Comparison Between Low Dose Ketamine VS Fentanyl Combined with Propofol in Patients Scheduled for Fractional Curettage; A Randomized Controlled Trial

Suppachai Poolsuppasit, M.D.*, Poom Tritrakarn, M.D.*, Shusee Visalyaputra, M.D.*, Nuchsaroch Pechpaisit, M.D.*, Roungsin Choavaratana, M.D., Ladda Phuampolprasert, B.Sc.*, Pathipa Suksopee, B.Sc.***

**Department of Anesthesiology, **Department of Gynecology and Obstetrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.*

ABSTRACT

Objective: Total intravenous anesthesia for uterine curettage with propofol is common in practice. Narcotics are used to decrease movement due to pain during the procedure. But narcotics may cause hypotension, hypoventilation, bradycardia, desaturation and apnea. We hypothesized that the use of ketamine instead of fentanyl can reduce the incidence of patients' movement and other complications mentioned above.

Methods: Eighty-four patients were enrolled into the study. The patients were randomized in to 2 groups: Fentanyl group (Propofol+Fentanyl) and Ketamine group (Propofol+Ketamine). Low dose of ketamine (0.3 mg/kg) or fentanyl (1 mcg/kg) was injected, followed by propofol 1.5 mg/kg, then uterine curettage was started along with propofol infusion of 5 mg/kg/hr. Patients' movement, respiratory rate, blood pressure, and O2 saturation were recorded every minute. After the procedure, the emergence duration and surgeon's satisfaction were recorded. The incidence of nausea/vomiting, dizziness and any other complaints were recorded for 24 hours postoperatively.

Results: There was no significant difference in patient's movement, surgeon's satisfaction and emergence duration between the two groups. Patients in ketamine group significantly showed lower incidences of respiratory depression as shown by less requirement of airway manipulation with assisted ventilation, and lower incidences of hypotension than patients in the fentanyl group (2.4% vs. 19%, p=0.029 and 7.2% vs. 52.4%, p<0.01, respectively).

Conclusion: The use of low dose ketamine with propofol in patients having uterine curettage can cause less hypotension and less respiratory depression than using fentanyl with propofol, without any difference in patients' movements and emergence from anesthesia.

Keywords: Ketamine, TIVA, movement, curettage, fentanyl

Siriraj Med J 2015;67:273-279
E-journal: http://www.sirirajmedj.com

INTRODUCTION

Propofol is often used for TIVA during a uterine curettage procedure. However, propofol has no analgesic effect; so, propofol alone is not enough to prevent patient's movement due to pain which may interfere with the procedure. Analgesic drugs often used with propofol are narcotics, but they may cause hypotension, bradycardia, hypoventilation and apnea.

Ketamine is a dissociative sedative phencyclidine derivative. Ketamine has an analgesic property which at low-dose has a minimal stimulant effect on the respiratory and circulatory systems.

Correspondence to: Poom Tritrakarn
E-mail: poompoosup@gmail.com

It may be better to use ketamine instead of narcotics. However, the use of ketamine may result in nausea, vomiting, delayed emergence and nightmare in a high dose.

The use of propofol combined with ketamine is an effective anesthesia technique with little or no effect on the respiratory and circulatory systems.[1-4] Kwok et al. did not encounter complications in the circulatory system and psychological symptoms when ketamine was provided at 0.15 mg/kg in patients who underwent laparoscopic gynecologic surgery.[5] Sandip et al found that children who received propofol with fentanyl would wake up faster than children who received ketamine with midazolam. However, the former group had much higher incidence of respiratory depression and airway obstruction.[6] In addition, studies have found that the use of propofol in combination with NSAIDS (flurbiprofen) can decrease the movement of the patient responding to pain during curettage and postoperative pain.[7] Another study found that the use of propofol combined with fentanyl in patients who underwent gynecological surgery have only additive, effect but not synergistic effect.[8]

Phadungchaichote et al[9] showed that ketamine in the medium dose of 0.5 mg/kg in combination with propofol produce incidences of hypotension at 25%, bradycardia at 10.7%, hypoventilation at 3.6% and desaturation at 10.7% compared to 55.4%. 30.6%, 19.6% and 42.9%, respectively, from the use of propofol combined with fentanyl. In this study, the medium dose of ketamine also caused more delayed emergence, but they did not compare the incidence of movement during curettage.

We hypothesized that the use of low dose ketamine (0.3 mg/kg) in combination with pro-pofol is adequate to decrease the chance of patients' movement, respiratory depression, airway manipulation, apnea, hypotension and bradycardia compared to the use of propofol combined with fentanyl in patients who undergo uterine curettage without any delayed emergence.

Primary objective: To find out if ketamine 0.3 mg/kg with propofol 1.5 mg/kg for bolus dose, then propofol 5 mg/kg/hr infusion will decrease incidence of movement at least 30% during curettage, compared with fentanyl 1 mcg/kg with propofol at the same dose.

Secondary objective: To find out if ketamine 0.3 mg/kg with propofol 1.5 mg/kg for bolus dose, then propofol 5 mg/kg/hr infusion will decrease incidence of respiratory depression, airway manipulation, apnea, hypotension and bradycardia during curettage, compared with fentanyl 1 mcg/kg with propofol at the same dose.

MATERIALS AND METHODS

A hospital ethical committee approval (SIRB 375/2552(EC3)) and clinical trial registry (TCTR20140828001) were obtained; then patients who would have uterine curettage in the next day were invited to participate in the research. The exclusion criteria were composed of patients younger than 18 or older than 60 years old, BMI more than 30 kg/m^2, ASA physical status more than II, allergic to propofol, ketamine or fentanyl, psychiatric problem that might get worse by ketamine, hypertension that needed medication, history of coronary artery disease and increased ICP.

After the consents were obtained, eighty-four patients were randomly divided into two groups by using the Research Randomizer program with block of 4, and then these labels were put in sealed envelopes.

When the patient came into the operating room, lactate Ringers solution was infused at 100 ml/hr. Non-invasive monitoring such as the ECG, and pulse oximetry were monitored including the non-invasive BP which was measured every 1 minute for 15 minutes. Oxygen was supplemented through oxygen masks for 5 L/min. Detection of apnea episodes was done by using a side stream capnograph's catheter inserted through the mask.

A research assistant who was not involved in monitoring opened the envelope. In the ketamine group, ketamine 0.3 mg/kg would be prepared to get 2 ml in a 2 ml syringe by adding normal saline solution. In the fentanyl group, fentanyl 1 mcg/kg would also be prepared for 2 ml in a 2 ml syringe. Either ketamine or fentanyl was given, followed by propofol 1.5 mg/kg mixed with 2% lidocaine 40 mg/10 ml solution. Propofol

might be added until no eyelash reflex was seen. Then the uterine curettage was started along with the infusion of propofol at 5 mg/kg/hr.

During the operation, we recorded the movement of the patient during curettage into a scale from 0 to 3 (0 = no movement, 1 = mild movement without propofol added, 2 = moderate movement that needed propofol added, but did not interrupt the procedure, 3 = marked movement that interrupted the procedure and needed to add more propofol to continue the procedure)

We also recorded each patient's BP, HR, SpO_2, apnea episode and airway manipulation episode throughout the operation. Strict safety protocol was applied to every patient as followed. If the blood pressure fell below 25% or lower than baseline, 6 mg of ephedrine would be given intravenously. If the heart rate was slower than 50 beat/minute, along with hypotension, 0.6 mg of atropine was injected. If the breathing was stopped for longer than 15 seconds, airway manipulation (head tilt and chin lift technique) was performed along with positive pressure ventilation with 100% oxygen via face mask. We also defined the term hypoventilation if the patient's breath was less than 8 times per minute. If this occurred with oxygen saturation less than 95%, airway manipulation was performed in the same way.

After the operation was finished, the propofol infusion was immediately stopped and detached. The anesthetist then tried to wake the patient every minute until the patient opened her eyes. The eye-opening time was recorded. Then the patients were moved to a recovery room. The surgical satisfaction was rated into a scale from 0 to 10 (0 meant least satisfied and 10 meant most satisfied) by the surgeon immediately after the operation.

In the recovery room, pain score, nausea, vomiting, dizziness and shivering were monitored and recorded. If the pain score (Visual Analog Scale = 0-10) was more than 6, 25 mcg of fentanyl was injected to relieve pain (maximum of 2 times). Otherwise two tablets of 500 mg-paracetamol were given. In cases where severe nausea or vomiting occurred more than 1 time, 10 mg of metoclopramide was given. Before being discharged from the recovery room, the patient was given a researcher-addressed postcard. The postcard asked about the pain scores at 6, 12, and 24 hours postoperative as well as nausea, vomiting and other complaints.

The sample size calculation was based on the result from the study of Seitonen et al,[10] in which 73% of patients who received propofol and alfentanil had movement responses during uterine curettage. We use Power and Sample size Calculations (PS) program version 3.0.2 with alpha =0.05, P0 = 0.73, P1= 0.43. (Clinical significant difference of 30 %, beta = 0.3). The result indicated that we needed a minimum of 42 patients for each group to complete the study.

Continuous data were presented as mean ± S.D., and categorical data were presented as frequency and percentage. The demographic data (age, weight, height and BMI) were compared between groups with student's T test. The incidence of movement during procedure, hypoventilation, apnea, bradycardia and hypotension were compared with Pearson's Chi-square test. The incidence of apnea, assisted ventilation, desaturation and other side effects were analyzed by Fisher's exact test. The duration of anesthesia and surgeon's satisfaction were compared with Mann-Whitney U test. A value of $p<0.05$ was considered statistically significant in all tests. For statistical analysis we used SPSS 15.0 for Windows. (Fig 1)

RESULTS

There were no statistically significant differences in the demographic data (age, weight, height, BMI and ASA) between the two groups. (Table 1)

The movement of patient during procedure was lower in the ketamine group (57.1% vs. 61.9%), although there was no statistical significance (p=0.65).

For the respiratory system, the ketamine group had a lower incidence of both hypoventilation and apnea episodes than the fentanyl group (16.7% vs. 31.0% and 2.4% vs. 7.1% respectively), but there was no statistical significance (p =0.124, 0.616 respectively). However, the

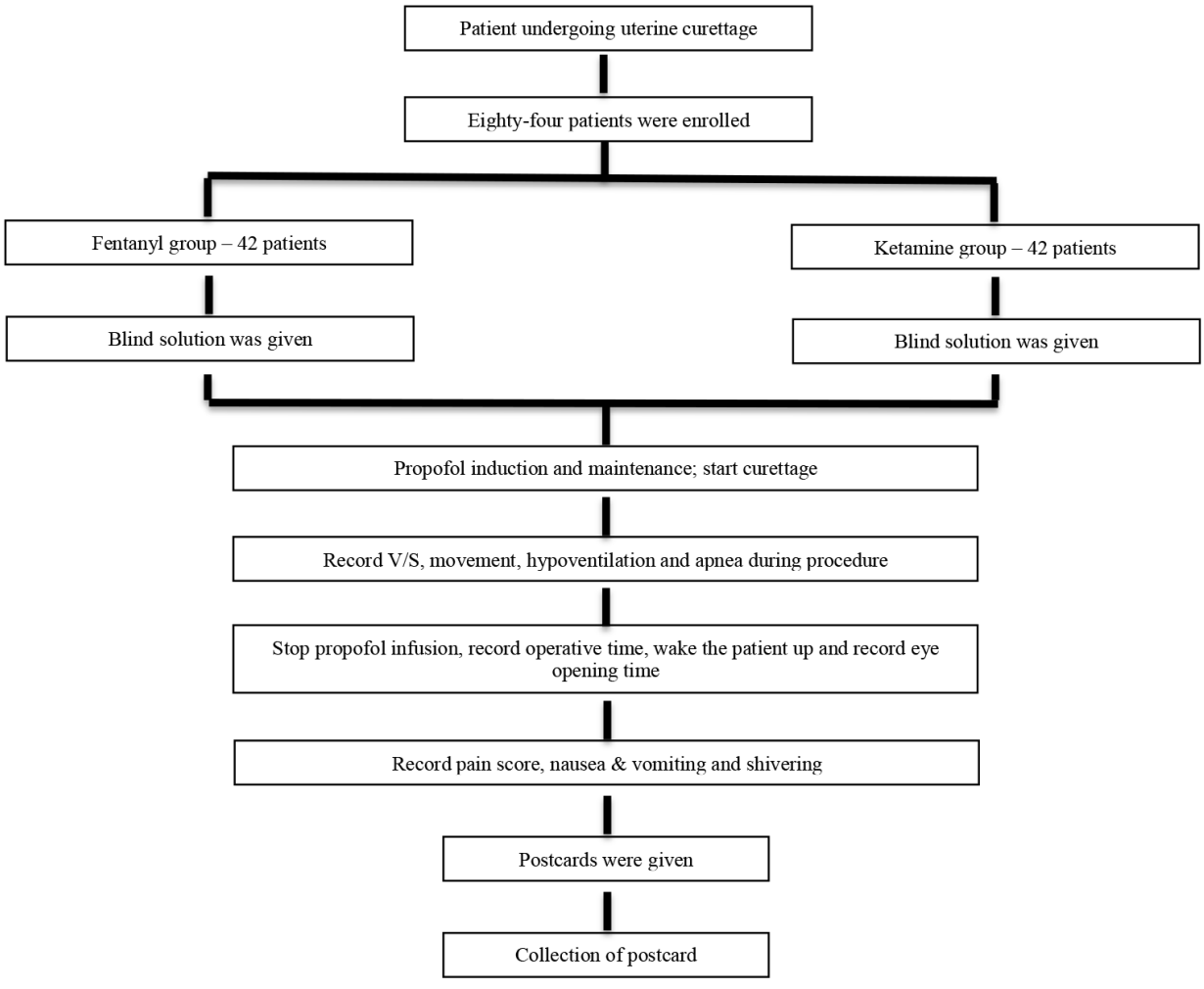

Fig 1. Flow chart

need to assist ventilation (by head tilt and chin lift technique and /or mask ventilation) in the ketamine group was significantly lower than the fentanyl group. (2.4% vs. 19%, p=0.029).

The incidence of hypotension (BP falling lower than 25% of baseline) within the first five or ten minutes in the fentanyl group was obviously higher than the ketamine group. (52.4% vs. 7.1%, p<0.01 and 57.5% vs. 9.7%, p<0.01). Table 4 and Fig 2 show the trends of SBP between the 2 groups.

There were 4 cases in the ketamine group that developed hypertension (BP>25% of baseline) intraoperatively, while none of the patients in the fentanyl group developed it. However, the difference was not statistically significant.

The incidences of bradycardia (HR<60) and desaturation (SpO_2 <95%) had no statistically significant difference between the two groups. (Table 2)

In comparison of anesthesia duration and surgical satisfaction, there was no significant difference between both groups. The mean anesthesia duration in the fentanyl group was 2.57 minutes longer than the ketamine group, but there was

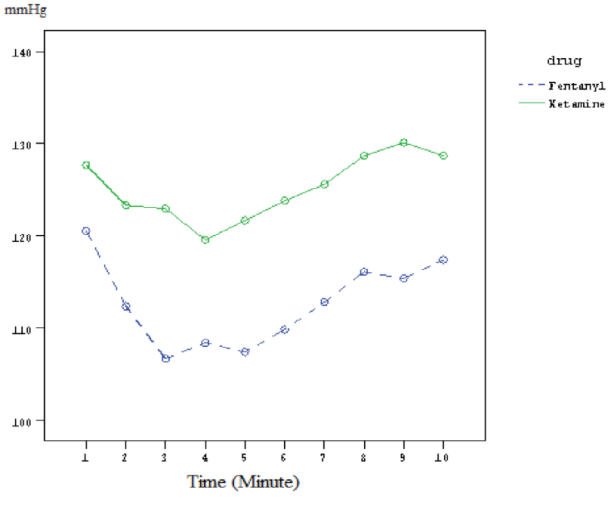

Fig 2. Trend of systolic blood pressure in 10 minutes

TABLE 1. Demographic data.

	Fentanyl (N=42)	Ketamine (N=42)	P-value
Age (year)	46.29 ± 7.93	45.64 ± 6.87	0.692
Weight (kg)	59.67 ± 9.80	58.08 ± 8.95	0.438
Height (cm)	157.33 ± 6.33	157.60 ± 5.12	0.835
BMI (kg/m^2)	24.15 ± 3.95	23.38 ± 3.41	0.343
ASA Ps class I	31 (73.8%)	30 (71.4%)	0.87
II	11 (26.2%)	12 (28.6%)	

ASA Ps=American Society of Anesthesiologist physical status

ASA I = A normal healthy patient

ASA II =A patient with mild systemic disease

BMI = body mass index

TABLE 2. Intraoperative results.

	Fentanyl (N=42)	Ketamine (N=42)	P-value
No movement	16 (38.1%)	18 (42.9%)	
Movement			
Mild (1)	0 (0%)	2 (4.8%)	
Moderate (2)	11 (26.2%)	6 (14.3%)	
Severe (3)	15 (35.7%)	16 (38.1%)	
Overall movement	26 (61.9%)	24 (57.1%)	0.657
Hypoventilation	13 (31%)	7 (16.7%)	0.124
Apnea	3 (7.1%)	1 (2.4%)	0.616
Assist ventilation	8 (19%)	1 (2.4%)	0.029
5 minutes			
Normotension	20 (47.6%)	39 (92.8%)	
Hypotension	22 (52.4%)	3 (7.2%)	<0.01
Total	42	42	
10 minutes			
Normotension	17 (42.5%)	28 (90.3%)	
Hypotension	23 (57.5%)	3 (9.7%)	<0.01
Hypertension	0 (0%)	4 (9.5%)	0.116
Total	40	31	
SpO_2 <95% in 5 minutes	6 (14.3%)	1 (2.4%)	0.109
HR <60 in 10 minutes	19 (45.2%)	15 (26.6%)	0.423

no statistical significance (p=0.062). When we calculated the mean duration of emergence from anesthesia, we found that it was almost 3 minutes in both groups and surprisingly equal. (Table 3)

The last table shows the incidence of adverse effects in our study that were collected from PACU and the postcards 24 hours later. There were 9 patients in the fentanyl group (21%) and 4 patients in the ketamine group (9%) who did not return the postcards. The incidence of vomiting in ketamine group was a bit higher, but it was still low at 3/38 (7.9%). (Table 4)

DISCUSSION

With incidence of movement of 57% in the ketamine group and 62% in the fentanyl group, our study showed that either use of fentanyl or ketamine during curettage has no significant difference in terms of patients' movement. This is

TABLE 3. Post-operative results.

	Fentanyl	Ketamine	P-value
Anesthesia duration (minute)	15.50 ± 7.00	12.93 ± 6.37	0.062
Emergence duration (minute)	2.95	2.95	
Surgical satisfaction score (0-10)	9.48	9.43	

Data show as mean ± S.D.

TABLE 4. Side effects at PACU and 24 hours post-operative.

	Fentanyl	Ketamine
At PACU	42	42
Nausea	0	1 (2.4%)
Vomiting	0	0
Shivering	0	1 (2.4%)
Dizziness	0	1 (2.4%)
24 hours (Total)	33	38
Nausea	5 (15.2%)	5 (13.2%)
Vomiting	0	3 (7.9%)
Dizziness	13	17

Data shown as n (%)

probably because the ketamine dose that we used might have been too small to prevent movement from pain in all patients. A little bigger dose of ketamine might be tried in further study. We are really concerned in this aspect, because the movement of patients during these procedures may cause harm such as uterine perforation. Also, these movements may affect the satisfaction of the gynecologists who performed the procedures as our result shows that the satisfactions were the same. This is interesting because ketamine may cause abnormal movements as a side effect. We think that the abnormal movement side effect of ketamine in a dose as low as 0.3 mg/kg was suppressed by propofol in our study.

In our study, the incidence of hypotension in the fentanyl group was higher than the ketamine group. This result was similar to the study by Phadungchaichote et al.[9] On the other hand, the incidence of bradycardia has no significant difference, from a previous study.[9] Some may ask about the hypertension side effect of ketamine. There were 4 cases in ketamine group that developed hypertension (BP>25% of baseline) intraoperatively, but they easily subsided without using any medication and had no sequelae. Although none of the patients in the fentanyl group developed hypertension, the result has no statistically significant difference between the groups.

The respiratory depressions after bolus dose of intravenous agents are common. In most of the cases, the patient can return spontaneous ventilation by themselves after surgical stimuli. In our study, these episodes occurred in first 5 minutes after the surgical procedure started in both groups. However, there was no statistically significant different between the 2 groups. However, when we compared the incidence of assisted ventilation, ketamine group was significantly lower than fentanyl group. As we already know that ketamine has minor or some stimulant effect on respiration, so this may be another advantage of ketamine instead of fentanyl in the respiration aspect. Further study may aim to clarify this.

David et al[11] found that patients undergoing procedural sedation and analgesia with propofol and fentanyl have more intrasedation events than propofol and ketamine, especially for desaturation events. It may be due to our safety protocol that we will assist by ventilating the patient immediately whenever the patients stopped breathing for more than 15 seconds. From this criterion, our study found only few cases that developed desaturation and no difference in both groups (SpO_2 <95%, 6 vs. 1 in fentanyl and ketamine groups, respectively), against the previous study.[9]

Our results about time are not in agreement with the previous study.[9] There was no difference in time used for the patients to open their eyes and to recover from anesthesia between both groups. Furthermore, the mean anesthetic duration in fentanyl group was a bit longer than ketamine.

In the postoperative period at PACU, we found that both groups had no significant

dif-ferences in incidence of the side effects of anesthesia. However, when patients returned home or ward 24 hours after the procedure (9 patients in fentanyl group and 4 patients in ketamine failed to follow up), nightmare and hallucination were side effects which we may concern, when we use ketamine in any procedure. We found no report of these side effects in our study.

From these results, we suggest that the use of low dose ketamine with propofol in patients having uterine curettage seems to be safer than fentanyl with propofol without making the procedure more difficult or causing delayed emergence.

CONCLUSION

The use of low dose ketamine with propofol in patients having fractional curettage can be an alternative choice of anesthesia without a difference in patients' movements and emergence from anesthesia compared to the use of fentanyl with propofol. Moreover this technique causes less hypotension and less respiratory depression.

ACKNOWLEDGMENTS

To all anesthetic residents and nurses in that time for their hard work on data collection and postoperative cares for the study. To Department of Anesthesiology, Siriraj Hospital for their support in all steps in this study. Also the last, we were supported by Siriraj research fund.

REFERENCES

1. Sicignano A, Bellato V, Cancellieri F, Foroni C, Giubelli D, Latis G, et al. Propofol-ketamine vs propofol-fentanyl in short gynecologic surgery. Minerva Anestesiol. 1990 Mar;56(3):61-6.
2. Cheng KI, Chu KS, Fang YR, Su KC, Lai TW, Chen YS, et al. Total intravenous anesthesia using propofol and ketamine for ambulatory gynecologic laparoscopy. Kaohsiung J Med Sci. 1999 Sep;15(9):536-41.
3. Adams HA, Beigl B, Schmitz CS, Baltes-Götz B. Total intravenous anesthesia (TIVA) in geriatric surgery. S-(+)-ketamine versus alfentanil. Anaesthesist. 1995 Dec;44 Suppl 3:S540-8.
4. Ravindra VP, Frederick BP. Ketamine and propofol in combination for sedation during laparoscopic tubal ligation. Anaesthetist 1991. p. 199-204.
5. Kwok FKR, Lim J, Chan TVM, Gin T, Chiu KYW. Preoperative ketamine improves postoperative analgesia after gynecologic laparoscopic surgery. Anesth Analg. 2004 Apr;98(4):1044-9
6. Godambe AS, Elliot V, Matheny D, Pershad J. Comparison of propofol/fentanyl versus ketamine/midazolam for brief orthopedic procedural sedation in a pediatric emergency department. Pediatrics. 2003 Jul;112(1 Pt 1):116-23.
7. Nishimine N. Anesthesia for dilatation and curettage with propofol and flurbiprofen. J Clin Anesth. 2005;29:685-8.
8. Ben-Shlomo I, Finger J, Bar-Av E, Perl AZ, Etchin A, Tverskoy M. Propofol and fentanyl act additively for induction of anaesthesia. Anaesthesia. 1993 Feb;48(2): 111-3.
9. Phadungchaichote N, Angkanarwiriyarak S, Chanvej L, Chongsuvivatvong V. Hemodynamic and adverse effects of propofol/ketamine compare to propofol/fentanyl in minor gynecologic patients. Thai J Anesth. 2002; 28:140-6.
10. Seitsonen ER, Cohen-Laroque ES, van Gils MJ, Korttila KT, Neuvonen PJ, Yli-Hankala AM. Propofol versus alfentanil to prevent movement responses during uterine curettage. Acta Anaesthesiol Scand. 2007 Jul;51(6):751-8.
11. David WM, Heather EM, Paul ED, Janet van V, Marco LAS. Subdissociative-dose Ketamine versus Fentanyl for Analgesia during Propofol Procedural Sedation: A Randomized Clinical Trial. Acad Emerg Med. 2008 Oct;15 (10):877-86.