The safety, benefits and effectiveness of different intravenous subanesthetic doses of ketamine when combined with small dose of midazolam before combined spinal epidural technique for Orthopedic Lower Extremity Surgery

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Abstract

In a double blind, randomized, and controlled study of 100 patients (aged 20-60 years), we compared the effect of intravenous (IV) coadministration of different small doses of ketamine (0.00, 0.15, 0.30, and 0.45 mg/kg) with midazolam 0.03 mg/kg in alleviating patient anxiety and pain during establishment of combined spinal epidural (CSE) technique. Patients received midazolam 0.03 mg/kg with placebo (Group C, n= 25) or ketamine 0.15 mg/kg IV (Group K1, n= 25), 0.30 mg/kg IV (Group K2, n= 25) or 0.45 mg/kg IV (Group K3, n= 25), 5 minutes before local analgesic infiltration at the site of SCE and 10 minutes before performing CSE. Scores for sedation, patient's behavior to CSE puncture, and ease of CSE establishment, the mean arterial blood pressure (MBP), heart rate (HR) and arterial oxygen saturation (SpO2) were recorded; the need for ephedrine, atropine and supplemental O2 inhalation was recorded. The incidence of adverse effects especially of unpleasant emergence reactions were recorded. Lastly, the quality of the CSE technique was assessed by the patient and a blind observer.

Patients in Group K2 who received midazolam 0.03 mg/kg with ketamine 0.3 mg/kg IV showed ideal scores for sedation, behavior to CSE puncture, and ease of placement of CSE, and best hemodynamic compensation for the inhibitory cardiovascular effects of spinal anesthesia and also for maintenance of normal SpO2. In addition group K2 showed the best quality of anesthesia when assisted by the patient and the blind observer, without significant unpleasant emergence reactions. We conclude that addition of ketamine 0.3 mg/kg to midazolam 0.03 mg was safe, useful, and effective in alleviating patient's anxiety and pain during placement of CSE.

Introduction

As a primary anesthetic, neuroaxial blocks have proved most useful for lower extremity surgery.\(^{(1)}\)

Anxiety and pain during performing lumbar puncture are two problems experienced during neuroaxial blockade. Also neuroaxial blocks typically produce variable degrees of cardiovascular system depression. To ensure patient comfort and safety during neuroaxial blockade, the sedation and analgesia should be provided before lumbar puncture with a suitable agents.\(^{(2)}\)

In sharp contrast with other anesthetic agents, ketamine is a potent analgesic at subanesthetic plasma concentration and has cardiovascular stimulatory effects with minimal effects on respiration.\(^{(3,4)}\)

Subanesthetic doses of ketamine supplemental with small doses of midazolam was found to be satisfactory for sedation and pain relief without evident hemodynamic or respiratory depression or psychotomimetic side effects.\(^{(2,5)}\)

The aim of the present study was to investigate the safety, benefits and effectiveness of different subanesthetic doses of ketamine supplemented with midazolam before performing neuroaxial blocks.

Methods

The study was done in the Main University Hospital of Menofiya and it was approved by local ethics committee and informed consent was obtained from 100 patients undergoing elective surgeries where combined spinal epidural anesthesia was indicated. Criteria for entry into this study were ASA physical status I or II, age 20-60 yr.; the exclusion criteria included known allergy, or contraindications for spinal anesthesia (e.g. coagulation defects, infection at the puncture site, or preexisting neurological deficits in the lower extremities).
This study was conducted in a randomized, controlled, and double blinded fashion. All drug solutions were prepared by an anesthetist who was not involved in the administration of anesthesia or in the observation of the patients; thus both the observer and the patients were blinded to the patient group assignment. The patients were randomly divided into four equal groups C, K₁, K₂, and K₃, each 25 patients.

On arrival in the operating room, an intravenous line was secured with an 18 G cannula, I.V. Ringer lactate solution 10 ml/kg were started and patients were monitored with ECG, non invasive automatic blood pressure and pulse oximetry. After a baseline measurement of mean arterial blood pressure (MBP), heart rate (HR) and arterial oxygen saturation (SpO₂), and a baseline level of sedation was determined using four-point patient sedation score (1= Awake and alert, 2= Awake and drowsy, 3= Asleep but arousable by verbal contact, 4= Asleep and not arousable by verbal contact). All patients in the four groups received I.V. midazolam 0.03 mg/kg in addition to placebo in group C, ketamine 0.15 mg/kg in group K₁, ketamine 0.30 mg/kg in group K₂, and ketamine 0.45 mg/kg in group K₃. After 5 minutes local analgesia using 3 ml of xylocaine 2% was infiltrated at the CSE placement site, then 5 minutes later CSE institution was done preferably in the sitting position while the patient was supported by two assistants and under continuous monitoring, because the midline anatomy is often easier to palpate than when the patient is in the lateral position. But was done in the lateral decubitus position for patients with hip or leg fracture who cannot tolerate sitting up due to pain.

An epidural catheter was placed at L₂-₃ interspace for postoperative analgesia, and spinal anesthesia was instituted with an intrathecal injection of a suitable doses of heavy marcain 0.5% according to the level of anesthesia needed. Intravenous fluids were continued for maintenance and replacement of fluid losses.

Incremental doses of ephedrine (10 mg IV) were administered when MBP was <80% of baseline level, and incremental doses of atropine (0.5 mg IV) were administered when HR was <50 beats/minute. Supplemental oxygen was given when SpO₂ was <95%. Apnea was defined that absence of respiratory movement was >15 sec.

At the time of institution of CSE the observer recorded the score for sedation, the score for patient's behaviour (Combative= 1, Anxious= 2, Calm= 3 and Sleeping= 4), and the score for ease of institution (Patient fight without success= 1, Patient fight with success= 2, Minor resistance= 3, No reaction= 4).

The MBP, HR, SpO₂ and level of sedation was recorded every 10 minutes for 30 minutes from administration of intrathecal anesthesia.

Lastly the patient and the observer were asked to grade satisfaction with the whole anesthetic experience in a 5 point score where [1= not satisfied at all and asking to avoid repeating that procedure in a further similar operation and 5=maximum satisfaction and asking to repeat the same procedure in a further similar operations].

The number of cases received ephedrine, atropine and supplemental O₂ inhalation in each group in the 1st 30 minutes was recorded.

The adverse effects in each group such as unpleasant emergence reactions (hallucination), airway obstruction apnea, nausea and vomiting, and excessive sedations were recorded.

Statistics: Data were analyzed using the Statview Statistical Package. Discrete variables were analyzed using an unpaired t-test or non-parametric tests. Categorical variables were analyzed using the Chi square or Fisher's exact test, as appropriate. In all cases a F value of <0.05 was considered significant.

Results
All groups were similar in age, sex, weight and height (Table 1).
On arrival in the operating room the means " SD of the MBP and the HR in the four groups were not significantly different (Figure 1). After premedication there was significant increase of MBP in groups K₁, K₂ and K₃ than in group C (100" 16, 105" 17 and 108" 15 versus 83" 15 mmHg respectively) and also increase of HR in groups K₁, K₂ and K₃ than group C (78" 10, 79" 9 and 83" 11 versus 70" 8 beat/min respectively) (Figure 1).

Ten minutes after CSE induction, the MBP was significantly higher in groups K₁, K₂ and K₃ than group C (96" 15, 98" 17 and 100" 17 versus 76" 13 mmHg) respectively and also the HR in groups K₁, K₂ and K₃ than group C (75" 9, 77" 8 and 80" 9 versus 65" 7 beat/min respectively) (Figure 1).

Twenty minutes after CSE induction the MBP was significantly higher in groups K₁, K₂ and K₃ than group C (93" 12, 94" 14 and 95" 15 versus 82" 12 mmHg) respectively. But there was no significant difference between the four groups as regard the heart rate (73" 8, 72" 8, 75" 9 and 74" 10 beats/min in groups C, K₁, K₂ and K₃) respectively (Figure 1).

Thirty minutes after CSE induction the MBP was not significantly different in the four groups (C, K₁, K₂ and K₃ was 86" 13, 87" 15, 90" 14 and 89" 15 mmHg) respectively, and also the HR in the four groups (C, K₁, K₂ and K₃ was 70" 10, 72" 9, 70" 8 and 74" 8 beat/min) respectively (Figure 1).

As regard the MBP and the Heart rate changes in the same group the MBP and HR decreased significantly after premedication in the control group (C) but increased significantly in the other three ketamine groups (K₁, K₂ and K₃) (Figure 1).

Ten minutes after CSE induction there was further significant decrease in MBP and HR in C group, on the other hand the MBP and HR was maintained in groups (K₁, K₂ and K₃). Twenty minutes after CSE induction the MBP was still significantly lower than the baseline in C group but significantly higher in K₁, K₂ and K₃ groups. The heart rate in the four groups C, K₁, K₂ and K₃ was not significantly different from the base-line value. Thirty minutes after CSE induction the MBP and Heart rate were not significantly different from the baseline (Figure 1).

At the time of CSE institution the mean score of sedation in groups C, K₁, K₂ and K₃ were (1.28"0.38, 2.32"0.17, 3.68"0.91) respectively where group K₂ patients lies in the category 3 where the patients are mostly asleep but arousable by verbal contact that is to the say the patients are mostly cooperative (Table 2).

The mean score of patient behaviour in groups C, K₁, K₂ and K₃ were (1.96"0.31, 2.56"0.72, 3.04"0.43 and 3.64"0.92) respectively where most patients of group K₂ lies in the category 3 where patients were calm and cooperative (Table 2).

The mean score of ease of CSE institution in groups C, K₁, K₂ and K₃ were (3.04"0.94, 3.6"1.21, 3.92"1.07 and 3.76"0.93) respectively where the patients of group K₂ had the highest score for ease of CSE institution (Table 2).

Thirty minutes after institution of CSE the means of patient's satisfaction score in groups C, K₁, K₂ and K₃ were (2.52"0.87, 2.8"0.74, 4.0"1.38 and 4.0"1.17) respectively, where patients of groups K₂ and K₃ had the highest satisfaction about the quality of CSE institution (Table 2).

The means of observer satisfaction score in groups C, K₁, K₂ and K₃ were (2.68"1.21, 2.92"1.40, 4.76"1.72 and 3.04"1.10) respectively, thus the highest observer satisfaction as regard the quality of CSE institution was in group K₂ patients (Table 2).

Patients in group C showed significantly higher incidence of Ephedrine and Atropine consumption 15 out of 25 cases and 10 out of 25 cases respectively than the other groups (Table 3).

Patients in group K₃ showed significantly highest incidence of unpleasant emergence reactions and also of excessive sedation but there was no difference between groups as regard the incidence of
Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group C n=25</th>
<th>Group K₁ n=25</th>
<th>Group K₂ n=25</th>
<th>Group K₃ n=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>35 ± 7</td>
<td>37 ± 6</td>
<td>33 ± 6</td>
<td>36 ± 5</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>11/14</td>
<td>13/12</td>
<td>12/13</td>
<td>13/12</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>76 ± 9</td>
<td>73 ± 10</td>
<td>72 ± 11</td>
<td>74 ± 12</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173 ± 17</td>
<td>170 ± 18</td>
<td>175 ± 16</td>
<td>170 ± 16</td>
</tr>
</tbody>
</table>

Table 2. Scores used for evaluation in the four studied groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group C n=25</th>
<th>Group K₁ n=25</th>
<th>Group K₂ n=25</th>
<th>Group K₃ n=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation score</td>
<td>1.28 ± 0.38</td>
<td>2.32 ± 0.17</td>
<td>3.00 ± 0.85*</td>
<td>3.68 ± 0.91**</td>
</tr>
<tr>
<td>Patient’s behaviour score</td>
<td>1.96 ± 0.31</td>
<td>2.56 ± 0.72</td>
<td>3.04 ± 0.43*</td>
<td>3.64 ± 0.92**</td>
</tr>
<tr>
<td>Ease of CSE institution score</td>
<td>3.04 ± 0.94</td>
<td>3.6 ± 1.21*</td>
<td>3.92 ± 1.07**</td>
<td>3.76 ± 0.93*</td>
</tr>
<tr>
<td>Patient satisfaction score</td>
<td>2.52 ± 0.87</td>
<td>2.8 ± 0.74</td>
<td>4.0 ± 1.38**</td>
<td>4.0 ± 1.17**</td>
</tr>
<tr>
<td>Observer satisfaction score</td>
<td>2.68 ± 1.21</td>
<td>2.92 ± 1.40</td>
<td>4.76 ± 1.72**</td>
<td>3.04 ± 1.10*</td>
</tr>
</tbody>
</table>

Table 3. Number of cases suffered adverse effects in each group.

<table>
<thead>
<tr>
<th></th>
<th>Group (C) n=25</th>
<th>Group K₁ n=25</th>
<th>Group K₂ n=25</th>
<th>Group K₃ n=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unpleasant emergence reactions</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>6*</td>
</tr>
<tr>
<td>Airway obstruction</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Apnea</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Excessive sedation</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>12*</td>
</tr>
<tr>
<td>Hypotension needed ephedrine</td>
<td>15*</td>
<td>7</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Bradycardia needed atropine</td>
<td>10*</td>
<td>5</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Hypoxia needed O₂ inhalation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2*</td>
</tr>
</tbody>
</table>

Discussion

The results of the present study indicate: (i) During performance of painful or uncomfortable procedures like CSE the use of midazolam and small doses of ketamine provided analgesia and anxiolysis with improvement of patient behavior to spinal puncture and easier performance of lumbar puncture and balanced the hypotensive effects of spinal anesthesia through its cardiovascular stimulating effects of ketamine. (ii) Increasing the dose of ketamine from 0.15 to 0.30 to 0.45 mg/kg improved the sedation, patient response,
ease of lumbar puncture and hemodynamic parameters but the incidence of unpleasant emergence reaction, was higher especially at doses 0.45 mg/kg of ketamine. (iii) The quality of neuroaxial block institution assisted by both the blinded observer and patient was best with the dose of 0.3 mg/kg ketamine. In group K3, because with smaller doses of ketamine in group K1, there was no adequate sedation or analgesia and there was some resistance to the procedure, while with larger doses of ketamine in group K3, the patients were over sedated, uncooperative and suffered more unpleasant emergence reactions. (iv) I.V. Ketamine in combination with midazolam allowed use to institute CSE anesthesia easier in the sitting position for patients who cannot tolerate sitting up due to pain e.g. patients with hip or leg fractures.

At the most basic level, neuroaxial block is indicated whenever the surgical procedure can be accomplished with a sensory level of anesthesia that does not produce adverse patient outcome.\(^{(1)}\)

One of the most important indication to neuroaxial block is patient refusal for fear of inability to maintain stillness during the needle puncture, thus exposing the neural structures to unacceptable risk of injury. The cardiovascular effects of neuroaxial block are similar in some ways to the combined use of intravenous alpha1 - and beta-adrenergic blockers: heart rate and arterial blood pressure decrease.

The sympathectomy that accompanies the techniques is dependent upon height of the block, with the sympathectomy typically described as extending for two to six dermatomes above the sensory level with spinal anesthesia.\(^{(10)}\)

Ketamine, a dissociative I.V. anesthetic was first used in humans in 1965.\(^{(11)}\) Over the years it has found many roles in anesthesia practice, and remains the subject of interest in clinical investigations.\(^{(12)}\) In recent years, investigators have led to a better understanding of its mechanism of action and its roles in analgesia and sedation.

The anesthetic and analgesic effects of ketamine are mediated primarily by non-competitive antagonism at the N-methyl-D-aspartate (NMDA) receptor. The NMDA receptor is an ionotropic receptor (ligand-gated ion channel) that is activated by glutamate the most abundant excitatory neurotransmitter in the central nervous system. Other mechanisms include binding to opioid receptors, with preference for \(\mu\) receptors, which is responsible for the analgesic effects of ketamine. The psychotomimetic properties of ketamine are though to be related to its interaction with receptors.\(^{(13)}\)

In contrast to other I.V. agents, ketamine is a potent analgesic at subanesthetic plasma concentrations and it increases arterial blood pressure, heart rate and cardiac output.\(^{(14)}\) These indirect cardiovascular effects are due to central stimulation of the sympathetic nervous system and inhibition of the reuptake of norepinephrine.\(^{(15)}\) Also in the respiratory system, ketamine support the chest wall muscle tone and maintains functional residual capacity of the lung\(^{(16)}\) and upper airway muscle tone is maintained.\(^{(17)}\)

In agreement with our study, Suzuki M et al.,\(^{(18)}\) found that ketamine in subanesthetic doses possesses analgesic properties. Also Kochs E et al.,\(^{(19)}\) reported that analgesic doses of ketamine 150-500 \(\mu\)g/kg produced dose dependent antinociception and cognitive, perceptual and mode disturbances, as well as psychotomimetic side effects. Aye T and Milne B,\(^{(16)}\) reported that the advantages of ketamine included maintaining spontaneous ventilation, avoiding institution of mechanical ventilation, increasing systemic vascular resistance and heart rate and maintaining cardiac contractility. So it is ideal for relief of pain and anxiety before performing neuroaxial block, where lumbar puncture is often painful.

Oda A et al.,\(^{(2)}\) concluded that ketamine, 5 mg IV, is effective as 50 \(\mu\)g fentanyl, IV, in alleviating patient anxiety and in providing adequate sedation during the procedures necessary for epidural
catheter placement, without inducing severe complications.

Maurset A et al., (20) reported that analgesia induced by 0.3 mg/kg I.V. ketamine was similar to that produced by 0.7 mg/kg pethidine. (20) Auden SM et al., (21) had found that the combination of ketamine and midazolam to be free of the negative side effects of ketamine alone and to provide rapid onset of deep sedation with minimal, if any, hemodynamic or respiratory compromise both components confer amnesia, and the combination was superior to i.m. meperidine, promathazine, and chlorpromazine.

Benzodiazepines and small dose ketamine are increasingly being used to improve patient comfort as a result of their anxiolytic, amnestic, sedative and analgesic properties. (22,23) Midazolam is theoretically preferable to diazepam for this purpose because its pharmacokinetic profile is similar to that of ketamine. (24) Midazolam is often combined with small-dose ketamine for sedation during local anesthesia because it attenuates its unpleasant emergence reactions. (22)

Deng XM et al., (9) reported that small doses of midazolam and ketamine before painful injection of local anesthetic solutions improved patients comfort as a result of their anxiolytic, amnestic, sedative and analgesic-like properties. However larger doses of ketamine produced more disruptive movements, blurred vision, dreaming, and postoperative vomiting. Suzuki M et al., (22) stated that subanesthetic doses of ketamine have been shown to produce a feeling of "high" and to be anxiolytic at low doses, but anxiogenic at higher doses.

Badrinath S, et al., (25) concluded that subhypnotic dosage of ketamine, administered in combination with propofol for sedation, contributed significant analgesia without hemodynamic and respiratory depression or psychotomimetic side effects, larger doses of ketamine were associated with a clinically significant increase in psychotomimetic side effects.

In conclusion, subanesthetic dose of ketamine especially 0.3 mg/kg supplemented with midazolam 0.03 mg/kg were best for sedation, pain relief, improved patient comfort, respiratory and cardiovascular stability without emergence psychic reaction when given before establishment of combined spinal epidural anesthesia.

References


