAS of pain for the three groups during the first 24 hr. There were no differences among the three groups. Time 0 = time of first request for postoperative analgesia.

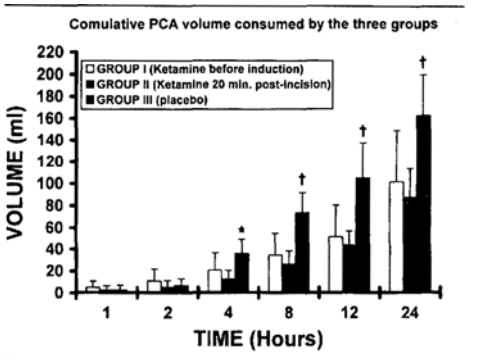

FIGURE 2 Mean ±SD comulative PCA volume consumed by the three groups during the first 24 hr postoperatively. The PCA volume consumed by patients in group III was higher than that consumed by patients in groups I and II. The difference was significant starting from the fourth hour onwards.
*$P < 0.05$, †$P < 0.001$.

was noted following the injection of the epidural bolus dose that resolved spontaneously in one to two hours (Table III).

Patients who had received epidural ketamine, whether before induction of GA or 20 min after skin incision (groups I and II) consumed less epidural PCA than did those in the placebo group (group III) (Figure 2). This difference was statistically significant from the fourth postoperative hour ($P < 0.05$) until the end of the study (Figure 2).

There were no differences among the three groups with regard to the incidence of side effects (Table IV).

Discussion

An important goal of modern anaesthesia is to ensure that patients having surgery awake from anaesthesia with good pain control and that this control is maintained well into the postoperative period. A good strategy to achieve this goal is to prevent rather than treat severe postoperative pain.

In this study we demonstrated, in a randomised placebo controlled double blinded design, that epidural injection of 30 mg ketamine reduces postoperative pain as evidenced by a prolongation of the time to first request for pain relief and a reduction in postoperative analgesic requirements during the first 24 hr after surgery and that this effect is manifest whether ketamine is given before induction of general anaesthesia or 20 min after skin incision. Our data support the previously reported data describing the use of epidural ketamine for control of postoperative pain in adults[8,9] and children.[10]

Preemptive analgesia has been the subject of several recent editorials and review articles.[1,6,8,11–14] As pointed out in a recent editorial,[6] a correct definition of preemptive analgesia should emphasise the importance of treatment that prevents the development of central hyperexcitability, *even if it occurs after surgery.* The emphasis should not be on the timing of treatment ini-

TABLE III Changes in the Bromage motor weakness Score (BS) during the study period.

Time (hr)	*Group I (ketamine before induction)*		*Group II (ketamine 20 min. post-incision)*		*Group III (placebo)*	
	Median	*Range*	*Median*	*Range*	*Median*	*Range*
0	0	0–0	0	0–0	0	0–0
1	1	0–2	1	0–2	0	0–2
2	0	0–1	0	0–1	0	0–1
4	0	0–1	0	0–1	0	0–1
8	0	0–1	0	0–1	0	0–1
12	0	0–1	0	0–1	0	0–1
24	0	0–1	0	0–1	0	0–1

P = NS.

TABLE IV Incidence of complications in the three groups

	Group I (ketamine before induction) n = 21	*Group II (ketamine 20 min. post-incision) n = 20*	*Group III (placebo) n = 20*
Nausea	9	8	11
Vomiting	0	1	0
Itching	2	2	3
Hypotension	0	0	0
Excessive sedation	0	0	0
Bad dreams or hallucinations	0	1	1

P = NS.

tiation but on the pathophysiologic phenomenon it should prevent: central hyperexcitability. A preemptive analgesic effect is manifested when analgesia extends beyond the expected duration of the administered drug.

In the clinical practice of preemptive analgesia, there are different approaches to inhibit nociceptive stimuli induced changes both peripherally and centrally.

Ketamine as an analgesic has gained major attention during the last few years because it is the most potent blocker of NMDA receptors available for clinical use. The NMDA receptors are regarded as receptors of pain memory that maintain neuroplasticity and hyperalgesia after the initial painful (surgical) stimulus has ended.[4] This has been proved by both electrophysiological[15] and behavioural[16] studies. It should be noted that many of these studies were carried out in intact animals under general anaesthesia. From these findings, It was suggested that NMDA mediated events, including central sensitisation to pain occur in humans in the presence of general anaesthesia.[5] Accordingly, blockade of NMDA receptors might preemptively inhibit central sensitisation to pain caused by surgically induced tissue trauma and inflammation.

Recent clinical controlled studies have addressed the role of ketamine in preemptive analgesia. A single dose of 0.15 mg·kg^{-1} ketamine *iv*, five minutes before skin incision reduced post cholecystectomy pain and morphine consumption.[17] Others reported that the use of a higher dose of 2 mg·kg^{-1} ketamine *iv* as bolus and infusion for both induction and maintenance of anaesthesia reduced post abdominal hysterectomy wound hyperalgesia without reducing the intensity of spontaneous or movement associated pain.[7] However, they did not discuss the incidence of ketamine side effects e.g., psychotomimetic effects.

We chose the epidural route for the administration of ketamine because of its safety[17,18] and efficacy.[8–10,19,20] Using the epidural route would give the highest concentration of ketamine at the affected spinal segments with the minimum systemic effects. Also, the elimination half life of epidural ketamine is longer than that following *iv* administration[20] and its CSF concentration is double that in plasma.[20]

As pointed out in a recent editorial,[6] it is difficult to demonstrate the isolated preemptive effect of one drug or of one method of antinociceptive treatment. We used the same doses of induction agents, nitrous oxide and isoflurane for all patients. These drugs might have contributed to the preemptive effect noted, but still the contribution is uniform for all patients. However, a synergistic or additive effect of these drugs with ketamine cannot be excluded in our patients.

We noted that patients who did not have epidural ketamine (group III), made their first request for postoperative analgesia 17 ± 6.8 min after arrival in the recovery room compared with 31.4 ± 23.8 and 44 ± 23.1 min for groups I (Ketamine before induction) and II (Ketamine 20 min after incision) respectively. The differences between group III and either groups I or II were statistically significant. Patients who received ketamine 20 min after skin incision, were the group with the longest time to first request for post operative analgesia. This may be explained by the duration of action of epidural ketamine. Other investigators[7,21] have reported a similar increase in the time to first request for postoperative analgesia following *iv* ketamine.

During the first four hours postoperatively, there were no differences among the three groups with regard to their pain scores or PCA consumption. This can be explained by the duration of action of the first postoperative epidural bolus (9 ml bupivacaine 0.25% + 50 µg fentanyl) which was given to all patients upon first request of analgesia. We gave this bolus to establish a sensory level of block sufficient to suppress postoperative pain during the initial hours of the postoperative period, thus allowing the patients to recover from the effects of general anaesthesia and become more able to make conscious decisions regarding the use of their PCA pumps. Effective pain relief in the immediate post-

operative period also limits the initiation of central sensitisation to the operative period. Following this bolus most patients had excellent pain relief demonstrated by a reduction in pain scores. Few patients triggered the PCA pump during the first four postoperative hours.

Patients who received epidural ketamine (groups I and II) consumed smaller volumes of PCA analgesic solution than those in the control group III, from the fourth hour postoperatively until the end of the 24 hr study, outlasting the expected duration of action of epidural ketamine, thus demonstrating a preemptive epidural effect.

We could not demonstrate any differences in pain scores or PCA analgesic consumption between patients who had ketamine before induction of general anaesthesia and those who had ketamine 20 min after skin incision. This might be explained partially by the mechanism of action of ketamine on the NMDA receptor complex, as an open channel blocker (use dependent), thus, inhibiting central neuroplasticity which requires some time to develop.[5] Normally, NMDA receptors are blocked by Mg^{++}. Following surgical trauma, afferent nociceptive barrage depolarises the channel and Mg^{+} leaves the receptor (the channel opens), that is the time when either agonists or antagonists (e.g., ketamine) of NMDA receptors can act. This supports the experimental finding that NMDA antagonists, in addition to preventing the induction of a state of central sensitisation, may also reduce sensitisation once it is established.[4] Our power calculations indicated that a larger study (116 patients in each group) was required to demonstrate a statistically significant difference in PCA analgesic consumption (30% reduction) between group I (ketamine before induction) and group II (ketamine 20 min. post-incision). These calculations also indicated that this study was able to detect a 30% reduction in the PCA requirements in either group I (ketamine before induction) or group II (ketamine 20 min. post-incision) as compared with the placebo group with a power higher than 95% ($\alpha < 0.05$ and $ß < 0.05$).

Our epidural PCA protocol was highly effective in controlling postoperative pain: no patient asked for additional analgesia. From the literature we found good support to our protocol of epidural ketamine and a mixture of low doses of local anaesthetic and opioid. The nociceptive responses of dorsal horn neurons to repeated C fibre stimulation were synergistically inhibited by the co-administration of low doses of ketamine with morphine.[22,28] Clinically, it was found that co-administration of epidural ketamine and morphine significantly enhanced postoperative pain relief after orthopaedic surgery.[23] On the other hand, it was postulated that the combined blockade of substance P and NMDA receptors might be effective in blocking nociceptive transmission in the spinal cord.[5,7] It has been reported that local anaesthetics inhibit the binding of substance P to its receptors as well as inhibiting substance P evoked increase of intracellular Ca^{+24}. This report further supports the use of a low concentration of a local anaesthetic as one component of an epidural analgesic mixture for postoperative pain. A recent study reported improved analgesia and an opioid sparing effect in patients treated with a combination of epidural bupivacaine and fentanyl following thoracotomy.[25]

The incidence of side effects was equally distributed among the three groups. Our patients did not suffer any increase in psychotomimetic effects typical of ketamine anaesthesia. This may be attributed to the low dose of ketamine used, the method of administration and benzodiazepine premedication.

We conclude that 30 mg epidural ketamine has a preemptive effect in reducing post abdominal hysterectomy pain and analgesic consumption and that this effect is manifest whether the injection was made before induction of general anaesthesia or 20 min after skin incision. There was no increased incidence of side effects attributed to ketamine.

Appendix

1. Sedation Score:
   (0) Awake (1) Drowsy
   (2) Asleep responds verbally (3) Asleep responds to tactile stimuli
   (4) Not responding.

2. Visual Analogue Score (VAS) of pain:
   The patients were asked to estimate their pain on vertical VAS 0–100 mm where 0 is marked no pain and 100 is marked the worst pain ever felt.

3. Prince Henry pain score(PHS):[26]
   (4) Patient has severe pain at rest.
   (3) Patient has slight pain at rest.
   (2) Patient has no pain at rest, but has pain upon taking a deep breath.
   (1) Patient has neither pain at rest nor upon taking a deep breath, but he has pain upon coughing.
   (0) Patient has no pain at rest, upon taking a deep breath or upon coughing.

4. A modified Bromage score: assesses the extent of motor weakness by examining movements of the hip, knee and ankle joints
   (0) All OK
   (1) Feet and knee OK
   (2) Feet OK
   (3) Paralysed.

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