An intraoperative pre-incision single dose of intravenous ketamine does not have an effect on postoperative analgesic requirements under clinical conditions

A. DULLENKOPF*, R. MÜLLER‡, F. DILLMANN‡, P. WIEDEMEIER§, T. R. HEGI§, S. GAUTSCHI**
Department of Anaesthesia and Intensive Care, Hospital Limmattal, Schlieren, Switzerland

SUMMARY
Evidence about the effectiveness of the N-methyl-D-aspartate antagonist ketamine to reduce postoperative acute and long-lasting pain is inconclusive. The aim of this study was to investigate effects of adding an intraoperative, pre-incision single intravenous dose of ketamine to a routine anaesthesia regimen on postoperative analgesic requirements, side-effects and persisting pain up to three months.

After obtaining Ethical Committee approval and written informed patient consent, 120 patients were included in this prospective, randomised, double-blinded, placebo-controlled study. Patients were randomised into three groups, receiving 0.15 mg/kg ketamine intravenously, 0.5 mg/kg ketamine intravenously or normal saline in groups low-dose ketamine, moderate-dose ketamine and placebo, respectively. Anaesthesia maintenance, intraoperative pain management and postoperative pain therapy were standardised. The primary study endpoint was consumption of morphine during the first 24 hours after surgery. Three months after surgery, pain scores were assessed. Data were compared by t-test and Kruskall-Wallis test with alpha=0.05.

There was no difference between the groups in the assessed variables.

These findings indicate that with the anaesthesia regimen described, and in the doses used, a single intravenous dose of ketamine does not reduce postoperative analgesic requirement or postoperative pain at three months.

Key Words: pain, postoperative, ketamine, therapeutic use

Perioperative pain therapy is one of the main tasks for the anaesthesiologist. Different receptor types are known to participate in generating acute and long-lasting postoperative pain. Opioid and N-methyl-D-aspartate (NMDA) receptors are among the most important, with NMDA receptors playing an important role in long-lasting hyperalgesia and persisting pain14.

Evidence about the effectiveness of the NMDA antagonist ketamine to reduce postoperative hyperalgesia and acute and long-lasting pain is inconclusive56. There is some evidence that a single dose of perioperatively administered ketamine can reduce postoperative analgesic requirement79. Administration of ketamine before surgical incision seems to be superior to administration at the end of surgery10. The latter may also delay emergence from anaesthesia. The side-effects of dysphoria, hallucinations and diplopia with higher doses of ketamine are well known89.

Many of the studies that have shown an effect on postoperative pain were not done under everyday clinical conditions5912. Often restrictive perioperative analgesic regimens were applied, which could have increased the effect of perioperative ketamine.

Uncertainty exists about the optimum dose of ketamine and the preferred mode and timing of administration. There is also uncertainty about which operations ketamine may benefit and the time span of any assumed positive effect, which has been reported to last up to several days in some studies51314.

The aim of this study was to investigate the effects of an intraoperative, pre-incision single intravenous (IV) administration of two different doses of ketamine on postoperative analgesic requirements after general surgical and orthopaedic procedures, when used as an adjunct to a routine perioperative analgesic regimen. Side-effects and persisting pain up to three months were also assessed.
MATERIALS AND METHODS

After obtaining Ethical Committee approval and written informed patient consent, 120 patients were recruited in this prospective, randomised, double-blinded, placebo-controlled study. Inclusion criteria were: general anaesthesia for general surgical or orthopaedic operations anticipated to last 30 to 120 minutes, assumed hospital stay of 48 hours and age 18 years or older. Exclusion criteria included contraindications to IV ketamine (e.g. insufficiently or untreated elevated arterial blood pressure, patients in whom an increase of arterial blood pressure would be potentially dangerous, patients with a history of previous stroke or intracerebral bleeding, arterial aneurysm, insufficiently treated hyperthyroidism, hypersensitivity to ketamine or its preservative benzethonium chloride), an ASA physical status greater than III, inability to communicate appropriately, pregnancy, severe renal and hepatic dysfunction, known allergies to any other study medications, contraindications to maintenance of general anaesthesia using propofol, actual therapy with psychoactive drugs or opiates, history of severe psychological disturbances, planned postoperative admission to the intensive care unit and patients weighing more than 120 kg.

Conduct of the study

A day before surgery the patients were instructed in the use of the visual analogue scale for pain (VAS, 0=no pain, 10=worst pain imaginable).

On the basis of a computer-generated block randomisation list with fixed block sizes of 20, patients were divided into three groups: low-dose ketamine group (Kl), moderate-dose ketamine group (Km) and placebo, normal saline group (P). The study medication for all three groups was prepared and blinded by the hospital pharmacist. A syringe containing 12 ml was provided for every patient. One ml of the study solution contained 1.5 mg, 5 mg or 0 mg of ketamine in groups Kl, Km and P, respectively. In all patients, 1 ml of the study solution was administered for every 10 kg of body weight, resulting in 0.15 mg/kg ketamine IV, 0.5 mg/kg ketamine IV or normal saline in groups Kl, Km and P, respectively. There was a randomisation decoding list available in case of emergency.

For premedication, 7.5 mg midazolam was administered to all patients orally 45 minutes before induction of anaesthesia. On arrival in the operating unit, electrocardiogram, blood pressure and pulse oximetry monitoring were commenced. Induction of general anaesthesia was achieved with propofol 1.5 to 2.5 mg/kg IV and fentanyl 1.5 mg/kg IV. If tracheal intubation was deemed necessary, muscle relaxation was achieved by atracurium 0.5 to 0.6 mg/kg of IV.

After securing the airway and before skin incision, the study medication was administered IV.

Anaesthesia was maintained with propofol, plus nitrous oxide in oxygen, supplemented by up to one additional fentanyl dose if required for intraoperative analgesia (0.75 to 1.5 mg/kg), and remifentanil infusion, dosed according to the attending anaesthetist. Fifteen minutes before the end of surgery, all patients were given ondansetron (a non-steroidal anti-inflammatory drug) 1 g IV. If there was a history of postoperative nausea or vomiting, ondansetron 4 mg IV was administered intraoperatively.

After emerging from anaesthesia, the patients were transferred to the post-anaesthesia care unit (PACU), where they stayed until they fulfilled the criteria for transfer to the ward. In the PACU, patients received analgesia with nurse-controlled morphine IV (in doses of 0.03 mg/kg) if they had a VAS ≥3. Additionally, paracetamol 1 g IV could be administered.

On the ward, all patients were given ondansetron 1 g IV up to four times per day, if necessary. The next step was paracetamol 1 g orally up to four times a day. Morphine 0.03 mg/kg IV was used as rescue medication. Rescue medication for postoperative nausea or vomiting consisted of ondansetron 4 mg IV up to twice daily.

Data assessment

The following data were recorded by a study nurse, who was blinded to treatment groups.

Intraoperatively

Doses of propofol, remifentanil and fentanyl administered, duration of anaesthesia, time from administration of study medication to emergence from anaesthesia and time from skin closure to emergence from anaesthesia were recorded.

PACU

Sedation was assessed on admission (0 to 10, 0=no response to stimuli at all, 10=completely alert). VAS was also assessed on admission, as was the amount of analgesia given and length of PACU stay.

Ward

All patients were interviewed on the first and second day after surgery about the occurrence of bad dreams, hallucinations or diplopia. At the end of the study period, patients were asked to classify their pain management as "excellent", "acceptable" or "poor".
Long-term outcome

Three months after surgery, all patients were contacted by mail and were asked to quantify their pain related to the site of the operation during rest and during movement using the VAS, and were again asked to classify their pain management as “excellent”, “acceptable” or “poor”.

Data analysis

Our primary hypothesis was that the lower ketamine dose would be sufficient to reduce morphine requirement and that there would be no further improvement with the higher ketamine dose. The primary endpoint of this study was the consumption of morphine during the first 24 hours after surgery. Data are given as mean ± standard deviation for normally distributed data or median (range) for non-normally distributed data.

Data of the different groups and general surgical versus orthopaedic procedures were compared by student t-test for unpaired comparisons for normally distributed data, Kruskal-Wallis test for non-normally distributed data or chi-square test for qualitative data.

RESULTS

One-hundred and twenty patients were recruited into the study, 75 undergoing general and 45 undergoing orthopaedic surgery. Ten patients had to be excluded after commencement of the study (seven because of protocol violation, two because they suffered an adverse reaction before administration of the study medication and one because of a change in surgical procedure).

There were no differences in demographic or anaesthesia-related data (Table 1). There was no lower requirement of morphine in the ketamine groups during the first 24 hours after surgery (Tables 2 and 3). This was true even when analysing the data separately for general and orthopaedic surgery patients. Patients from group Km spent a longer time in PACU than patients from group P (131.5 ± 48.4 vs 108.9 ± 29.1 minutes, P = 0.02).

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic and anaesthesia-related data</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>KL</th>
<th>Km</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>36</td>
<td>41</td>
<td>33</td>
</tr>
<tr>
<td>Age (y)</td>
<td>48.6 ± 17.8</td>
<td>56.2 ± 17.6</td>
<td>52.3 ± 17.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.0 ± 14.8</td>
<td>74.5 ± 16.6</td>
<td>74.7 ± 11.0</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.68 ± 0.08</td>
<td>1.68 ± 0.11</td>
<td>1.69 ± 0.09</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8 ± 4.7</td>
<td>26.3 ± 5.4</td>
<td>26.0 ± 5.0</td>
</tr>
<tr>
<td>Gender (n, female/male)</td>
<td>26/10</td>
<td>21/20</td>
<td>18/15</td>
</tr>
<tr>
<td>Operating time (min)</td>
<td>95.2 ± 40.6</td>
<td>102.3 ± 55.6</td>
<td>101.6 ± 47.5</td>
</tr>
<tr>
<td>Anaesthesia time (min)</td>
<td>122.5 ± 44.3</td>
<td>120.8 ± 58.4</td>
<td>124.5 ± 54.1</td>
</tr>
<tr>
<td>Intraoperative propofol (mg)</td>
<td>768.6 ± 396.7</td>
<td>775.0 ± 467.3</td>
<td>800.0 ± 332.6</td>
</tr>
<tr>
<td>Intraoperative fentanyl (µg)</td>
<td>0.25 ± 0.08</td>
<td>0.26 ± 0.09</td>
<td>0.23 ± 0.10</td>
</tr>
<tr>
<td>Intraoperative remifentanil (µg)</td>
<td>0.47 ± 0.37</td>
<td>0.49 ± 0.40</td>
<td>0.39 ± 0.38</td>
</tr>
<tr>
<td>PONV prophylactics (n, yes/no)</td>
<td>5/31</td>
<td>6/35</td>
<td>6/27</td>
</tr>
<tr>
<td>Time from skin closure to awakening (min)</td>
<td>10.2 ± 6.6</td>
<td>9.2 ± 7.6</td>
<td>8.6 ± 7.7</td>
</tr>
</tbody>
</table>

BMI = body mass index, PONV = postoperative nausea and vomiting. Mean ± standard deviation.

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACU data</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>KL</th>
<th>Km</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in PACU (min)</td>
<td>111.6 ± 35.6; 0.74</td>
<td>131.5 ± 48.4; 0.02</td>
<td>108.9 ± 29.1</td>
</tr>
<tr>
<td>Sedation score arriving in PACU (0-10)</td>
<td>3; 0-8</td>
<td>3; 0-8</td>
<td>4; 0-9; 0.91</td>
</tr>
<tr>
<td>Pain score arriving in PACU (0-10)</td>
<td>3; 0-10</td>
<td>4; 0-9</td>
<td>4; 0-9; 0.94</td>
</tr>
<tr>
<td>Morphine in PACU (mg)</td>
<td>7.4 ± 6.9; 0.56</td>
<td>8.3 ± 7.3; 0.98</td>
<td>8.3 ± 6.8</td>
</tr>
</tbody>
</table>

PACU = post-anesthesia care unit. Data are mean ± SD or median; range with a P value for comparing groups against group P (t-test for unpaired values for length of stay and morphine consumption) and Kruskal-Wallis test for comparing sedation and pain scores.

Anaesthesia and Intensive Care, Vol. 37, No. 5, September 2009
One patient in group Km complained about bad dreams and another about hallucinations. One patient from each group complained of diplopia. Excessive salivation was recorded for one patient from both group Km and P. One patient in group Km complained about delayed awakening compared with previous anaesthetics.

Only 80 of the 110 patients responded three months postoperatively (return rate 73%). Patient satisfaction did not differ between the three groups. Three months after the operation, there were no significant differences in pain between the three groups. However, when considering the orthopaedic subgroup, group P had the worst pain ($P=0.041$).

**DISCUSSION**

In this prospective, randomised, double-blinded, placebo-controlled study we investigated whether single IV boluses of ketamine in two different doses had an effect on the 24-hour morphine consumption after moderate surgery, when administered in addition to a standard anaesthesia regimen.

The main finding was that neither of the two doses reduced postoperative morphine consumption in this setting. Side-effects were not a problem. Patients from group Km spent longer time in PACU than patients from group P ($P=0.02$).

Perioperative pain is a major concern for patients requiring surgery. Multi-modal strategies are employed in pain therapy, mainly involving opioids and non-steroidal anti-inflammatory analgesics. Ketamine may be a useful adjunct, possibly by reducing the amount of required analgesics and associated side-effects, such as nausea, dizziness and sedation.

Ketamine is a widely known NMDA receptor antagonist. It can be used for induction of anaesthesia, for intra- and postoperative analgesia and as an adjunct in chronic pain states. The NMDA receptor seems to play an important role in central nervous system sensitisation and plasticity after receiving nociceptive impulses. This has caused renewed interest in the drug as an adjunct to multimodal pain treatment. However, the results so far remain controversial, with some of the positive results having been obtained using anaesthesia regimens not accepted as standard.

The implications of our findings are that the perioperative administration of ketamine in the mentioned doses is not justified for all patients when using the anaesthesia and analgesic regimen described. In particular, the administration of the higher ketamine dose does not seem to be justified. It is possible that ketamine may be a more effective pre-emptive agent in orthopaedic patients, but this requires further investigation. The clinical relevance of the longer time spent in the PACU must also be considered. While there was no statistically significant difference between groups KI and P, the study had limited power.

Many published studies have reported a positive effect of perioperative ketamine. Interestingly, some of the most impressive results with a reduction in morphine consumption of 47% were from orthopaedic patients. One of the differences to our study, however, was the use of alfentanil for intraoperative analgesia, which has a shorter duration of action than the fentanyl we used.

The side-effect of hallucinations has been reported in the literature as occurring in 0.8% of patients undergoing general anaesthesia when receiving ketamine. Nightmares were reported in 2.4%, pleasant dreams, which were not addressed in our study, in 18.2% and visual disturbances in 6.2%. In our study, nightmares were reported in 1.2% (one of 77 patients).
Notably, our study is one of the largest addressing this topic. In their review, Elia et al included studies with a median number of patients receiving ketamine of 25 (range 10 to 105)\(^6\).

There are some limitations of this study. First and most importantly, we were using nitrous oxide for maintenance of anaesthesia in our protocol. This is because the study was designed as part of our quality management process to decide if the administration of ketamine should have a place in our anaesthesia protocol. This is a problem because, like ketamine, nitrous oxide is known to be a NMDA-antagonist. However, it is a very fast reacting anaesthetic agent and to our knowledge, there is no evidence of nitrous oxide exerting significant effects on postoperative pain for several hours. Furthermore, it was used in some of the referenced studies\(^6,10,11,16,17\). The subgroup analysis of our orthopaedic patients warrants caution because of the small number of patients included. Remifentanil has the potential to be associated with difficult-to-control pain in the postoperative period, which may reflect a hyperalgesic state. The role of ketamine in this context is not clear, and may depend on the type of procedure and on the mode of administration and dose.

In conclusion, our findings indicate that when used in addition to the anaesthesia and analgesia regimen in this study, single IV doses of ketamine do not reduce postoperative analgesic requirement or postoperative pain at three months.

REFERENCES