Effect of ketamine as an adjunct to intravenous patient-controlled analgesia, in patients at high risk of postoperative nausea and vomiting undergoing lumbar spinal surgery

J. W. Song1,2, J. K. Shim1,2, Y. Song1,2, S. Y. Yang4, S. J. Park1 and Y. L. Kwak1,2,3*

1 Department of Anaesthesiology and Pain Medicine and 2 Anaesthesia and Pain Research Institute, 3 Severance Biomedical Science Institute, Yonsei University College of Medicine, 250 Seongsan-no, Seodaemun-gu, Seoul, Republic of Korea
4 Department of Anaesthesiology and Pain Medicine, Chung-Ang University College of Medicine, 84 Heukseouk-Ro, Dongjak-gu, Seoul, Republic of Korea

* Corresponding author: Department of Anaesthesiology and Pain Medicine, Anaesthesia and Pain Research Institute and Severance Biomedical Science Institute, Yonsei University College of Medicine, 250 Seongsan-no, Seodaemun-gu, Seoul 120–752, Republic of Korea
E-mail: ylkwak@yuhs.ac

Editor’s key points

- Reduction in postoperative nausea and vomiting (PONV) is important to improve outcomes.
- Reducing opioid consumption, with multimodal analgesia, is one approach where ketamine may be useful.
- In this study of high-risk patients, ketamine exacerbated PONV, although opioid consumption was reduced.
- Further research is needed to clarify the role of ketamine as an adjuvant analgesic.

Background. We evaluated the effect of ketamine as an adjunct to a fentanyl-based i.v. patient-controlled analgesia (IV-PCA) on postoperative nausea and vomiting (PONV) in patients at high risk of PONV undergoing lumbar spinal surgery.

Methods. Fifty non-smoking female patients were evenly randomized to either the control or ketamine group. According to randomization, patients received either ketamine 0.3 mg kg⁻¹ i.v. or normal saline after anaesthetic induction with fentanyl-based IV-PCA either with or without ketamine mixture (3 mg kg⁻¹ in 180 ml). The incidence and severity of PONV, volume of IV-PCA consumed, and pain intensity were assessed in the postanaesthesia care unit, and at postoperative 6, 12, 24, 36, and 48 h.

Results. The overall incidence of PONV during the first 48 h after surgery was similar between the two groups (68 vs 56%, ketamine and control group, \(P = 0.382\)). The total dose of fentanyl used during the first 48 h after operation was lower in the ketamine group than in the control group [mean (sd)], 773 (202) \(\mu\)g vs 957 (308) \(\mu\)g, \(P = 0.035\)]. The intensity of nausea (11-point verbal numerical rating scale) was higher in the ketamine group during the first 6 h after operation [median (interquartile range), 6 (3–7) vs 2 (1.5–3.5), \(P = 0.039\)], postoperative 12–24 h [5 (4–7) vs 2 (1–3), \(P = 0.014\)], and postoperative 36–48 h [5 (4–7) vs 2 (1–3), \(P = 0.036\)]. Pain intensities were similar between the groups.

Conclusions. Ketamine did not reduce the incidence of PONV and exerted a negative influence on the severity of nausea. It was, however, able to reduce postoperative fentanyl consumption in patients at high risk of PONV.

Keywords: analgesia, patient-controlled; ketamine; postoperative nausea and vomiting

Accepted for publication: 6 March 2013

Opioid-based i.v. patient-controlled analgesia (IV-PCA) is a well-established therapy to prevent postoperative pain control in patients undergoing spinal surgery.¹ Despite the excellent analgesic effect, however, opioids increase the incidence of PONV, which frequently complicates the postoperative course of patients. In addition to the use of postoperative opioids, female gender, a history of motion sickness or PONV, and non-smoking status are major risk factors that increase the incidence of PONV. When three or four of these risk factors were present, the reported incidence of PONV increased up to 61 and 79%, respectively.² A variety of pharmacologic agents has been used to prevent PONV as a single drug or in combination.³ Besides using the anti-emetic agents, studies using a multimodal regimen including non-steroidal anti-inflammatory agents or tramadol to reduce opioid consumption showed promising results in terms of the incidence of opioid related side-effects including PONV.⁴ ⁵

Ketamine is an anaesthetic agent with N-methyl-D-aspartate (NMDA)-antagonistic properties. Subanaesthetic doses of ketamine prevent central sensitization, development of acute opioid tolerance, and hyperalgesia.⁶ A large number of clinical trials have evaluated the efficacy of ketamine as an adjuvant to opioids for acute postoperative pain and some of those studies demonstrated opioid sparing effect and subsequent reduction in the incidence of PONV.⁷ ⁸ However, significant heterogeneity exists in the previous studies with...
conflicting results. Moreover, none of those studies had focused on the reduction in PONV incidence, especially in high-risk patients, in whom the benefit of opioid-based IV-PCA can be deprived because of severe PONV.

In the present study, we evaluated the effect of subanaesthetic dose of ketamine added to fentanyl-based IV-PCA on the incidence of PONV in highly susceptible patients to PONV undergoing lumbar spinal surgery.

Methods

Study population

After approval from the Institutional Ethics Committee, this study was registered with clinicaltrials.gov (unique identifier: NCT01394406). Fifty patients were enrolled and written informed consent was obtained from all of them. The inclusion criteria were non-smoking female patients between 20 and 65 yr of age, who were ASA physical status I or II and undergoing 1–2 level posterior lumbar spinal fusion surgery. According to Apfel’s simplified risk score for predicting PONV, these patients had at least three risk factors of PONV (female gender, non-smoking status, and postoperative opioids), and thus, the estimated incidence of PONV was >61%. Exclusion criteria were patients with history of receiving anti-emetics within 1 day before surgery, opioid administration within 1 week of surgery, regular administration of corticosteroids, a history of psychiatric disorder, drug or alcohol abuse, gastrointestinal motility disorder, severe hepatic or renal disease, insulin dependent diabetes, or patients who were admitted to the intensive care unit after operation.

Study design

Using a random number table, patients were randomly allocated to either the control or ketamine group. The group assignment was secured in sequentially numbered opaque envelopes. The envelope was opened on the day of operation by a nurse who was not involved in managing or evaluating the patients, and either ketamine or an equal volume of normal saline was prepared as assigned. The group assignment was blinded to both patients and investigators until the end of the study.

Anaesthesia was induced with propofol 2 mg kg\(^{-1}\), remifentanil 1 \(\mu g\) kg\(^{-1}\), and rocuronium 0.8 mg kg\(^{-1}\) and maintained with sevoflurane inhaled at an end tidal concentration of 1.5–2.5% in 50% oxygen/air mixture and 0.1–0.2 \(\mu g\) kg\(^{-1}\) min\(^{-1}\) of remifentanil. Immediately after the induction of anaesthesia, 0.3 mg kg\(^{-1}\) of ketamine was injected to the patients in the ketamine group, while the same volume of normal saline was injected to the patients in the control group and IV-PCA was commenced. The PCA regimen consisted of fentanyl 20 \(\mu g\) kg\(^{-1}\) and ondansetron 8 mg (total volume including saline: 180 ml) and was programmed to deliver 2 ml h\(^{-1}\) as a background infusion and a bolus of 2 ml on-demand, with a 15 min lockout time during a 48 h period. Ketamine 3 mg kg\(^{-1}\) was mixed to IV-PCA in the ketamine group and the same volume of normal saline was mixed to IV-PCA in the control group. Fentanyl 0.5 \(\mu g\) kg\(^{-1}\) and ondansetron 4 mg was injected intravenously at 20 min before the end of operation in both groups. After operation, meperidine 25 mg i.v. was injected when the patient reported resting pain intensity >40 mm on an 100 mm-visual analogue scale (VAS, 0—no pain, 100—worst and intolerable pain) or requested an analgesic agent. Ondansetron 4 mg i.v. was administered when the patient had nausea >6 by an 11-point verbal numerical rating scale (VNRS, 0—10, 0—no nausea, 10—worst and intolerable nausea) or requested an anti-emetic agent. If severe nausea persisted despite the pharmacologic treatment, the IV-PCA infusion was stopped temporarily for 2 h.

Data collection

Nausea, presence of retching or vomiting, degree of nausea, pain intensity, cumulative volume of IV-PCA consumed, adverse events, and the amount of additional analgesics or anti-emetics were assessed 30 min after admission in the post-anesthesia care unit (PACU), and at 6, 12, 24, 36 and 48 h after surgery. Patients were asked to rate their worst nausea and resting pain during each time period. Pain on movement was assessed while patients were trying to lift their legs at supine position. Adverse events included headache, dizziness, drowsiness, hallucination, nightmare, and dysphoria.

Statistical analysis

In a preliminary study, 70% of non-smoking, female patients with IV-PCA had PONV. Twenty-three patients per group were needed to reduce the PONV incidence to 30% at an \(\alpha\) level of 0.05 and a power of 80%. Considering the drop-out rate, the study size was set to 25 patients per group. All results were shown as mean (sd) or median (interquartile range), or number of patients (percentage). Patient characteristics were analysed by independent \(t\)-test, \(\chi^2\) test, or Fisher’s exact test where appropriate. The incidence of nausea, retching or vomiting, and adverse events was analysed by \(\chi^2\) test or Fisher’s exact test. The cumulative volume of PCA consumed was compared by independent \(t\)-test. Pain intensities were analysed by repeated measures of analysis of variance. The severity of nausea, amount of rescue analgesic, and anti-emetics were analysed by Mann–Whitney \(U\)-test. Analyses were based on per-protocol except the overall incidence of PONV and adverse events during postoperative 48 h. Statistical analysis was performed with SAS (version 9.1.3, SAS Institute, Inc., Cary, NC, USA). A \(P\)-value of <0.05 was considered to be significant.

Results

All patients successfully completed the study except one patient in the ketamine group who had hallucinations at 6 h after operation (Fig. 1). This patient was excluded from analysis of cumulative volume of PCA consumed, pain intensities, incidence of PONV after postoperative 6 h, amount of rescue analgesics, and anti-emetics. Preoperative patient characteristics, duration of anaesthesia, and total amount of remifentanil administered during operation were similar between the groups (Table 1).
The ketamine group had a significantly higher incidence of nausea during postoperative 0–6 h (52 vs 12%, χ² test, P=0.016), while the overall incidence of nausea and vomiting during postoperative 48 h was not different between the groups (68 vs 56% in the ketamine and the control group, χ² test, P=0.382). Among those patients who experienced nausea, the intensity of nausea assessed by VNRS was significantly higher in the ketamine group during postoperative 0–6 h [6 (3–7) vs 2 (1.5–3.5), P=0.039], postoperative 12–24 h [5 (4–7) vs 2 (1–3), P=0.014], and postoperative 36–48 h [5 (4–7) vs 2 (1–3), P=0.036, Mann–Whitney U-test, Table 2].

There were no differences in the pain intensity at rest, or on movement between the groups during the study period (Table 3). The cumulative dose of fentanyl consumed during postoperative 48 h was significantly lower in the ketamine group than in the control group [773 (202) μg vs 957 (308) μg, independent t-test, P=0.035, Table 4]. The total dose of ketamine consumed during postoperative 48 h in the ketamine group was 116 (30) mg.

Significantly more patients in the ketamine group had dizziness during postoperative 48 h than in the control group (36 vs 12%, χ² test, P=0.047). Psychomimetic adverse events including hallucination, nightmare, or dysphoria were reported in three patients in the ketamine group (one patient with hallucination at postoperative 6 h, one patient with nightmare at postoperative 36 h and one patient with dysphoria at...
postoperative 36 h), while no patient in the control group experienced those symptoms throughout the study period. The amount of rescue analgesics and anti-emetics were similar between the groups (Table 5).

**Discussion**

In this prospective, double-blind, randomized controlled study, the effect of subanaesthetic dose of ketamine as an adjunct to a fentanyl-based IV-PCA on PONV in highly susceptible patients undergoing lumbar spinal surgery did not reduce the incidence of PONV. In contrast to our expectations, decreased opioid consumption in the ketamine group did not lead to a subsequent reduction in the incidence of PONV. Moreover, ketamine administration was associated with increased nausea and psychomimetic side-effects. After spinal surgery, adequate management for postoperative pain is essential to facilitate early rehabilitation and patient's recovery. Opioid-based IV-PCA is being widely used for that purpose. However, the incidence of PONV in non-smoking women treated with opioid-based IV-PCA may reach up to 60%. Vomiting may result in dehydration, electrolyte imbalance, disruption of the wound, and increased pain. Specific to lumbar spinal surgery, elevated abdominal pressure by PONV can be transferred to the epidural venous plexus and might raise the possibility of epidural haematoma formation. It is important, therefore, to institute effective anti-emetic strategies when opioid-based IV-PCA is to be used in patients at high risk of PONV.

In addition to prophylactic administration of anti-emetic agents, attempts to prevent PONV by reducing opioid consumption with adjuvant analgesics were similar between the groups (Table 5).
regimen.\textsuperscript{7,8,12,13} Furthermore, a Cochrane review analysing 37 studies found that perioperative ketamine reduced the incidence of PONV.\textsuperscript{8} While neutral results in terms of PONV incidence had also been reported,\textsuperscript{12,13} a recent systematic review showed that the incidence of PONV was significantly less in the ketamine groups when only efficacious studies in terms of pain control were analysed.\textsuperscript{7} As of yet, studies that primarily focused on the opioid-sparing effect and PONV incidence had not been performed in PONV-susceptible patients, in whom significant postoperative pain is anticipated and is expected to complicate postoperative pain management.

Our results indicate that, despite significant reductions in postoperative fentanyl requirements, perioperative ketamine administration was associated with increased intensity of nausea and adverse side-effects. It is difficult to make direct comparisons of the results of the current trial with those of the previous studies, as most of the previous studies used intermittent boluses of morphine for pain control and the current trial addressed a specific subset of patients at increased risk of developing PONV. The results of the current trial were contrary to our hypothesis, which was based on evidence from a substantial number of previous studies. These studies showed a reduced incidence or attenuated severity of PONV in association with perioperative ketamine administration, although the evaluation of PONV was not a primary endpoint in any of these studies.

Possible explanations for these contradictory results are given in the following.

First, patients at high-risk of PONV, using Apfel's scoring system, were specifically enrolled in this study and the overall incidence of PONV was substantially higher in both control and ketamine groups compared with previous studies.\textsuperscript{14–17} Secondly, in relation to the specific type of patients, gender may also account for the observed adverse influence of ketamine. Greater vulnerability to PONV in female patients is thought to be related, although not fully elucidated, to the effect of oestrogen on serotonin pathways.\textsuperscript{18} Ketamine can induce nausea,\textsuperscript{19} possibly by inhibition of serotonin uptake at synaptic terminals.\textsuperscript{20} Also, gender dependent difference in psychopathological effects of ketamine has been described.\textsuperscript{21}

Indeed, in a recent study, a low dose pre-emptive S-ketamine infusion in patients who underwent Caesarean section under spinal anaesthesia increased the incidence of vomiting and psychogenic side-effects.\textsuperscript{22} While the impact of gender on the effect of ketamine as an adjunctive analgesic during the perioperative period has not been specifically investigated yet, previously observed results merit further studies to clarify this issue with a larger sample size.

Thirdly, the amount of reduction in fentanyl consumption in this study may not have been sufficient to decrease opioid-related adverse effects. In the current study, patients in the ketamine group consumed \(\sim 20\)% less fentanyl than the control group during postoperative 48 h, while previous efficacious studies reported 25–50\% reduction in postoperative opioid requirements.\textsuperscript{15,17,23} This may be attributable to the fact that we used a relatively low dose of ketamine, which is a potential limitation of this study. Ketamine has no anti-emetic property \textit{per se} and may even stimulate nausea.\textsuperscript{19} It was reported that minimum plasma concentration of ketamine to suppress hyperalgesia was 60 \(\mu\)g ml\(^{-1}\),\textsuperscript{1,2,4} which could be achieved by 0.5 mg kg\(^{-1}\) i.v. bolus followed by a continuous infusion of 2 mg kg\(^{-1}\) min\(^{-1}\).\textsuperscript{25} The dose of continuous infusion of ketamine ranged from 0.8 to 2.5 mg kg\(^{-1}\) min\(^{-1}\) in previous trials,\textsuperscript{14,15,17,23,26} while the dose of basal infusion was 0.56 mg kg\(^{-1}\) min\(^{-1}\) in our study. In the institutional preliminary studies, we used 2 and 1 mg kg\(^{-1}\) min\(^{-1}\) of ketamine infusion, both of which were associated with unacceptably high incidence of psychomimetic adverse effects and severe nausea requiring discontinuation of the IV-PCA. Thus, we had to use a smaller dose of ketamine. Ketamine is catalysed by cytochrome P450 (CYP) enzymes, and CYP3A4 and CYP2B6 are the major enzymes responsible for ketamine N-demethylation.\textsuperscript{27,28} Wide interindividual variability in the expression and the activity of CYP2B6 and CYP3A4, possibly because of genetic polymorphism, ethnic differences, or both, does exist and may result in variable response to drugs metabolized by this enzyme.\textsuperscript{29,30} Yet, a clear relationship between the genetic variation and clinical phenotype remains elusive and is beyond the scope of this study. Nevertheless, in patients at high-risk of developing PONV, potential side-effects of ketamine might be unmasked especially if opioid consumption could not be decreased sufficiently. Accordingly, ketamine as an adjunct to IV-PCA may not be beneficial to reducing PONV in patients at high risk of PONV. Combination of multiple anti-emetic agents such as draperidol, ondansetron or dexamethasone, or application of total i.v. anaesthesia based on propofol instead of volatile anaesthetics could be a better choice than ketamine in highly susceptible patients to PONV, because all these anti-emetic interventions has shown to be effective and act independently.\textsuperscript{21}

In conclusion, subanaesthetic dose of ketamine mixed in fentanyl-based IV-PCA reduced the postoperative 48 h cumulative fentanyl consumption in high-risk patients for PONV undergoing lumbar spinal surgery, with comparable analgesic effect. However, it could not reduce the incidence of PONV and furthermore, it increased the severity of nausea and incidence of dizziness. The use of ketamine as an adjunct to a

\begin{table}
\begin{center}
\begin{tabular}{|l|c|c|c|}
\hline
          & Control & Ketamine & P-value \\
\hline
Headache   & 5 (20\%) & 7 (28\%) & 0.508 \\
Dizziness  & 3 (12\%) & 9 (36\%) & 0.047 \\
Drowsiness & 4 (16\%) & 5 (20\%) & 1.000 \\
Hallucination/nightmare/dysphoria & 0 (0\%) & 3 (12\%) & 0.235 \\
Anti-emetics (ondansetron, mg) & 12 (8–16) & 16 (8–20) & 0.668 \\
Analgesics (meperidine, mg) & 50 (25–75) & 50 (25–75) & 0.547 \\
\hline
\end{tabular}
\end{center}
\caption{Adverse events and cumulative dose of rescue anti-emetics/analgescs \(\geq 48\) h. Values are expressed as number of patients (percentage) or median (interquartile range)}
\end{table}
fentanyl-based IV-PCA should be done cautiously in this subset of patients.

Declaration of interest
None declared.

Funding
Financial support for the study was provided solely from departmental sources.

References

Handling editor: L. Colvin