Effect of ketamine added to intravenous patient-controlled analgesia on postoperative nausea and vomiting in patients undergoing lumbar spinal surgery

Soo Jung Park

Department of Medicine

The Graduate School, Yonsei University

Effect of ketamine added to intravenous patient-controlled analgesia on postoperative nausea and vomiting in patients undergoing lumbar spinal surgery

Directed by Professor Soon Ho Nam

The Master's Thesis
submitted to the Department of Medicine
the Graduate School of Yonsei University
in partial fulfillment of the requirements for
the degree of Master of Medical science

Soo Jung Park

June 2013

This certifies that the Master's Thesis of
Soo Jung Park is approved.

Thesis Supervisor : Soon Ho Nam

Thesis Committee Member#1 : Young Lan Kwak

Thesis Committee Member#2 : Keung Nyun Kim

The Graduate School
Yonsei University

June 2013

ACKNOWLEDGEMENTS

This dissertation could not be fructified without the supports, advices and encouragements of many people and colleagues. First of all, I'd like to thank all patients who generously decided to participate in this study. And I would like to express sincere gratitude to professor Soon Ho Nam, my academic advisor and who provided the best tutelage and support possible and allowed me to develop.

Likewise, I would like to thank professor Young Lan Kwak, Professor Jae Kwang Shim, who did not hesitate give advice and assistance for this thesis, despite my lack of knowledge and experience on the thesis at the start of the program. Sincere thanks also go to professor Jong Wook Song, for giving me a lot of help and advices throughout the study. Also I'd like to thank Professor Keung Nyun Kim, who, while being extremely busy with surgery, took valuable time to share in this study.

<TABLE OF CONTENTS>

LIST OF TABLES

Abstract

Effect of ketamine added to intravenous patient-controlled analgesia on postoperative nausea and vomiting in patients undergoing lumbar spinal surgery

Soo Jung Park

Department of Medicine

The Graduate School, Yonsei University

(Directed by Professor Soon Ho Nam)

Opioid based intravenous patient-controlled analgesia (IV PCA) is a safe and effective way of postoperative analgesia while increases the postoperative nausea and vomiting (PONV). Mixture of subanesthetic dose of ketamine in IV PCA was reported to reduce the usage of opioid with improved quality of postoperative analgesia. In this randomized, double-blind, prospective study, we evaluated whether the ketamine, mixed to fentanyl based IV PCA, could reduce the opioid consumption and PONV in patients with high risk for PONV undergoing lumbar spinal surgery.

Fifty nonsmoking female patients between 20 ~ 65 years old undergoing lumbar spinal surgery were selected and randomized into 2 groups, as the control group and the ketamine group. Immediately after the induction of anesthesia, 0.5 mg/kg of ketamine or the same volume of normal saline was injected in the patients of

ketamine and control group, respectively. IV PCA was composed with fentanyl 20 μg/kg and ondansetron 8 mg (total volume 180 ml, basal rate 2 ml/hr, bolus 2 ml, lock-out-time 15 minutes). Ketamine 3 mg/kg 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. Pain, nausea, vomiting, other side effects, the volume of IV PCA used, and additional use of analgesics or antiemetics were recorded in the postanesthesia care unit and at 6, 12, 24, 36 and 48 hr after the operation.

Patient's characteristics were similar between the 2 groups. The intensity of pain was similar in both groups, whereas the volume of IV PCA used at 48 hr after operation was significantly less in the ketamine group than in the control group. Additional use of analgesics and antiemetics, the incidence and intensity of PONV were not different between the groups. The incidence of dizziness was significantly higher in the ketamine group.

Although addition of subanesthetic dose of ketamine to fentanyl based IV PCA demonstrated opioid sparing effect, regarding no beneficial effect on the incidence of PONV and the increased incidence of dizziness in the ketamine group, it was not likely to exert clinical advantage in high risk patient for PONV undergoing lumbar surgery.

Key Words : ketamine, opioid based intravenous patient-controlled analgesia, postoperative nausea

Effect of ketamine added to intravenous patient-controlled analgesia on postoperative nausea and vomiting in patients undergoing lumbar spinal surgery

Soo Jung Park

Department of Medicine

The Graduate School, Yonsei University

(Directed by Professor Soon Ho Nam)

I. INTRODUCTION

Opioid based intravenous patient-controlled analgesia (IV PCA) is an effective and safe way with high satisfaction rate in postoperative pain control in patients undergoing spinal surgery.[1] Despite the excellent analgesic effect, however, opioid increases the incidence of postoperative nausea and vomiting (PONV).[2] In addition to postoperative opioid, female gender, history of motion sickness or PONV, and nonsmoking are major factors increasing the incidence of PONV. When three or four of these risk factors were present, the incidence of PONV increased up to 61% and 79%.[2] Some medications, including nonsteroidal anti-inflammatory agents (NSAIDs) or tramadol, mixed to opioid based PCA revealed to improve the efficacy of analgesia and reduce the incidence of side effects including PONV.[3, 4]

Ketamine is an anesthetic agent with N-methyl-D-aspartate (NMDA)

antagonistic properties. Due to its analgesic potency and NMDA-antagonistic properties, ketamine has been also used as an adjuvant to opioid in treating the refractory pain in cancer patients, the neuropathic pain, and the acute postoperative pain.[5] Furthermore, for the treatment of postoperative pain, ketamine can be administered before and after incision, or during the postoperative period as an adjuvant to systemic opioid.

Several studies investigated the adjuvant use of ketamine with various doses and timing of administration, and showed variable results.[6-11] Prophylactic intravenous ketamine and ketamine mixed in PCA significantly decreased postoperative pain score without any impact on opioid-related adverse effects.[12] Additionally, some trials reported significantly less incidence of nausea in the ketamine treated groups.[5,13,14] Although ketamine can induce psychotomimetic adverse effects, many trials did not observe any increased incidence of psychotomimetic adverse effects with the use of ketamine.[5,12,15-18]

In patients following lumbar spinal surgery, opioid-based IV PCA is being most widely used. The baseline risk for PONV among nonsmoking women receiving opioid-based IV PCA, however, is high, reaching about 60% of incidence of PONV.[2] To avoid unnecessary prolongation of hospital stay, it is important not only to reduce pain intensity using adequate PCA regimen but also to prevent IV PCA related PONV.

If the ketamine mixed to IV PCA could reduce the consumption of opioid, it could also reduce the opioid related PONV. Thus, in the present study, we evaluated the effect of subanesthetic dose of ketamine mixed into fentanyl based IV PCA, on the incidence of PONV in high risk patients for PONV undergoing spinal surgery.

II. PATIENTS AND METHODS

1. Patient selection

After institutional review board approval and written informed consent, 50 nonsmoking female patients between 20 ~ 65 years old, with American Society of Anesthesiologists physical status I or II undergoing spinal surgery were selected. The risk factors of PONV was evaluated by the simplified risk score in the study of Apfel, et al.[2] The risk factors included female gender, nonsmoker, postoperative opioid usage, and history of motion sickness or PONV. The patients had 3 or 4 risk factors of PONV, thus, the estimated incidence of PONV was 61 ~ 79%.

Exclusion criteria were patients with history of receiving antiemetics in 24 hr before surgery, opioid or steroid use, psychiatric disorder and abusing drugs or alcohol, gastrointestinal motility dysfunction, severe hepatic or renal disease, insulin dependent diabetes and administration to intensive care unit after surgery.

Complete blood cell count, routine chemistry (total protein, albumin, blood urea nitrogen, creatinine, aspartate aminotransferase, alanin aminotransferase, bilirubin, electrolyte), coagulation test (prothrombin time, activated partial thromboplastin time), uninanalysis, electrocardiography (EKG), chest X-ray were evaluated as a screening test. With random sampling using random number table, patients were divided into the two groups: ketamine group (n = 25) and control group (n = 25).

2. Study design

Anesthesia was induced with propofol 1 ~ 2 mg/kg, remifentanil 1 μg/kg and rocuronium 0.8 mg/kg, and maintained with 50% oxygen and air, sevoflurane and remifentanil 0.1 ~ 0.2 μg/kg/min. Immediately after the induction of anesthesia, 0.5 mg/kg 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.

The PCA regimen consisted of fentanyl 20 ㎍/kg and ondansetron 8 mg (total volume including saline: 180 ml) and was programmed to deliver 2 ml/hr as background infusion and 2 ml per demand with a 15 min lockout during 48 hr period. Automed 3200 (Ace Medical, Seoul, Korea) was used as PCA device in this study. Ketamine 3 mg/kg 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 ㎍/kg and ondansetron 4 mg was injected intravenously at 20 min before the end of operation in both groups. The arterial oxygen saturation (SpO_2), EKG, heart rate, end tidal CO_2, body temperature and noninvasively measured blood pressure were monitored and recorded every 5 min throughout the surgery in all patients.

3. Data collection

The intensities and incidence of pain, nausea and vomiting, other adverse events, the volume of IV PCA used, and additional use of analgesics or antiemetics were recorded in the postanesthesia care unit (PACU) and at 6, 12, 24, 36 and 48 hr after operation. Intensity of pain was recorded while movement and resting, with visual analogue scale (VAS, 0: no pain ~ 10: worst possible pain). The intensity of nausea was recorded with verbal numerical rating scale (VNRS, 0: no nausea ~ 10: worst possible nausea).

Adverse events included headache, dizziness, drowsiness, hallucination, nightmare and dysphoria. Degree of patient's satisfaction at 48 hr after operation was recorded at the aspect of pain control and severity of adverse events, by 4 degrees (excellent - good - fair - poor).

If the intensity of nausea exceeds VNRS > 6 or when patient asks, ondansetron 4

mg was injected intravenously. When the intensity of pain exceeds VAS > 6 or when patient asks, pethidine 25 mg was injected intravenously. At the visit of patients, if there're any adverse events, patients were treated with adequate symptomatic treatment. If the adverse events continue, despite the symptomatic management, infusion of IV PCA was stopped for 2 hr. Every patient received instruction about possible adverse events, and way to contact the investigators.

4. Statistical analysis

In a preliminary study, 70% of non-smoking, female patients with IV PCA had PONV, 23 patients per group were needed to reduce the PONV incidence to 30% at an α level of 0.05 and 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 patient (percentage). Patient characteristics were analyzed by independent *t*-test, χ^2 test or Fisher's exact test where appropriate. The incidences of nausea, retching or vomiting, adverse events were analyzed by χ^2 test or Fisher's exact test. The cumulative volume of PCA consumed was compared by independent *t*-test. Pain intensities were analyzed by repeated measures of ANOVA. The severity of nausea, amount of rescue analgesic and antiemetics were analyzed by Mann-Whitney U test. Analyses were based on per-protocol except the overall incidence of PONV and adverse events during postoperative 48 hr. Statistical analysis was performed with SAS (version 9.1.3, SAS Institute, Inc. Cary, NC, USA). A P-value of less than 0.05 was considered to be significant.

III. RESULTS

All 50 patients primarily enrolled in this study completed the study. Demographic characteristics, duration of anesthesia, and total amount of remifentanil used during operation were similar between the groups (Table 1).

Table 1. Preoperative and intraoperative patient's data

	Control (n = 25)	Ketamine (n = 25)	P-value
Age (yr)	58 ± 10	57 ± 10	0.724
Height (cm)	157 ± 5	157 ± 6	0.882
Weight (kg)	60 ± 10	59 ± 7	0.883
Duration of anesthesia (min)	191 ± 58	208 ± 67	0.350
Total dose of remifentanil (μg)	776 ± 230	724 ± 247	0.438
Hypertension	7 (28)	11 (44)	0.377
Diabetes	5 (20)	4 (16)	1.000
Motion sickness	3 (12)	4 (16)	1.000
Previous PONV	0 (0)	1 (4)	1.000
Simplified risk score			
3	3 (12)	3 (12)	1.000
4	0 (0)	1 (1)	1.000

Data is marked both as mean ± SD and number of patients (percent). Significant differences are expressed with P-value (< 0.05). But significant differences does not exist between the two groups. Simplified risk score is graded by the score of Apfel, et al.[2]
PONV = postoperative nausea and vomiting

Intensities of pain at rest and movement, were similar between the groups (Table 2).

Table 2. Intensities of postoperative pain

	Control (n = 25)	Ketamine (n = 25)	P-value
Pain at rest			
PACU	3.9 ± 2.8	4.2 ± 2.0	0.646
0 ~ 6 hr	3.8 ± 2.1	3.7 ± 2.3	0.899
6 ~ 12 hr	3.5 ± 2.6	3.2 ± 2.0	0.623
12 ~ 24 hr	2.3 ± 1.5	2.5 ± 1.8	0.669
24 ~ 36 hr	2.4 ± 1.5	2.5 ± 1.9	0.803
36 ~ 48 hr	2.0 ± 1.5	2.2 ± 1.4	0.508
Pain on moving			
PACU	5.0 ± 2.2	5.2 ± 2.2	0.849
0 ~ 6 hr	6.0 ± 2.2	5.8 ± 2.2	0.849
6 ~ 12 hr	5.4 ± 2.6	5.0 ± 1.6	0.482
12 ~ 24 hr	4.6 ± 2.5	4.4 ± 1.7	0.740
24 ~ 36 hr	4.3 ± 2.3	4.2 ± 1.8	0.840
36 ~ 48 hr	4.0 ± 2.1	4.2 ± 2.0	0.680

Data is presented as mean ± SD. Data is graded by visual analogue scale.

Significant differences are expressed with P-value (< 0.05), but there are no statistically significant differences.

PACU = postanesthesia care unit

The total volume of IV PCA infused for postoperative 48 hr was much less in the ketamine group than in the control group (143.9 ± 35.1 ml vs. 117.4 ± 29.5 ml in the control and ketamine group, respectively, p = 0.015) (Table 3).

Table 3. Cumulative volume of patient-controlled analgesia consumed

	Control (n = 25)	Ketamine (n = 25)	P-value
PACU (ml)	5.7± 3.4	7.2 ± 3.1	0.115
0 ~ 6 hr (ml)	23.1 ± 11.1	21.9 ± 9.0	0.672
6 ~ 12 hr (ml)	43.9 ± 20.7	36.1 ± 12.3	0.127
12 ~ 24 hr (ml)	74.5 ± 26.1	60.1 ± 20.7*	0.041
24 ~ 36 hr (ml)	108.5 ± 33.3	85.2 ± 27.5*	0.014
36 ~ 48 hr (ml)	143.9 ± 35.1	117.4 ± 29.5*	0.015

Value is marked as mean ± SD.

* ; P-value < 0.05, compared with control group.

The cumulative volume of patient-controlled analgesia is significantly smaller than that of the ketamine group 24 hr after operation.

PACU = postanesthesia care unit

Opioid consumption after 24 hr was significantly less in the ketamine group.

The incidence and severity of PONV were not different between the two groups (Table 4).

Table 4. Incidence of nausea and vomiting, and severity of nausea

	Incidence			Severity (mild/moderate/severe)		
	Control	Ketamine	P - value	Control	Ketamine	P-value
Nausea						
PACU	3 (12)	3 (12)	1.000	0 / 1 / 2	1 / 1 / 1	1.000
0~6 hr	4 (16)	13 (52) *	0.016	3 / 1 / 0	5 / 4 / 4	0.513
6~12 hr	7 (28)	11 (44)	0.377	4 / 3 / 0	5 / 5 / 1	1.000
12~24 hr	9 (36)	7 (28)	0.496	7 / 2 / 0	1 / 4 / 2 *	0.031
24~36 hr	8 (32)	7 (28)	0.758	4 / 4 / 1	3 / 3 / 1	1.000
36~48 hr	6 (24)	7 (28)	0.747	5 / 1 / 0	1 / 4 / 2 *	0.041
0~48 hr	14 (56)	17 (69)	0.382	6 / 6 / 2	3 / 8 / 6	0.277
Vomiting						
PACU	0 (0)	1 (3)	1.000			
0~6 hr	1 (4)	4 (13)	0.367			
6~12 hr	2 (8)	2 (8)	1.000			
12~24 hr	1 (4)	2 (8)	1.000			
24~36 hr	2 (8)	1 (4)	1.000			
36~48 hr	0 (0)	2 (8)	0.490			
0~48 hr	4 (16)	5 (20)	1.000			

Value is marked as number of patients (percent).

* ; P-value < 0.05, compared with the control group.

The frequency and severity of PONV visibly increased in the ketamine group during several time intervals; frequency increases during 0~6 hr. Severity increases during 12~24 hr and 36~48 hr time intervals. But overall, no significant difference appears during 0~48 hr.

PACU = postanesthesia care unit, PONV = postoperative nausea and vomiting

There were no significant complications, which could threat the patient's survival or can prolong the day of hospitalization. The incidence of dizziness was significantly higher in the ketamine group (12% vs. 36%, P = 0.047). The amount of postoperative use of ondansetron as an antiemetic was similar between the groups. Postoperative use of pethidine as an adjunctive analgesic was also similar between the groups. Patient's satisfaction level about pain control was similar between the groups. Psychotomimetic adverse events occurred in 3 patients in the ketamine group while no patient experienced psychotomimetic event in the control group, although it was not statistically significant (Table 5).

Table 5. Adverse events and cumulative dose of rescue antiemetics /analgesics and patients' satisfaction

	Control (n = 25)	Ketamine (n = 25)	P-value
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
Antiemetics (ondansetron mg)	12 [8-16]	16 [8-20]	0.668
Analgesics (pethidine mg)	50 [25-75]	50 [25-75]	0.547
Satisfaction (excellent/good/fair/poor) – in the aspect of pain	1/13/10/1	2/15/6/2	0.621
Satisfaction (excellent/good/fair/poor) – in the severity of adverse event	2/14/8/1	3/11/5/6	0.204

Value is marked by means ± SD, median [interquartile range] or number of patients (percent).
* ; P-value < 0.05, compared with control group.
The overall frequency of dizziness is higher in the ketamine group.

IV. DISCUSSION

In this prospective study investigated the effect of the subanesthetic dose of ketamine mixed in fentanyl based IV PCA on postoperative pain and PONV in high risk patients for PONV undergoing spinal surgery, ketamine did not exert advantageous impact on the incidence and severity of PONV, while it reduced the amount of delivered IV PCA volume for 48 hr after operation with comparable pain control. Furthermore, the higher incidence of dizziness was observed in the ketamine group.

In patients following spinal surgery, appropriate management for postoperative pain is critical to facilitate early rehabilitation, improve patient's recovery and thus prevent development of chronic pain syndrome.[19] Opioid-based IV PCA is being most widely used for postoperative pain control with high satisfaction rate in patients undergoing spinal surgery. However, the baseline risk for PONV in nonsmoking women treated with opioid-based IV PCA reaches about 60%.[2] Vomiting may cause dehydration, electrolyte imbalance, disruption of the surgical repair, and increase the perception of pain and consequently, delayed recovery.[20, 21] In the case of lumbar spine surgery, although not validated, the increase in abdominal pressure elicited by PONV can be transferred to the epidural venous plexus which might result in epidural hematoma since the inferior vena cava and epidural venous plexus having direct communication[22]. Therefore, when patients with high risk of PONV are planned to receive opioid-based IV PCA, the importance of multimodal prophylactic management to reduce the incidence of PONV seem mandatory.[2] The authors supposed to complementary support to reduce opioid consumption with comparable analgesic effect would be the best way to reduce the incidence of opioid related adverse events.[23]

Ketamine is a widely used anesthetic agent with NMDA antagonistic effect. Ketamine produces dose-dependent central nervous system depression leading to a dissociative anesthetic state, characterized by profound analgesia and amnesia. Opioid is known to produce not only analgesia, but also hyperalgesia, which is considered to be induced by central sensitization. Decreasing inhibitory input increases the synaptic efficacy or membrane excitability mediated by neurokinin and NMDA receptor mechanism. Prolonged sensory afferent activation (C-fiber) is associated with this mechanism. Spinally released peptides in association with glutamate activate NMDA receptors, and while opioid only delay the onset of NMDA receptor activation and sometimes induces postoperative hyperalgesia. Ketamine has analgesic competence by its own, and also have possibility to reduce opioid-induced hyperalgesia with its NMDA-receptor blocking activity. Therefore, ketamine mixed in IV PCA, could induce additional analgesic effect on opioid, and reduce the postoperative consumption of opioid, reducing the central sensitization which could mitigate the opioid related adverse effects including nausea and vomiting.[24]

There have been several trials that demonstrating the efficacy of ketamine mixed to opioid based IV PCA in patients underwent microdiscectomy[13], laparotomy[25] and kidney donation.[14] In those three studies, morphine based PCA was used and significant reduction of morphine consumption (50.5 ~ 65.8%) and PONV were observed. Average consumption of ketamine was 0.23 ~ 2.5 μg/kg/min for 24 hr. In terms of the incidence and severity of PONV, only the intensity of the nausea was evaluated in two studies and it was significantly reduced in both studies; 2.20 vs. 1.39 by numerical score of 1 to 5,[14] and 0.8 vs. 0.2 by numerical score of 0 to 3 ($P = 0.004$).[25] Another study evaluated only the incidence of nausea and showed the decrease in the incidence of nausea (6 vs. 1 person, $P = 0.03$).[13] There was no

significant increase in psychotomimetic adverse events in all previously mentioned studies. In the current study, average 1.95 mg/kg of ketamine was used via IV PCA for 48 hr and the average consumption of ketamine was about 0.74 μg/kg/min for 24 hr. This was similar or lesser compared to other studies. The resulting percentage of reduced volume of PCA was 80.7% in 24 hr (74.5 ml vs. 60.1 ml, P = 0.041), 81.6% in 48 hr (143.9 ml vs. 117.4 ml, P = 0.015) in this study. The incidence and severity of PONV however, did not decrease in the ketamine group in this study. As our study was performed in higher risk patients for PONV, the incidence of PONV was 52 ~ 65% for all along the 48 hr which was much higher than those of previous studies. It is difficult to make direct comparisons of the results of the current trial to 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 female patients who are at increased risk of developing PONV. The results of the current trial was contrary to our expectations, since a substantial number of previous studies showed the reduced incidence of attenuated severity of PONV in association with perioperative ketamine administration although the evaluation of PONV was not a primary endpoint in all if these studies.

Plausible explanations for these contradictory results are as follows. Firstly, the decrease of opioid consumption could not be enough to mask the additional effect of ketamine. Both ketamine[26] and opioid can cause nausea and vomiting. Although mixture of opioid and ketamine could reduce nausea and vomiting in other studies, it may due to a morphine-sparing effect or to other as yet undetermined factors. Despite that similar or less dose of ketamine was used in the current study, reduction rate of dose of consumed opioid was relatively smaller in this study (reduction of opioid consumption, around 20% vs. around 40%). Thus, the degree of potency to decrease PONV might be loosening in this study. Secondly, the patient enrolled in

this study were all in very high risk of PONV, and multimodal antiemetic therapy is not very effective in the patients with continuous opioid infusion.[27] Therefore, due to the patient characteristics, the ketmaine should be not enough to reduce the incidence of PONV. Thirdly, 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 estrogen on serotonin pathways.[28] Ketamine can induce nausea[26], possibly by inhibition of serotonin uptake at synaptic terminals.[29] Also gender dependent defference in psychopathological effects of ketamine has been described.[30] Indeed, in a recent study, a low dose preemptive S-ketamine infusion in patients who underwent cesarean section under spinal anesthesia increased the incidence of vomiting and psychogenic side effects.[31] 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.

The patients in this study had shown to have increased incidence of dizziness, and several but not statistically relevant psychotomimetic adverse events. Ketamine is catalyzed by cytochrome P450 (CYP) enzymes, and CYP3A4 and CYP2B6 are the major enzymes responsible for ketamine N-demethylation.[32,33] Wide interindividual variability in the expression and activity of CYP2B6 and CYP3A4, possibly due to genetic polymorphism and/or ethnic differences, exist and may result in variable response to drugs metabolized by this enzyme.[34, 35] Yet, a clear relationship between the genetic variation and clinical phenotype remain 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 would not be decreased sufficiently.

V. CONCLUSION

In this study, subanesthetic dose of ketamine mixed in fentanyl based IV PCA was able to reduce the total infused volume of IV PCA for 48 hr in high risk patients for PONV undergoing lumbar spinal surgery, with comparable analgesic effect. However, it could not reduce the incidence of PONV and increased the incidence of dizziness. Adjunctive use of ketamine would not be recommended to reduce opioid related complications in this subset of patient.

REFERENCES

1. Gepstein R, Arinzon Z, Folman Y, Shuval I, Shabat S. Efficacy and complications of patient-controlled analgesia treatment after spinal surgery. Surg Neurol 2007;67:360-6.

2. Apfel CC, Laara E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology 1999;91:693-700.

3. Marret E, Kurdi O, Zufferey P, Bonnet F. Effects of nonsteroidal antiinflammatory drugs on patient-controlled analgesia morphine side effects: meta-analysis of randomized controlled trials. Anesthesiology 2005;102:1249-60.

4. Webb AR, Leong S, Myles PS, Burn SJ. The addition of a tramadol infusion to morphine patient-controlled analgesia after abdominal surgery: a double-blinded, placebo-controlled randomized trial. Anesth Analg 2002;95:1713-8.

5. Bell RF, Dahl JB, Moore RA, Kalso E. Peri-operative ketamine for acute post-operative pain: a quantitative and qualitative systematic review (Cochrane review). Acta Anaesthesiol Scand 2005;49:1405-28.

6. Burstal R, Danjoux G, Hayes C, Lantry G. PCA ketamine and morphine after abdominal hysterectomy. Anaesth Intensive Care 2001;29:246-51.

7. Michelet P, Guervilly C, Helaine A, Avaro JP, Blayac D, Gaillat F, et al. Adding ketamine to morphine for patient-controlled analgesia after thoracic surgery: influence on morphine consumption, respiratory function, and nocturnal desaturation. Br J Anaesth 2007;99:396-403.

8. Murdoch CJ, Crooks BA, Miller CD. Effect of the addition of ketamine to morphine in patient-controlled analgesia. Anaesthesia 2002;57:484-8.

9. Nesher N, Ekstein MP, Paz Y, Marouani N, Chazan S, Weinbroum AA. Morphine with adjuvant ketamine vs higher dose of morphine alone for immediate postthoracotomy analgesia. Chest 2009;136:245-52.

10. Reeves M, Lindholm DE, Myles PS, Fletcher H, Hunt JO. Adding ketamine to morphine for patient-controlled analgesia after major abdominal surgery: a double-blinded, randomized controlled trial. Anesth Analg 2001;93:116-20.

11. Sveticic G, Farzanegan F, Zmoos P, Zmoos S, Eichenberger U, Curatolo M. Is the combination of morphine with ketamine better than morphine alone for postoperative intravenous patient-controlled analgesia? Anesth Analg 2008;106:287-93.

12. Elia N, Tramer MR. Ketamine and postoperative pain--a quantitative systematic review of randomised trials. Pain 2005;113:61-70.

13. Adriaenssens G, Vermeyen KM, Hoffmann VL, Mertens E, Adriaensen HF. Postoperative analgesia with i.v. patient-controlled morphine: effect of adding ketamine. Br J Anaesth 1999;83:393-6.

14. Javery KB, Ussery TW, Steger HG, Colclough GW. Comparison of morphine and morphine with ketamine for postoperative analgesia. Can J Anaesth 1996;43:212-5.

15. Aveline C, Hetet HL, Vautier P, Gautier JF, Bonnet F. Peroperative ketamine and morphine for postoperative pain control after lumbar disk surgery. Eur J Pain 2006;10:653-8.

16. Webb AR, Skinner BS, Leong S, Kolawole H, Crofts T, Taverner M, et al. The addition of a small-dose ketamine infusion to tramadol for postoperative analgesia: a double-blinded, placebo-controlled, randomized trial after abdominal surgery. Anesth Analg 2007;104:912-7.

17. Yamauchi M, Asano M, Watanabe M, Iwasaki S, Furuse S, Namiki A. Continuous low-dose ketamine improves the analgesic effects of fentanyl patient-controlled analgesia after cervical spine surgery. Anesth Analg 2008;107:1041-4.

18. Zakine J, Samarcq D, Lorne E, Moubarak M, Montravers P, Beloucif S, et al. Postoperative ketamine administration decreases morphine consumption in major

abdominal surgery: a prospective, randomized, double-blind, controlled study. Anesth Analg 2008;106:1856-61.

19. Bonnet F, Marret E. Postoperative pain management and outcome after surgery. Best Pract Res Clin Anaesthesiol 2007;21:99-107.

20. Jellish WS, Leonetti JP, Sawicki K, Anderson D, Origitano TC. Morphine/ondansetron PCA for postoperative pain, nausea, and vomiting after skull base surgery. Otolaryngol Head Neck Surg 2006;135:175-81.

21. Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment, and prevention. Anesthesiology 1992;77:162-84.

22. Paksoy Y, Gormus N. Epidural venous plexus enlargements presenting with radiculopathy and back pain in patients with inferior vena cava obstruction or occlusion. Spine 2004;29:2419-24.

23. Roberts GW, Bekker TB, Carlsen HH, Moffatt CH, Slattery PJ, McClure AF. Postoperative nausea and vomiting are strongly influenced by postoperative opioid use in a dose-related manner. Anesth Analg 2005;101:1343-8.

24. Joly V, Richebe P, Guignard B, Fletcher D, Maurette P, Sessler DI, et al. Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. Anesthesiology 2005;103:147-55.

25. Stubhaug A, Breivik H, Eide PK, Kreunen M, Foss A. Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. Acta Anaesthesiol Scand 1997;41:1124-32.

26. Ghoneim MM, Hinrichs JV, Mewaldt SP, Petersen RC. Ketamine: behavioral effects of subanesthetic doses. J Clin Psychopharmacol 1985;5;70-7.

27. Chandrakantan A, Glass PS. Multimodal therapies for postoperative nausea and vomiting, and pain. Br J Anaesth 2011;107 (S1):27-40.

28. Rybaczyk LA, Bashaw MJ, Pathak DR, Moody SM, Gilders RM, Holzschu DL.

An overlooed connection: serotonergic medication of estrogen-related physiology and pathology. BMC Womens Health 2005;5:12.

29. Martin DC, Watkins CA, Adams RJ, Nason LA. Anesthetic effects on 5-hydroxytryptamine uptake by rat brain synaptosomes. Braine Res. 1988;455:360-5.

30. Bovill JG, Coppel DL, Dundee JW, Moore J. Current status of ketamine aneaesthesia. Lancet 1971;1:1285-8.

31. Suppa E, Valente A, Catarci S, Zanfini Ba, Draisci G. A study of low-dose S-ketamine infusion as "preventive" pain treatment of cesarean section with spinal anesthesia: benefits and side effects. Minerva Anestesiol 2012;78:774-81.

32. Yanagihara Y, Kariya S, Ohtani M, Uchino K, Aoyama T, Yamamura Y, et al. Involvement of CYP2B6 in n-demethylation of ketamine in human liver microsomes. Drug Metab Dispos. 2011;29:887-90.

33. Hijazi Y, Boulieu R. Contribution of CYP3A4, CYP2C9 isoforms to N-demethylation of ketamine in human liver microsomes. Drug Metab Dispos. 2002;30:853-8.

34. Mo SL, Liu YH, Duan W, Wei MQ, Kanwar JR, Zhou SF. Substrate specificity, regulation, and polymorphism of human cytochrome P450 2B6. Curr Drug Matab 2009;10:730-53.

35. Lamba JK, Lin YS, Schuetz EG, Thummel KE. Genetic contribution to variable human CYP3A-mediated metabilism. Adv Drug Deliv Rev 2002;54:1271-94.

ABSTRACT (IN KOREAN)

요추수술환자에서 정맥내 자가통증조절장치에 혼합된 케타민의 수술 후 오심 및 구토에 대한 효과

<지도교수 남순호 >

연세대학교 대학원 의학과

박 수 정

아편유사제를 사용한 정맥내 자가통증조절장치(intravenous patient controlled analgesia, IV PCA)는 요추수술을 받는 환자에서 효과적이고 안전한 제통법이나 수술 후 오심·구토(postoperative nausea and vomiting, PONV) 발생을 증가시키며, 특히 위험인자를 갖고 있는 환자들에서 이를 시행하는 경우 PONV의 발생빈도는 매우 높다. 케타민을 수술 중 또는 후에 준마취농도로 투여하면 아편유사제 사용량을 줄이면서 효과적으로 수술 후 통증조절을 할 수 있다는 연구들이 있었다. 본 연구에서는 펜타닐을 사용한 IV PCA에 혼합된 케타민이 PONV의 고위험군 환자에서 아편유사제 사용량을 감소시키고 이와 관련된 PONV를 줄일 수 있는 지 알아보고자 하였다.

요추수술을 받는 비흡연 여성 환자 50명을 무작위로 두 군으로 나누어 케타민군(n = 25)은 펜타닐 20 μg/kg과 케타민 3 mg/kg, 대조군(n = 25)은 펜타닐 20 μg/kg을 IV PCA에 주입하였고, 두 군 모두 온단세트론 8 mg과 생리식염수를 첨가하여 총 용량 180 ml의 IV PCA를 조제하였다. 마취 유도 직후 케타민군은 케타민 0.5 mg/kg를, 대조군은 동량의 식염수를 정맥주사 하였다. IV PCA는 기저주입속도 2 ml/h, 일시정주량 2 ml, 잠금 시간 15분으로 하였다. 회복실 입실 30분 후, 수술 후 6, 12, 24, 36, 48시간에 PCA 사용량, PONV, 통증, 기타 부작용 및 추가 진통제와 진토제 사용량을 조사하였다.

수술 후 48시간 동안 소비된 PCA 용량은 케타민군에서 더 적었다(143.9 ± 35.1 ml vs. 117.4 ± 29.5 ml, P = 0.015). 수술 후 48시간 동안의 오심 발생빈도는 대조군(56%)과 케타민군(68%) 간에 차이가 없었으나 수술 후 6시간 동안의 오심 발생빈도는 케타민군에서 더 높았고(16% vs. 52%, P = 0.016) 케타민군에서 어지러움증이 더 많이 발생하였다(12% vs. 36%, P = 0.047). 수술 후 통증 정도와 추가 진통제 및 진토제 사용량은 양군 간 차이가 없었다.

요추수술을 시행 받는 환자 중 PONV의 고위험군 환자에서 펜타닐을 사용한 IV PCA에 케타민을 혼합하였을 때 PCA 사용량은 줄일 수 있었으나 PONV의 발생빈도를 낮추지 못하였고 사용 중 어지러움증이 더 자주 발생하였던 바 이러한 환자 군에서 케타민을 보조적으로 사용하는 것은 도움이 되지 못한다고 생각한다.

핵심 되는 말: 수술 후 오심, 아편유사제를 사용한 자가통증조절장치, 케타민